differential extinction coefficient between oxidized and reduced form of the enzyme a value of 13.1 × 10^3 M^{-1} cm^{-1} at 450 nm.

Conclusions

The main conclusions emerging from the present study may be summarized as follows.

When using one-electron redox cosubstrates, cyclic voltammetry may be efficiently applied to the simultaneous determination of the rate constants of both the reductive half-reaction and of the oxidation of the reduced enzyme. It suffices to create experimental conditions in which the kinetics of the catalytic reaction significantly deviate from first-order conditions and to treat the data accordingly. The determination of the oxidation rate constant may then be achieved by decreasing the mediator concentration so as to reach the first-order behavior under controlled conditions.

This procedure avoids the danger of significantly underestimating the oxidation rate constant when this is large. From this application, it is now possible to understand why glucose oxidase electrodes using positively charged ferrocenium mediators are insensitive to dioxygen. The oxidation rate constant thus found at pH = 7 is indeed larger than that observed with dioxygen.

Clear variations of the oxidation rate constants with pH have been found. They indicate that the pK_as involved are those of the $FADH_2$/$FADH^\bullet$ and $FADH^\bullet$/$FAD^{\bullet-}$ acid–base couples and may thus be rationalized by a kinetic scheme in which the various protonated and deprotonated forms present at the three successive oxidation states of the flavin are taken into account.

Analysis of the catalytic response in the most basic and most acidic sides of the pH range as a function of the electron-transfer driving force offered by the various mediators investigated points to the intermediacy of a precursor complex between the mediator and a site close to the flavin. The interference of the thermodynamics and kinetics of the formation of this precursor complex thus allows differentiation of the one-electron redox mediators by the enzyme.

It is also interesting to note that extensive glycosylation in the recombinant enzyme we have investigated left practically unaltered the catalytic activity for what is regarded as both the reductive half-reaction and the oxidation of the reduced form of the enzyme by the one-electron redox mediators.

Acknowledgment. We are grateful to Dr. A. de Baetselier (ICP-UCL, Brussel) for the generous gift of the recombinant glucose oxidase. We thank Dr. C. P. Andrieux (Laboratoire d'Electrochimie Molèculaire de l'Universitè de Paris VII) for his help in the numerical computations of eqs IV–VII.

Potassium Cryptate Catalysis in the Elimination Reaction of a Sulfonate Ester

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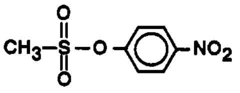
Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario, K7L 3N6 Canada. *Received June 1, 1992*

Abstract: In the reaction of *p*-nitrophenyl methanesulfonate (**1**) with alkali-metal ethoxides, it is found that potassium ethoxide in the presence of excess 2.2.2 cryptand is more reactive than potassium ethoxide alone or in the presence of excess 18-crown-6. An upward curvature in the plot of k_{obs} vs $[KOEt]_0$ in the presence of 2.2.2 cryptand is interpreted as arising from parallel reactions of free ethoxide ion and the ion pair of ethoxide ion with cryptated potassium ion ($[K \subset 2.2.2]^+EtO^-$), the latter being more reactive than the former. It is shown that the ester reacts predominantly by an E1cb-type elimination mechanism, and the potassium cryptate appears to stabilize the transition state for leaving-group departure by electrostatic interactions through an 18-membered ring "window" in the cryptand.

Introduction

We have been engaged in systematic studies of the mechanisms of reaction of alkali-metal ethoxides with carbon-, phosphorus-, and sulfur-based esters designed to reveal the effect of variation of both the alkali-metal ion and the nature of the substrate ester in these reactions. Our studies have revealed a spectrum of different metal ion effects, ranging from catalysis by all of the alkali-metal ions to inhibition by all.[1] Throughout these studies, crown ethers and cryptands were used to complex the metal ions in order to access the reactivity of free ethoxide ion. In the course of this work, we have discovered a system in which the 2.2.2 cryptate of potassium ion ($K^+ \subset 2.2.2$) appears to act as a catalyst. These results, which concern the reaction of *p*-nitrophenyl methanesulfonate (**1**) with alkali-metal ethoxides, are reported here and are contrasted to results for other methanesulfonate esters, including the *p*-trifluoromethylphenyl ester (**2**).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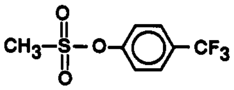
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Results

