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"New" Catalysts for the Ester-Interchange Reaction: The Role of Alkali-Metal Alkoxide Clusters in Achieving Unprecedented Reaction Rates

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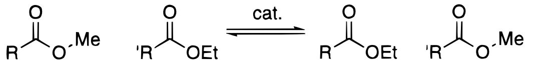
Abstract: The catalytic effect of alkali-metal *tert*-butoxide clusters on the rate of ester interchange for several pairs of esters has been determined in nonpolar and weakly polar solvents. Reactivities increase in the order ($Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$) with the fastest rates reaching 10^7 catalytic turnovers per hour (TO/h). Ester interchange rates were sensitive to the size of both the transferring OR groups and the ester substituent. Phenyl esters did not exchange with aliphatic esters due to nonstatistical breakdown patterns in the tetrahedral intermediate. A first-order equilibration analysis on the interchange between *tert*-butyl acetate (*t*BuAc) and methyl benzoate (MeBz) (5 mol % NaO*t*Bu) indicated enhanced reaction rates as the reaction proceeded. Isolation and quenching (DCl/D_2O) of precipitated catalyst points to a mechanism whereby sequential methoxy incorporation into the catalyst cluster increases activity, but eventually precipitates out of solution as a 3:1 OMe:O*t*Bu cluster. The rate law was determined to be $k_{obs}[MeBz]^1[tBuAc]^0[NaOtBu]^x$, where $x = 1.2(1)$, 1.4(1), and 0.85(1) in hexane, ether, and THF, respectively, under conditions where tetrameric catalyst aggregates are expected. Reaction rates were generally observed to be higher in nonpolar solvents (hexane > toluene, ether > THF). Eyring analysis over a 40 °C range yielded $\Delta H^\ddagger = 10.0(1)$ kcal mol^{-1} and $\Delta S^\ddagger = -32(3)$ eu. A Hammett (σ) plot generated with para-substituted methyl benzoates gave $\rho = +2.35$ ($R = 0.996$). These results are interpreted in terms of a catalytic cycle composed of two coupled transesterification reactions with a turnover-limiting addition of a *tert*-butoxy-containing cluster (tetramer) to methyl benzoate. Catalyst relative reactivities ($Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$) are interpreted in terms of competitive electrostatic interactions between the alkali-metal and ground-state and transition-state anions. This analysis predicts the observed linear dependence between $\log(k_{obs})$ and $1/r_{ionic}$.

Introduction

The transesterification reaction is one of the most important ways of manipulating the ester functionality as exemplified by the many protocols that have been developed for carrying out this reaction. These include basic,[1] acidic,[1a] and metal-catalyzed variants,[2] with most methods being protic in nature.[1a] A process capable of catalyzing the transesterification reaction with high rates and under mild conditions is broadly applicable to fine chemical and polymer synthesis.



(1)

We recently reported that alkali-metal alkoxide clusters serve as highly active catalysts (up to 10^6 turnovers (TO)/ h) for the ester interchange reaction (eq 1).[3a,4] Reactivities were high enough to realize a convenient method for the synthesis of *tert*-butyl esters.[3b] At that time we speculated that the mechanism involved a coupled transesterification mediated by a soluble alkali-metal alkoxide (Scheme 1). Preliminary experiments suggested that the catalyst was aggregated and that high activity was intimately associated with the presence of clusters.

While the correlation between solution structure, aggregation state, and reactivity has been extensively studied for lithium alkyls,[5] enolates,[6] phenoxides,[7] and amides,[8] much less is known

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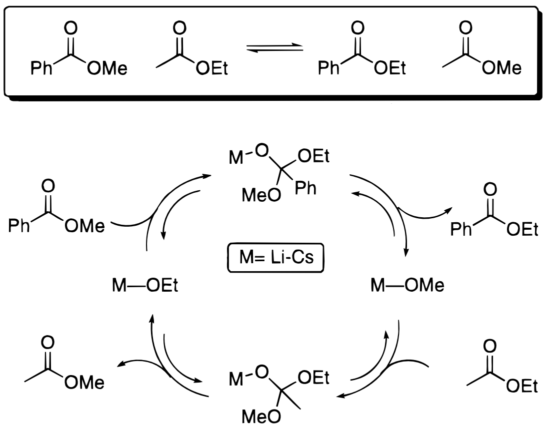
(5) (a) Power, P. P. *Acc. Chem. Res.* **1988**, *21*, 147−153. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810−1815. (c) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805−1810. (d) Bates, R. B.; Ogle, C. A. *Carbanion Chemistry*; Springer-Verlag: New York, 1983.