Kinetic data for the reaction of *p*-nitrophenyl methanesulfonate (**1**) with various alkali-metal ethoxide species are shown in Figure 1 and Table I. The observed rate constants increase in the order LiOEt < NaOEt < CsOEt ≈ KOEt ≈ KOEt + 18C6 < KOEt + 2.2.2. A striking result in this system is the fact that potassium ethoxide in the presence of excess 2.2.2 cryptand is more reactive than either potassium ethoxide alone or potassium ethoxide in the presence of excess 18-crown-6 (Figure 1). If the data for KOEt + 18C6 are taken to represent free ethoxide ion, as will be argued below, it follows that the potassium cryptate catalyzes the reaction which is inhibited by some uncomplexed alkali-metal ions (Li^+, Na^+) and relatively unaffected by others (K^+, Cs^+).

As seen in Figure 1, the plot of k_{obs} vs $[MOEt]_0$ for KOEt + 2.2.2 shows marked upward curvature, while plots for other ethoxide species are only slightly curved. In our previous treatment of ester ethanolysis reactions, curvature in plots of k_{obs} vs $[MOEt]_0$

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(1) (a) Buncel, E.; Dunn, E. J.; Bannard, R. A. B.; Purdon, J. G. *J. Chem. Soc., Chem. Commun.* **1984**, 162. (b) Dunn, E. J.; Buncel, E. *Can. J. Chem.* **1989**, *67*, 1440. (c) Buncel, E.; Pregel, M. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1566. (d) Dunn, E. J.; Moir, R. Y.; Buncel, E.; Purdon, J. G.; Bannard, R. A. B. *Can. J. Chem.* **1990**, *68*, 1837. (e) Pregel, M. J.; Dunn, E. J.; Buncel, E. *Can. J. Chem.* **1990**, *68*, 1846. (f) Pregel, M. J.; Buncel, E. *J. Am. Chem. Soc.* **1991**, *113*, 3545. (g) Pregel, M. J.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 307. (h) Pregel, M. J.; Buncel, E. *J. Org. Chem.* **1991**, *56*, 5583.

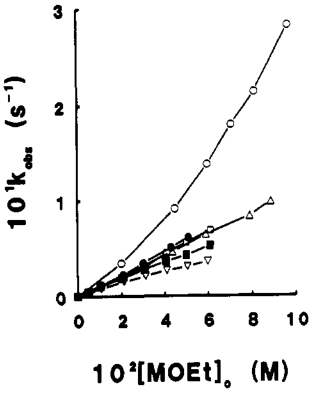

Figure 1. Kinetic data for the reaction of *p*-nitrophenyl methanesulfonate (**1**) with LiOEt (▽), NaOEt (■), KOEt (△), CsOEt (□), KOEt in the presence of excess 18-crown-6 (●), and KOEt in the presence of excess 2.2.2 cryptand (○) in anhydrous ethanol at 25 °C.

Table I. Kinetic Data for the Reaction of **1** with Alkali-Metal Ethoxides in EtOH at 25 °C

$[\mathrm{MOEt}]_0$ (10^{-2} M)	k_{obs} (10^{-2} s^{-1})	$[\mathrm{MOEt}]_0$ (10^{-2} M)	k_{obs} (10^{-2} s^{-1})	$[\mathrm{MOEt}]_0$ (10^{-2} M)	k_{obs} (10^{-2} s^{-1})
		LiOEt			
1.06	0.810	3.10	2.11	5.05	3.09
2.10	1.52	4.09	2.68	5.99	3.64
		NaOEt			
0.461	0.437	3.05	2.79	4.99	4.27
1.02	1.04	4.04	3.62	6.08	5.27
2.01	1.89				
		KOEt			
1.48	1.47	4.34	4.64	7.01	8.17
1.94	2.00	5.69	5.79	7.88	8.39
2.92	3.04	5.89	6.45	8.85	9.89
		CsOEt			
0.543	0.545	3.11	3.06	4.99	5.59
1.08	1.05	4.07	4.51	6.10	6.88
2.11	2.02				
		KOEt + 18C6, [KOEt]/[18C6] = 2.5–2.8			
0.510	0.581	2.07	2.23	4.27	5.06
1.07	1.17	2.99	3.45	5.07	6.11
		KOEt + 2.2.2, [2.2.2]/[KOEt] = 1.5			
1.05	1.45	4.02	8.00	7.06	18.0
1.99	3.45	4.47	9.15	8.11	21.5
2.97	5.09	5.97	13.8		

Table II. Second-Order Rate Constants for the Reaction of Free Ethoxide Ion and Alkali-Metal Ethoxide Ion Pairs with **1**[a]

	$k_{\mathrm{EtO^-}}$ (M^{-1} s^{-1})	k_{MOEt} (M^{-1} s^{-1})
LiOEt	1.04 ± 0.06	0.48 ± 0.04
NaOEt	1.11 ± 0.12	0.75 ± 0.08
KOEt	0.93 ± 0.10	1.17 ± 0.10
CsOEt	0.75 ± 0.26	1.27 ± 0.16
KOEt + 18C6	1.05 ± 0.04	

[a] Ion pairing treatment of the kinetic data gave the values for LiOEt, NaOEt, KOEt, and CsOEt. The value for KOEt + 18C6 is from the slope of the plot of k_{obs} vs $[\mathrm{MOEt}]_0$. Error limits span a 95% confidence interval.

Table III. Effect of Adding 2.2.2 Cryptand to the Reaction of **1** with KOEt in EtOH at 25 °C[a]

[2.2.2]/ $[\mathrm{KOEt}]_0$	k_{obs}/ $[\mathrm{KOEt}]_0$ (M^{-1} s^{-1})	[2.2.2]/ $[\mathrm{KOEt}]_0$	k_{obs}/ $[\mathrm{KOEt}]_0$ (M^{-1} s^{-1})	[2.2.2]/ $[\mathrm{KOEt}]_0$	k_{obs}/ $[\mathrm{KOEt}]_0$ (M^{-1} s^{-1})
0.000	1.048	1.044	1.209	1.855	1.226
0.348	1.118	1.276	1.232	2.088	1.219
0.696	1.181	1.623	1.274	2.318	1.296
1.044	1.254	1.623	1.231	2.551	1.242

[a] $[\mathrm{KOEt}]_0 = 5.4 \times 10^{-3}$M.

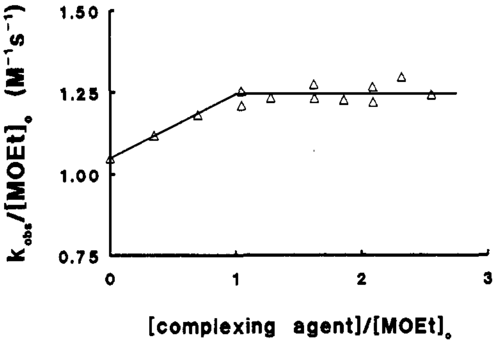

Figure 2. Effect of added 2.2.2 cryptand on the reaction of **1** with KOEt in ethanol at 25 °C ($[\mathrm{KOEt}]_0 = 5.4 \times 10^{-2}$ M).

was explained as arising from ion pairing between the alkali-metal counterion and ethoxide ion.[1] The free and ion-paired ethoxide species react with the ester in parallel but at different rates. An ion-pair association constant, K_a, governs the equilibrium between free ions and ion pairs (eq 1). The observed rate constant is a sum of contributions from the free ion and ion-pair pathways (eq 2). As the total base concentration increases, the proportion of ion pairs (MOEt) relative to free ions (M^+, EtO^-) increases, and the balance between the free ion and ion-pair pathways changes in favor of the ion-pair pathway. Since free ions and ion pairs differ in reactivity, this results in curved plots of observed rate constant versus total base concentration. Upward curvature is seen when $k_{\mathrm{MOEt}} > k_{\mathrm{EtO^-}}$ and downward curvature is seen when $k_{\mathrm{MOEt}} < k_{\mathrm{EtO^-}}$. Thus, upward curvature in plots of k_{obs} vs $[\mathrm{MOEt}]_0$, as in the case of KOEt + 2.2.2, suggests that the ion pair ($[\mathrm{K} \subset 2.2.2]^+\mathrm{EtO}^-$) is more reactive than free ethoxide ion, i.e., $[\mathrm{K} \subset 2.2.2]^+$ is a catalyst.

$$\mathrm{M^+ + EtO^-} \overset{K_a}{\rightleftharpoons} \mathrm{MOEt} \qquad K_a = [\mathrm{MOEt}]/[\mathrm{M^+}][\mathrm{EtO^-}] \quad (1)$$