(6) (a) Jackman, L. M.; Bortiatynski, J. *Adv. Carbanion Chem.* **1992**, *1*, 45−87. (b) Seebach, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654. (c) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737−2769.

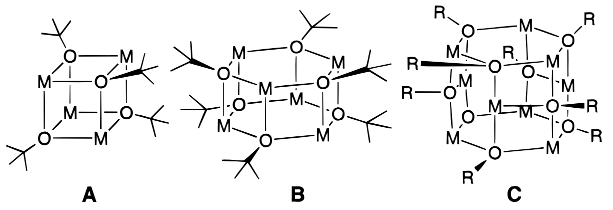
(7) See ref 6a and the following: (a) Jackman, L. M.; Cizmeciyan, D.; Williard, P. G.; Nichols, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 6262−6267. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829−3935. (c) Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177−4184.

Scheme 1

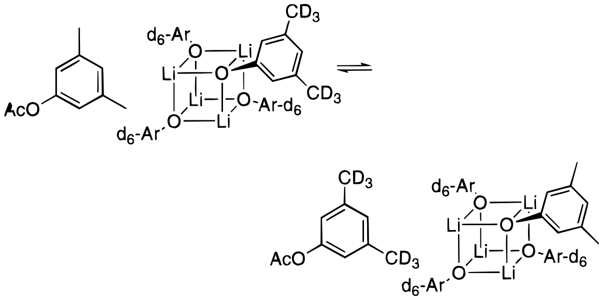


about this correlation in heavier alkali-metal alkoxides.[9,10] Since heavy alkali-metal alkoxides are superior ester-interchange catalysts ($Cs^+ > Rb^+ > K^+ > Na^+$), we have initiated experiments to determine the fundamental relationship between structure and reactivity in these compounds. These data will ultimately lead to more reactive, selective, and stable catalysts.

The solid-state, solution, and gas-phase structures of several soluble alkali-metal alkoxides have been reported. In the solid-state, lithium neophyloxide ($LiOCMe_2Ph$) adopts a hexameric structure of type **B**, which persists in nonpolar solvents (up to 80 °C)[11] but is broken down to a tetra-solvated tetramer in donor solvents such as THF.[12] Mass spectrometry experiments also establish that hexamers are the dominant form in the gas phase.[13] Sodium alkoxides are also highly aggregated as the solid-state structure of NaO*t*Bu contains a one-to-one ratio of a **B**-type hexamer and a **C**-type nonomer.[14] Cryoscopy in both benzene and cyclohexane report an average solution aggregation number of 8.3 over a wide concentration range (0.06−0.3 M), consistent with a mixture of hexamers and nonomers.[11] FT-IR experiments confirmed these observations and noted that, in strong donor solvents such as THF, high-symmetry tetrameric clusters dominate, **A**.[15] The heavier alkali-metal alkoxides KO*t*Bu, RbO*t*Bu, and CsO*t*Bu are tetramers in the solid state[16] and at least for potassium are known to be tetramers in toluene, ether, and THF solutions.[15] In general, the lighter, smaller, alkali-metal *tert*-alkoxides (Li and Na) form higher aggregates (6−9) that in the presence of good donor solvents reorganize to tetramers, while heavier alkali metals (K, Rb, and Cs) prefer tetrameric structures in solution (K) and in the solid state (**A**).[16]



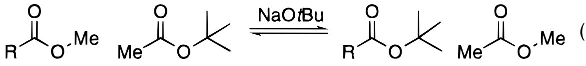
Details relating aggregate structure to reactivity have been provided by Jackman, who has documented conditions where lithium 3,5-dimethylphenolate exists in solution as dimers and tetramers (pyridine), tetramers (THF), and tetramers and hexamers (dioxolane).[17] Careful kinetic studies for the degenerate transesterification reaction in eq 2 revealed that the clusters were the primary reactants and that each aggregate had a unique reactivity (tetramer shown). For example, in pyridine, the dimer is 13 times more reactive than the tetramer ($K_{eq} = 330\ M^{-1}$ at 35 °C), and in dioxolane, the hexamer is 5.5 times more reactive than the tetramer ($K_{eq} = 0.57\ M^{-1/3}$ at 35 °C).