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

K_a values for alkali-metal ethoxides in anhydrous ethanol at 25 °C have been determined,[2] so equilibrium concentrations of free ions and ion pairs can be calculated since the total base concentration is known and $[\mathrm{M^+}] = [\mathrm{EtO^-}]$ at equilibrium. Consequently, variation of the observed pseudo-first-order rate constant with the total base concentration may be used to determine second-order rate constants for free ethoxide and metal-ethoxide ion pairs using eq 3. The second-order rate constants

$$k_{obs}/[\mathrm{EtO^-}] = k_{\mathrm{EtO^-}} + k_{\mathrm{MOEt}}K_a[\mathrm{EtO^-}] \quad (3)$$

for the reaction of **1** with LiOEt, NaOEt, KOEt, and CsOEt are presented in Table II. The second-order rate constant for the reaction of KOEt + 18C6 (the slope of a plot of k_{obs} vs $[\mathrm{MOEt}]_0$), is also found in Table II.

The data in Table II show that the rate constants for ethoxide ion derived from the rate data for LiOEt, NaOEt, KOEt, and CsOEt are roughly equal to the rate constant for ethoxide ion calculated from the slope of the plot of k_{obs} vs $[\mathrm{MOEt}]_0$ for KOEt + 18C6. Therefore, the reactivity of KOEt + 18C6 is identical to that of free ethoxide ion. The ion pairing treatment also confirms that $\mathrm{Li^+}$ and $\mathrm{Na^+}$ inhibit the reaction ($k_{\mathrm{MOEt}} < k_{\mathrm{EtO^-}}$), while $\mathrm{K^+}$ has little effect and $\mathrm{Cs^+}$ may be weakly catalytic. It is interesting that $[\mathrm{K} \subset 2.2.2]^+$ should have such a pronounced effect on the reaction rate, while uncomplexed potassium ion apparently has little or no effect.

The unequal reactivity of KOEt + 2.2.2 and KOEt + 18C6 in the present study is notable because it implies participation of either the complexing agent(s) or the potassium complex(es) in the reaction. In order to distinguish these two possibilities, the effects of successive additions of 2.2.2 on the reaction of KOEt were investigated (Figure 2, Table III). It is seen that the

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(2) Barthel, J.; Justice, J.-C.; Wachter, R. *Z. Phys. Chem. Neue Folge* **1973**, *84*, 100.

Table IV. Effect of Adding 2.2.2 Cryptand and of Adding 18-Crown-6 Ether to the Reaction of **1** with KOEt in EtOH at 25 °C[a]

[2.2.2]/ $[KOEt]_0$	$k_{obs}/[KOEt]_0$ (M^{-1} s^{-1})	[18C6]/ $[KOEt]_0$	$k_{obs}/[KOEt]_0$ (M^{-1} s^{-1})
0.272	1.35	0.000	1.19
0.543	1.74	0.545	1.75
0.815	2.09	0.908	1.97
1.09	2.33	1.09	2.01
1.36	2.39	1.36	2.07
1.63	2.22	2.27	1.95
1.90	2.33	3.18	1.94
2.17	2.44		

[a] $[KOEt]_0 = 5.4 \times 10^{-2}$ M.

Table V. Effect of Adding 2.1.1 Cryptand to the Reaction of **1** with LiOEt in EtOH at 25 °C[a]

[2.1.1]/ $[LiOEt]_0$	$k_{obs}/$ $[LiOEt]_0$ (M^{-1} s^{-1})	[2.1.1]/ $[LiOEt]_0$	$k_{obs}/$ $[LiOEt]_0$ (M^{-1} s^{-1})	[2.1.1]/ $[LiOEt]_0$	$k_{obs}/$ $[LiOEt]_0$ (M^{-1} s^{-1})
0.000	0.647	1.01	1.90	1.69	1.79
0.280	0.900	1.21	1.91	2.02	2.12
0.610	1.30	1.33	1.89	2.42	1.92
0.810	1.52	1.41	2.00	3.03	1.81

[a] $[LiOEt]_0 = 2.9 \times 10^{-2}$ M.

observed rate constant increases until 1 equiv of cryptand has been added, and further additions of cryptand have no effect on the rate (the value of $k_{obs}/[MOEt]_0$ levels off to 1.24 ± 0.02 M^{-1} s^{-1} (95% confidence interval)). This result implicates the potassium cryptate of 2.2.2 as the catalytic species since the rate increases when 2.2.2 is added only when free K^+ is available to form additional cryptate. Once all of the potassium is in the form of cryptate, further addition of cryptand has no effect on the rate. In addition, this result allows the conclusion that cryptand alone does not affect the rate of reaction since in the plateau region cryptand is added but the rate remains unchanged.

Given that the 2.2.2 cryptate of K^+ appears to be catalytic, it was of interest to investigate other complexes. In Figure 3a (Table IV) are compared the effects of successive additions of 2.2.2 and 18-crown-6 on the reaction of KOEt with **1**. It is significant that the plateau reactivity of KOEt + 2.2.2 is greater than that of KOEt + 18C6. A similar comparison of KOEt + 18C6 with LiOEt + 2.1.1 is shown in Figure 3b (Tables IV and V). In this case, the limiting reactivities of KOEt + 18C6 and LiOEt + 2.1.1 are identical. We infer that the 18-crown-6 coronate of K^+ and the 2.1.1 cryptate of Li^+ do not participate in the rate process and that the plateau region corresponds to the reaction of free ethoxide ion in both cases.

A previous study showed that ester **1** reacts with alkali-metal ethoxides in ethanol predominantly by an E1cb-type elimination mechanism via a sulfene[3] intermediate (Scheme I).[1g] Evidence was also obtained for nucleophilic substitution at sulfonyl sulfur as a minor pathway. Similarly, *m*-nitrophenyl methanesulfonate was found to react by parallel E1cb-type elimination and nucleophilic substitution mechanisms, while the available evidence indicated that the *p*-trifluoromethyl-substituted ester (**2**) reacts solely by nucleophilic substitution at sulfur. Therefore, **1** falls in a region of mechanistic crossover between E1cb-type elimination and substitution at sulfonyl sulfur, in which elimination is favored by increased nucleofugality of the substituted phenolate moiety.[4]

Kinetic results for *p*-nitrophenyl methanesulfonate differ from the results for *p*-trifluoromethylphenyl methanesulfonate (**2**) in several important ways. In the reaction of **2** and in reactions of aryl benzenesulfonates with ethoxides, all of which proceed by nucleophilic substitution at sulfur, it is found that KOEt + 2.2.2, KOEt + 18C6, and LiOEt + 2.1.1 give identical kinetic behavior, and plots of k_{obs} vs $[MOEt]_0$ show only slight upward curvature.[1d,g] Also, the order of reactivities of the various ethoxide species changes on going from **1** (KOEt + 2.2.2 > CsOEt ≈ KOEt + 18C6 ≈ KOEt > NaOEt > LiOEt) to **2** (KOEt > CsOEt > NaOEt > EtO^- > LiOEt).[1d] These anomalous results may be linked to a change in mechanism from substitution (**2**) to elimination–addition (**1**).

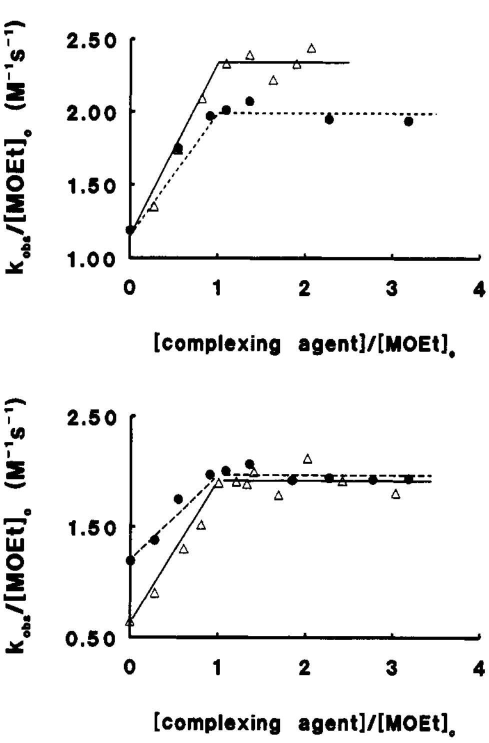

Figure 3. (a) Effect of added 2.2.2 cryptand (△) and 18-crown-6 (●) on the reaction of **1** with KOEt in ethanol at 25 °C ($[KOEt]_0 = 5.4 \times 10^{-2}$ M). (b) Effect of added 18-crown-6 on the reaction of **1** with KOEt (●) and effect of added 2.1.1 cryptand on the reaction of **1** with LiOEt (△) in ethanol at 25 °C ($[KOEt]_0 = 5.4 \times 10^{-2}$ M, $[LiOEt]_0 = 2.9 \times 10^{-2}$ M).