(2)

Despite the high-level understanding of the Jackman system, analogous data on the reactivity of heavy alkali-metal alkoxides and aryl oxides with aliphatic and aromatic esters is not available. This paper reports our studies addressing the underlying mechanistic features of the alkali-metal alkoxide-cluster-catalyzed ester interchange reaction. The primary focus is on the kinetics of the equilibration of a mixture of esters as a function of the nature of the metal cation, solvent, electronic and steric perturbations, concentration, and temperature. Future submissions will address the structural aspects of catalyst intermediates.

Results

Effect of Ester Structure on Reactivity. Using *tert*-butyl acetate (*t*BuAc) as the test substrate the rate of *tert*-butoxide incorporation into various methyl esters was determined using 5 mol % NaO*t*Bu in THF (eq 3). The relative rates were found to generally parallel the steric bulk of the R group as expressed by their respective *A* values (Table 1).[18] The exception to this trend was methyl benzoate (MeBz), the enhanced rate likely reflecting an electronic effect.


(3)

The effect on rate of the transferring alkoxide group was also examined (eq 4, Table 2). In the case of MeBz and ethyl

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[8] (a) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573−5582 and references therein. (b) Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* **1995**, *60*, 7660−7669. (c) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227−234. (d) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

[9] Msayib, K. J.; Watt, C. I. F. *Chem. Soc. Rev.* **1992**, 237−243.

[10] For a series of MOPh (M = Li, Na, K, Rb, Cs) high-resolution powder structures, see: Dinnebier, R. E.; Pink, M. Sieler, J.; Stephens, P. W. *Inorg. Chem.* **1997**, *36*, 3398−3401.

[11] For a compilation of aggregation states for lithium, sodium, and potassium *tert*-butoxides in various solvents, see: Halaska, W.; Lochmann, L.; Lim, D. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3245−3253.

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[17] Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 3451−3458.

[18] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; p 135.

Table 1. First-Order Rate Constants for the Equilibration of Various Methyl Esters (Eq 3)[a]

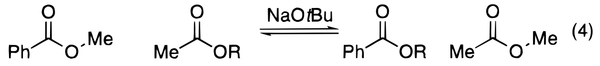
R group	A-value[b]	k_{obs} (s^{-1}(x 10^{-3}))(rel. rate)
*n*Pr	1.8	2.78(100)
Ph	2.9	1.3(47)
*i*Pr	2.1	0.17(6)
*t*Bu	>4.5	N.R.(<1)

[a] 0.8 M in each ester, 40 mM NaO*t*Bu in THF. See the Experimental Section for full details. [b] In units of kcal mol^{-1} (ref 25).

Table 2. Effect of the Transferring OR Group on the Rate of Equilibration (Eq 4)[a]

R group	k_{obs}(s^{-1})	$t_{1/2}$ (s)	N_t (h^{-1})[b]
Et	>0.2	<2	>173,000
*i*Pr	>0.2	<2	>173,000
*t*Bu	1.3 X 10^{-3}	535	270
Ph	0	-	-

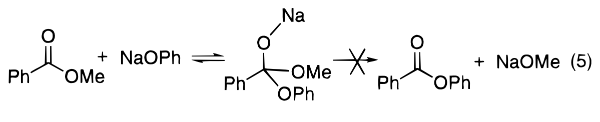
[a] 0.8 M in each ester, 40 mM NaO*t*Bu in THF. See the Experimental Section for full details. [b] Based on a tetrameric catalyst.