Discussion

In our previous studies of nucleophilic substitution reactions of phosphinate and sulfonate esters, it was found that metal ions were catalysts and/or inhibitors, but complexed metal ions had no effect on the rate.[1] Therefore, it can be inferred that the unusual effects observed for KOEt + 2.2.2 in the present case arise from the elimination–addition part of the reaction and not from the minor competing nucleophilic substitution reaction.

Scheme I

$$CH_3SO_2OAr + EtO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^-CH_2SO_2OAr + EtOH$$

$${}^-CH_2SO_2OAr \xrightarrow{k_2} CH_2{=}SO_2 + ArO^-$$

$$CH_2{=}SO_2 + EtOH \xrightarrow{\text{fast}} CH_3SO_2OEt$$

The effects of the potassium cryptate on the reaction rate could conceivably arise from interactions with the following species: ethoxide ion, sulfonate ester, the transition state for deprotonation (**3**), the carbanion intermediate (**4**), and the transition state for elimination (**5**).

It has been found that quinuclidine, a base which has a structure analogous to that of 2.2.2, retards the hydrolysis of aryl arenesulfonate esters.[5] The protonated form of this bicyclic base forms complexes with arenesulfonate esters, and this partially protects the esters from hydrolysis. However, quinuclidine does not affect the hydrolysis of *p*-nitrophenyl methanesulfonate.[5] Quinuclidine in its neutral form has also been found to form adducts with sulfenes.[6]

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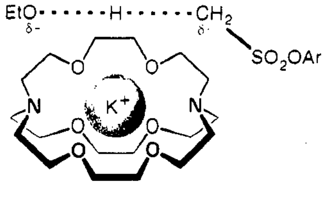
(3) King, J. F. *Acc. Chem. Res.* **1975**, *8*, 10.

(4) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.

(5) Suh, J.; Suh, M. K.; Cho, S. H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 685.



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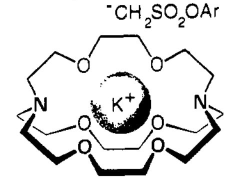

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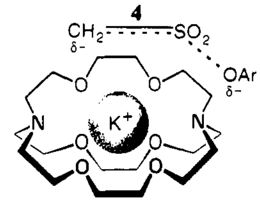

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From our previous studies, there is no evidence for significant interactions of coronates or cryptates with ethoxide ion or with sulfonate esters: plots of k_{obs} vs $[MOEt]_0$ for KOEt + 18C6, KOEt + 2.2.2, and LiOEt + 2.1.1 were superimposable, and the second-order rate constant derived from the slope of this plot was identical to the second-order rate constant for free ethoxide ion obtained from ion pairing treatment of the data for alkali-metal ethoxides.[1d,g]

In the present case, it may be shown that neither deprotonation/reprotonation (k_1/k_{-1}) nor elimination (k_2) is clearly rate limiting. The relative rates of the two steps are compared by means of experiments in deuteriated ethanol solvent (EtOD). Deprotonation/reprotonation results in uptake of deuterium into the methyl group of the unreacted ester, and the extent of uptake is compared to the extent of overall reaction in quenched reaction mixtures. The extent of deuteriation is assessed by ^{1}H NMR integration of extracted ester, while the extent of reaction is measured by the absorbance of released *p*-nitrophenoxide ion. Table VI shows the data comparing the extent of deuteriation with the extent of reaction for the reaction of various ethoxide species with **1**. It is clear that the extents of deuteriation and reaction are similar in all cases, so the rates of deprotonation/reprotonation must also be similar. Furthermore, the ratio of the extent of deuteriation to the extent of reaction decreases along the series: KOEt > KOEt + 18C6 > KOEt + 2.2.2, indicating that the mechanism becomes more E1cb$_{irrev}$-like along this series. Thus, the reaction of KOEt + 2.2.2 is more E1cb$_{irrev}$-like than the reaction of free ethoxide, i.e., elimination (k_2) is accelerated relative to deprotonation/reprotonation (k_1/k_{-1}).

A reasonable explanation of the observed results is that the cryptate stabilizes the transition states for deprotonation (**3**) and elimination (**5**), thereby catalyzing the reaction. From the results presented above, the cryptate accelerates the overall reaction relative to the rate of deprotonation/reprotonation so the predominant effect must be stabilization of **5** and catalysis of leaving group expulsion (k_2).

The question of how the cryptated potassium ion interacts with the intermediate and transition state must now be addressed. According to Lehn, in alkali-metal ion-crown ether complexes, the complexed cation is accessible from above and below the plane of the crown ether.[7] Similarly, the complexed cation in a cryptate may interact with an anion through the face of the cryptand, especially when the face is an 18-membered ring, as in the case of 2.2.2. Consistent with this postulate, studies of the conductivity of 2.2.2 complexes of alkali-metal halides in methanol have yielded evidence for the association of halide ions with the complexed cations, with equilibrium constants for association ranging from 20 to 68 M^{-1}.[8] Recent molecular dynamics simulations of the hydration of 2.2.2 cryptates, which did not consider cation–anion interactions, revealed nevertheless that cryptated metal ions are not totally shielded and that cation-dependent cation-solvent interactions exist.[9] Calculations on the potassium cryptate of 2.2.2 showed that there are water molecules directly coordinated to the metal ion and a coordination number of ~1.3 was calculated for K$^+$. Such "through the window" interactions may be the origin of the catalytic activity of the potassium cryptate in the present system.

Table VI. Comparison of the Extent of Deuterium Uptake into Unreacted Ester **1** with the Extent of Reaction for Quenched Reactions in EtOD

base	% deuteriation	% reaction
KOEt	92	63
KOEt + 18C6	85	70
KOEt + 2.2.2	36	54

Catalysis by a cryptated potassium ion has been previously observed in a study of the anionic polymerization of α-methyl-α-propyl-β-propiolactone in THF at −20 °C.[10] However, in this case the cryptate catalyzed the nucleophilic attack of a carboxylate on a lactone.

Comparing the lithium cryptate, potassium coronate, and free metal ions, $[Li^+ \subset 2.1.1]$ may be unable to interact with other species (intermediate or transition states) because the cryptand does not have an 18-membered ring window allowing access to the exterior. In contrast, $[K^+ \subset 18C6]$, K$^+$, and Li$^+$ may not be large enough to stabilize large anionic species or may be too accessible and may be solvated by ethanol in preference to interactions with other species, preventing interactions with the intermediate or transition states.

Conclusions

In conclusion, while cryptates are usually considered to be kinetically-inert species, in the reaction of alkali-metal ethoxides with *p*-nitrophenyl methanesulfonate (**1**), the 2.2.2 cryptate of potassium ion ($[K^+ \subset 2.2.2]$) acts as a catalyst, apparently by lowering the free energy for the elimination step in an elimination–addition (E1cb) type mechanism. Further studies are underway to define the scope of these effects and the nature of the interactions of complexed cations with ground-state and transition-state species.

Experimental Section

Materials. The general procedure of Crossland and Servis was followed for the synthesis of ester **1**.[11] The crude product was repeatedly recrystallized from ethanol to a constant melting point (87–88 °C, lit.: 82–83,[12a] 88–89,[12b] 93–93.5,[12c] 94 °C[12d]). The purified ester gave excellent ^{1}H, ^{13}C NMR and IR spectra as well as elemental analysis.

Anhydrous ethanol, 18-crown-6, cryptands, and alkali-metal ethoxides were prepared and/or purified as described previously.[1d,f–h] Deuteriated ethanol (Aldrich 99.5^+ atom% D) was dried by distillation from magnesium and iodine.

Kinetic Methods. Reaction rates were measured by following UV-visible absorbance changes due to the release of aryl oxide ion using a Perkin-Elmer Lambda 5 spectrophotometer. All reactions were carried out under pseudo-first-order conditions with the base concentration at least 10 times greater than the substrate concentration and usually more

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than 20 times greater. The solutions were equilibrated to 25.0 °C in the thermostatted cell block of the spectrophotometer and maintained at 25.0 ± 0.1 °C during reactions.

Rate constants were calculated from at least 30 absorbance readings spanning 3 half-lives. 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. It is estimated that the error in any particular measured rate constant is not greater than ca. ±3%.