(4)

acetate, 5 mol % of NaO*t*Bu was found to affect the equilibration in <5 s. By assuming that six half-lives are required to reach near-equilibrium and that a minimum of 40 turnovers are necessary to progress one half-live (2 TO per productive event, tetrameric catalyst), we estimate that 240 productive TO/mol of catalyst tetramer are required to reach equilibrium. The observed reactivity for NaO*t*Bu therefore reflects a minimum reactivity of 173 000 TO/h. The isopropyl acetate was similarly at equilibrium after a 5-s quench. Not surprisingly, the rates for establishing equilibrium were sensitive to the size of the R substituent with R = Et, *i*Pr ≫ *t*Bu ≫ Ph. Although *tert*-butyl pivalate was not readily accessible using NaO*t*Bu, the more reactive KO*t*Bu catalyst (vide infra) was able to achieve a ~23% conversion to this hindered ester over 4 h. We do not yet know if this value reflects a true equilibrium, as steric effects will certainly disfavor *tert*-butyl pivalate.[19]

Worthy of note is the complete lack of reactivity using phenyl acetate. We attribute this to a nonstatistical breakdown of the tetrahedral intermediate; the pK_a's of the conjugate acids (MeOH = 29, PhOH = 18)[20] ensure that phenoxide ejection dominates, and no productive turnovers occur (eq 5). The corollary to these observations is that the pK_a of the conjugate acids of the two competing leaving groups be sufficiently close that the relative breakdown rates of the tetrahedral intermediate be competitive.



(5)

To test this hypothesis, the cross interchange of two active esters containing leaving groups of similar ability (pK_a: PhOH = 18, pentanethiol = 17)[20] was attempted with 5 mol % KO*t*Bu (eq 6). This reaction proceeds to ~30% conversion and then halts, proving, at least in principle, that pK_a matching allows suitable reacting partners to be identified a priori. No attempt was made to optimize this process.

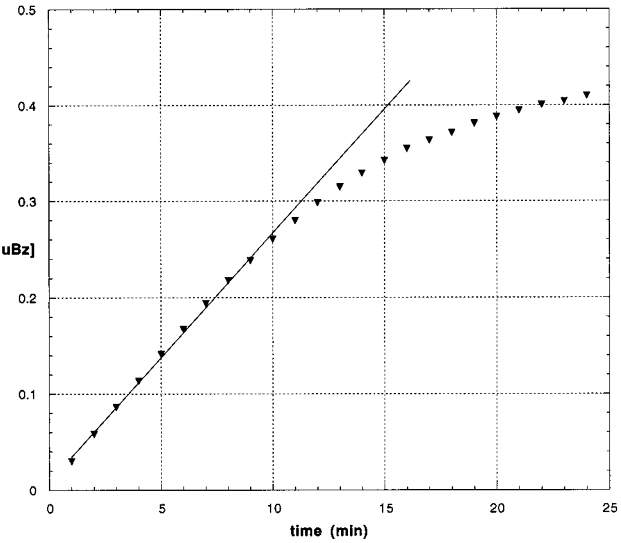
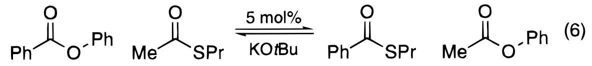
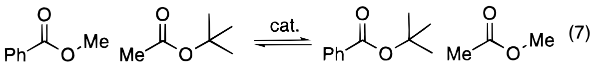


Figure 1. [*t*BuBz] vs time showing initial zero-order kinetics followed by a rapid deviation from linearity (eq 7). The half-lives for conversion to equilibrium are 8.0, 6.5, 3.8, 3.5, and 3.0 min. The line represents a linear fit to the first 10 min (~1.5 half-lives) (0.8 M in each ester, 40 mM (5 mol %) NaO*t*Bu, $[tBuBz]_{eq}$= 0.426 M).



(6)

Rate of Approach to Equilibrium of a Test Reaction. Reactions utilizing *t*BuAc and MeBz led to convenient rates that were amenable to aliquot quenching techniques coupled with GC analysis. Thus, the reaction depicted in eq 7 was chosen for an in-depth analysis. The conversion of MeBz to *t*BuBz with 5 mol % NaO*t*Bu in THF was analyzed to ~4 half-lives. A plot of the increasing concentration of *t*BuBz vs time is shown in Figure 1 and highlights the gross features of an initially zero-order reaction that rapidly deviates from linearity after ~1.5 half-lives. From the first half-life the initial rate could be measured. Alternatively, treating the data with a first-order relaxation approach (i.e., MeBz relaxing to an equilibrium mixture of MeBz and *t*BuBz) generates a plot wherein the data deviates from linearity after 1 half-life and reaches equilibrium at a rate faster than expected by extrapolating the first half-life. A simple first-order equilibration scenario is inadequate for describing the time course of the reaction, but it is useful for determining initial rate constants.[21]



(7)

The approach to equilibrium of the reaction in eq 7 is characterized by a gradual clouding of the solution, roughly coinciding with the deviations from zero-order kinetics (Figure 1). Isolation of the catalyst which precipitates from eq 7 (using 10 mol % NaO*t*Bu in hexane) followed by quenching with DCl/D_2O establishes that the ratio of methoxide to *tert*-butoxide in the precipitate is 3:1 as judged by ^{1}H NMR. Since $(NaOtBu)_x$ (x = 6, 9) clusters are soluble in hexane (the aggregation state is unknown in 1.6 M ester) and NaOMe is an insoluble sheetlike material,[22] it follows that clusters containing mixed ratios of −O*t*Bu and −OMe groups must exist in solution. It is reasonable to suggest that the observed 3:1 OMe:O*t*Bu ratio

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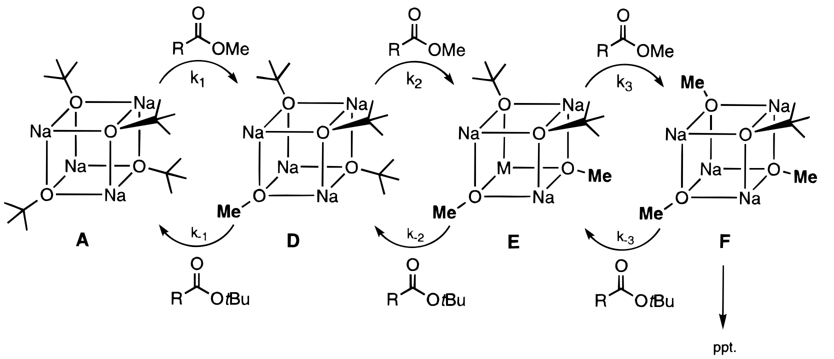
(19) In cases involving primary and secondary alkoxy substituents, equilibrium is usually represented by a ~1:1:1:1 ratio of esters. Conversion to a single product has been achieved by selectively removing a volatile product ester, see ref 3b.

(20) Bordwell F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

Scheme 2



represents a tetrameric cluster such as **F** (Scheme 2) that is no longer soluble in the reaction media. Conversely, ratios of 1:3 (**D**) or 2:2 (**E**) must represent viable alkoxide cluster catalysts that are soluble in the mixture of ester and solvent. The observed rate accelerations suggest that as methyl groups are substituted for *tert*-butyl groups via the ester interchange the decreased steric hindrance in the cluster results in increased catalytic activity. Precedence for heterosubstituted alkoxide clusters is found in the work of Jackman, where LiI and $LiClO_4$ were found to incorporate into an aryl oxide tetramer to form $Li_4(OAr)_3(X)$, where X = I^-, ClO_4^-, and $Li_4(OAr)_2(ClO_4)_2$.[23,24]

Effect of Alkali Metal Cation on Reaction Rates. The ability of various alkali-metal *tert*-butoxides to affect the equilibration of the reaction in eq 7 was determined and the results summarized in Table 3. A dramatic trend is observed where the larger/heavier alkali metals give rise to faster rates (Figure 2),[25] the highest rates being near the limit of reproducible kinetics.

Assuming that 40 productive turnovers of a tetrameric catalyst are required to complete a single half-life (vide supra), turnover frequencies have been calculated for each metal. That N_t for *n*-alkyl ester interchange is ~100 times faster than *tert*-butyl esters (Table 2) suggests that initial N_t's for *n*-alkyl esters using the fastest Cs catalysts should approach 1×10^7 h^{-1}. In contrast, the lanthanide alkoxide-based ester interchange catalyst previously reported by Kiji has a maximum reported N_t of ~20 h^{-1} (10 °C) for an analogous process.[4]