Deuterium Uptake Experiments. The extent of deuterium uptake and the extent of reaction were measured as described previously.[1g] The following is a representative procedure used to evaluate the extent of deuterium exchange at the methyl position and simultaneously the extent of reaction of a methanesulfonate ester.

p-Nitrophenyl methanesulfonate (**1**) (0.0560 g, 0.260 mmol) was weighed into a flask equipped with a nitrogen inlet and magnetic stirrer and dissolved in magnesium-dried deuteriated ethanol (EtOD, 15.0 mL) under a stream of nitrogen. A stock solution of base was prepared by mixing potassium ethoxide (2.00 mL of 1.68 M KOEt in EtOD) and crown ether (6.00 mL of 0.980 M 18-crown-6 in EtOD) solutions in a sealed vial. A portion (6.00 mL, 2.52 mmol KOEt, 4.41 mmol 18-crown-6) of the resulting solution was added to the rapidly stirred ester solution. After stirring briefly under nitrogen, the reaction was stopped by addition of saturated aqueous $NaHCO_3$ solution (10 mL). Precipitated salts were filtered off, the filtrate was extracted with diethyl ether (6 × 20 mL), and the aqueous solution was saved. The ether extracts were concentrated on a rotary evaporator to 30 mL, then extracted with 5% aqueous Na_2CO_3 solution (6 × 30 mL) and saturated aqueous KCl solution (4 × 30 mL), then dried (anhydrous Na_2SO_4), filtered, and concentrated. (The aqueous carbonate extracts were also saved.)

The extent of deuterium incorporation into the methyl position of the unreacted ester was determined using ^1H NMR by integration of the residual methyl resonance against the aromatic resonances. The methyl signal showed small upfield shifts (ca. 0.015 ppm) and splittings due to H–D coupling ($J_{CH_2D} \approx 2.4$ Hz) which are characteristic of partial deuteriation of methyl groups.[13] Overlapping spectra of all three species having protons at the methyl position were observed.

The combined aqueous extracts were adjusted to pH > 10 with aqueous NaOH solution and made up to the mark in a 250-mL volumetric flask, and the absorbance of the resulting solution at 400 nm was measured. This value was used to calculate the extent of reaction (amount of *p*-nitrophenoxide released) using the measured extinction coefficient of *p*-nitrophenoxide under identical conditions.

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Solvation Changes Accompanying Proton Transfer from a Carbon Acid to Alkoxide Bases As Revealed by Kinetic Isotope Effects

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Abstract: Primary hydrogen isotope effects are reported for the elimination of 4-nitrophenol from 4-(4-nitrophenoxy)-2-butanone in methanolic methoxide at 20 °C and in aqueous hydroxide at 25 °C. The isotope effects do not change significantly when the isotopic composition of the solvents is changed: $(k_H/k_D)_{MeOH} = 6.48 \pm 0.22$, $(k_H/k_D)_{MeOD} = 6.40 \pm 0.24$; and $(k_H/k_D)_{HOH}$ = 7.54 [illegible] 0.11, $(k_H/k_D)_{DOD} = 7.48 \pm 0.21$. Kinetic solvent isotope effects (using the undeuterated substrate) are $k_{MeOD}/k_{MeOH} = 2.195 \pm 0.064$ and $k_{DOD}/k_{HOH} = 1.526 \pm 0.029$. The experimental results are compared with model vibrational analysis calculations and about 60 literature examples of related solvent isotope effects on proton-transfer rates. The observations of primary hydrogen isotope effects that are unchanged upon isotopic substitution in protonic sites of the solvent were used to conclude that solvent reorganization is not coupled to proton transfer in the reaction coordinate.

The role of solvent reorganization during the course of proton-transfer reactions has been examined from a variety of perspectives.[1] We have investigated the nature of solvation changes that occur in the course of a specific class of proton-transfer reactions, from carbon acid to alkoxide base, in protic solvents. Our perspective of the problem concerns the solvation changes that occur at the alkoxide base as it becomes a solvent molecule during the course of the reaction. We are interested in learning (1) the extent of solvent reorganization at the rate-limiting step for the proton-transfer process and (2) the degree to which the motion of solvent reorganization is coupled to the proton-transfer event.

Extent of solvent reorganization refers to the progress of solvation changes that has occurred between the reactant state and the transition state for the reaction. A convenient measure of the extent of solvent reorganization can be derived from the kinetic solvent isotope effect and an appropriate equilibrium solvent isotope effect.[2] If the equilibrium and kinetic solvent isotope

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