Effect of Solvent on the Rate of Equilibration. Again using eq 7 as a test reaction, the rate of equilibration of MeBz and *t*BuBz was determined in various solvents (Table 4). Although CH_2Cl_2 and DME are exceptional the general trend is that poor donor solvents give faster rates (hexane > toluene ≥ ether > THF). This effect has previously been observed by Jackman et al.[17] for the degenerate transesterification reaction in eq 2 under conditions where the tetramer is the dominant species. This is most reasonably interpreted as a result of competitive inhibition by donor solvents for the preequilibrium binding site on the cluster (vide infra).[26] Consistent with this proposal are the relative rates of THF, 2-Me-THF, and 2,5-Me_2-THF, which have similar dielectric constants but progressively poorer donor

Table 3. Effect of Alkali-Metal Cation on the Approach to Equilibrium of Eq 7[a]

Metal	Ionic Radii (Å)[b]	k_{obs}(s^{-1} x 10^{-3})	$t_{1/2}$(s)	N_t (h^{-1})[f]
Li^+	0.76	0.3 [c,e]	>2100 [c,e]	<17
Na^+	1.02	1.3 ± 0.3	540 ± 80	70
K^+	1.38	32.0 [e]	20 [e]	180
Rb^+	1.52	≥90 [d,e]	~6 [d,e]	6000
Cs^+	1.67	≥140 [d,e]	~5 [d,e]	7200

[a] Reaction conditions: 0.8 M in each ester, 40 mM in MO*t*Bu (5 mol %) in THF under argon atmosphere. [b] See footnote 25. [c] Ill-behaved kinetics—reaction never reached equilibrium. [d] Lower limit—reaction rates were too fast to accurately measure (equilibrium in ~15–30 s). [e] Single measurement. [f] Turnover frequency through first half-life.

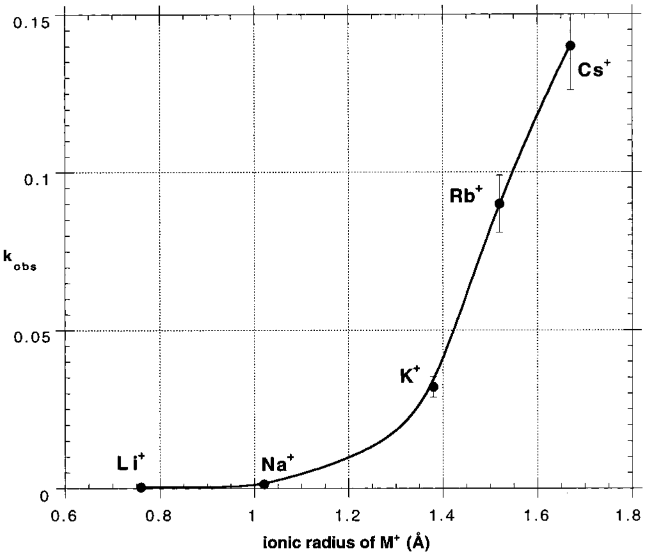


Figure 2. Observed initial rates (one half-life) for eq 7 vs six-coordinate ionic radius of the metal counterion[25] (0.8 M in each ester, 40 mM in MO*t*Bu, THF). The line represents a smooth curve through the data points.

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(21) Such a treatment is in principle justified on the basis of the observation that the reaction is first order in MeBz and zero order in *t*BuAc. This is consistent with Scheme 1, wherein the rate-determining step is *tert*-butoxide addition to MeBz and is followed by a fast second step. Since the concentrations of the two products are necessarily equal, the reverse process must also have a rate-determining step that is first order in one of the esters (we do not yet know which).

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(23) (a) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101–4109. (b) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202–1210.

(24) For studies relating to Li-enolate/LiCl(Br) aggregate structure and reactivities, see also: (a) Abu-Hasanayn F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136–8137. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829–8830. (c) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805–2806. (d) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494–4499. (e) Jackman, L. M.; Haddon, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 3687–3692. For an example of a lithium enolate/lithium amide aggregate structure, see: (f) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602–8604.

(25) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751–767.

Table 4. Effect of Solvent on the Rate of Approach to Equilibrium for Eq 7[a]

Solvent	k_{obs}(s^{-1}(x 10^{-3}))	$t_{1/2}$(s)
Hexanes	7.0 ± 0.9	100
DME	4.8[b]	145
Toluene	3.6[b]	195
*t*BuOMe	3.4[b]	205
Ether	3.4 ± 0.2	205
CH_2Cl_2	1.6[b]	435
THF	1.3 ± 0.3	535
2-Me-THF	1.3[b]	535
2,5-Me_2-THF	2.3[b]	300

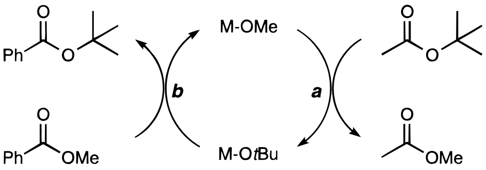
[a] Reaction conditions: 0.8 M in each ester, 40 mM NaO*t*Bu. Reactions were monitored to 25% conversion by GC and analyzed using standard approach to equilibrium kinetic expressions. [b] Single measurement.

Table 5. Effect of Ester Concentration on the Initial Rate of Reaction for Eq 7[a]

[*t*BuAc] (M)	initial rate (M/s (x 10^{-4}))	[MeBz] (M)	initial rate (M/s (x 10^{-4}))
0.40	4.2	0.40	1.9
0.60	3.8	0.60	3.1
0.79	3.8	0.79	3.8
0.99	3.9	0.99	4.9
1.19	3.8	1.19	6.5

[a] Reaction conditions: 0.8 M in second ester, total volume = 6.3 mL, [NaO*t*Bu] = 40 mM, in THF at room temperature.

Scheme 3



properties.[27] The steric encumbrances of α-methyl substituents on the solvent result in slight rate increases but are still slower than reactions carried out in ether, toluene, or hexane. The overall rate effect spans a factor of ~5.5. This relatively small difference is likely due to the dielectric/donor buffering of the solvent by the 1.6 M concentration of esters.[28]

Rate Law Determination. The initial rate of *t*BuBz formation ($v_{initial}$, M s^{-1}) was determined by independently varying the concentrations of *t*BuAc and MeBz over a 10-fold range. The concentration of the catalyst (40 mM) and nonvarying ester (0.80 M) were kept constant by varying the volume of THF added to the reaction solutions. A plot of log($v_{initial}$) vs log[*t*BuAc] and log($v_{initial}$) vs log[MeBz] yielded slopes of −0.1(1) and 1.1(1), indicating zero- and first-order dependencies on *t*BuAc and MeBz, respectively (Table 5). A simplified mechanistic scenario for the forward direction of this reaction is shown in Scheme 3. A priori, it was not clear whether addition of a bulky *tert*-butoxide to MeBz or the addition of methoxide to the bulky *t*BuAc would be rate-limiting. The reaction orders in esters, however, clearly implicate the involvement of MeBz in the turnover-limiting step (Scheme 3, **b**).

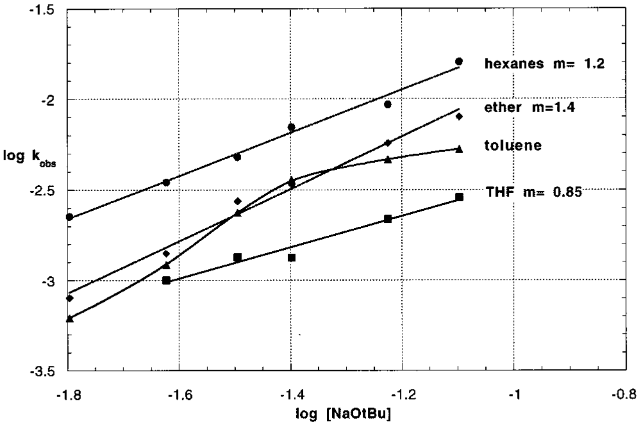


Figure 3. Log of observed first-order relaxation constants for eq 7 versus log [NaO*t*Bu]. The line through the toluene data is a smooth curve.

Table 6. Initial Rates of Reaction of Eq 7 as a Function of Temperature[a]

Temperature (K)	rate (M/s (x 10^{-4}))
283	1.55
288	1.94
298	3.83
303	5.49
308	7.58
313	9.46

[a] Reaction conditions: 0.8 M in each ester, 40 mM in NaO*t*Bu, in THF.

The rate of equilibration of the process in eq 7 was also determined as a function of catalyst concentration in various solvents. In THF a fractional order of 0.85(2) was obtained from the log k_{obs} vs log [NaO*t*Bu] plot (Figure 3). In hexane and ether, fractional orders in NaO*t*Bu are also obtained but are greater than unity (1.2(1) and 1.4(1), respectively). In toluene a nonlinear relationship was observed.

The rate law for the reaction in eq 7 can thus be expressed as

$$v = k_{obs}[t\text{BuAc}]^0[\text{MeBz}]^1[\text{NaO}t\text{Bu}]^x$$

$$\begin{array}{ll} x = 0.85(2) & \text{(THF)} \\ = 1.2(1) & \text{(hexane)} \\ = 1.4(1) & \text{(ether)} \\ = 0.9\text{-}1.8 & \text{(toluene)} \end{array}$$

Determination of Activation Energies. The rate of equilibration of the process in eq 7 was measured over a 40 °C temperature range (Table 6), and Eyring analysis yielded apparent activation energies for the addition of NaO*t*Bu to MeBz of $\Delta H^{\ddagger} = 10.0(1)$ kcal mol^{-1} and and $\Delta S^{\ddagger} = -32(3)$ eu. Striking is the large and negative entropy of activation for this process. Since the preceding rate-law implicated a rate-determining addition of *tert*-butoxide to MeBz, the activation parameters naturally reflect this addition process. What is less clear, however, is the number of elementary processes that combine to make up the pathway to the transition state (vide infra). Therefore, although the activation entropy reflects a good deal of order being built up in the transition state, this must be interpreted cautiously.

Linear Free Energy Relationships. Measuring the initial rate of approach to equilibrium for various para-substituted

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(26) *tert*-Butyl isobutyrate has been observed to tetrasolvate $(NaOtBu)_4$, see ref 11. Complexes wherein *tert*-butyl isobutyrate and pivalate coordinate to each lithium atom of lithium hexamethyldisilazide dimers $(LiHMDS)_2$ have been crystallographically and spectroscopically characterized, see: Williard, P. G.; Liu, Q.-Y.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 348−350.

(27) Pomarenko, S. M.; Mushtakova, S. P.; Demakhin, A. G.; Faifel, B. L.; Kal'manovich, D. G. *Russ. J. Gen. Chem.* **1995**, *65*, 160−167.

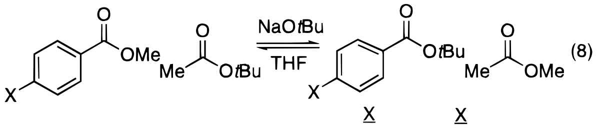
(28) For a tabulation of ΔH_{rxn} of various nonprotic solvents with BF_3, see: Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296−1304. Relevent enthalpies in this context are as follows: dichloromethane, 10(3); methyl benzoate, 59(1); ethyl acetate, 75.5(3); diethyl ether, 78.8(4); THF, 90.4(3) kcal mol^{-1}.

Table 7. Initial Rate of Reaction Eq 8 as a Function of Para Substituent[a]

substrate	σ	initial rate (M/s (x 10^{-4}))	substrate	σ	initial rate (M/s (x 10^{-4}))
1a	-0.27	0.86	**1e**	0.23	12
1b	-0.20	0.87	**1f**	0.54	59
1c	-0.17	1.8	**1g**	0.66	140
1d	0	3.8			

[a] Reaction conditions: 0.8 M in each ester, 40 mM in NaO*t*Bu, THF.

methyl benzoates (eq 8) allowed a Hammett plot to be constructed (Table 7). Consistent with the first-order dependence on MeBz in the rate law, an excellent correlation was observed with the Hammett σ-scale ($R = 0.996$) and a ρ of $+2.35$ was obtained. The magnitude and sign of ρ compares favorably with the measured ρ of $+2.3$ for the saponification of para-substituted methyl benzoates in 60% aqueous acetone[29] and a ρ of $+1.8-2.2$ for the transesterification of aryl benzoates by metal ethoxides in ethanol.[30] In both cases, hydroxide and ethoxide addition are turnover limiting. These data point to a rate-determining *tert*-butoxide addition step that is highly sensitive to the electrophilicity of the carbonyl carbon. In comparison, the acid-catalyzed hydrolysis of ethyl benzoates occurs in 60% aqueous acetone solution with a ρ of $+0.11$ indicating few parallels to this mechanistic pathway.[29]



(8)

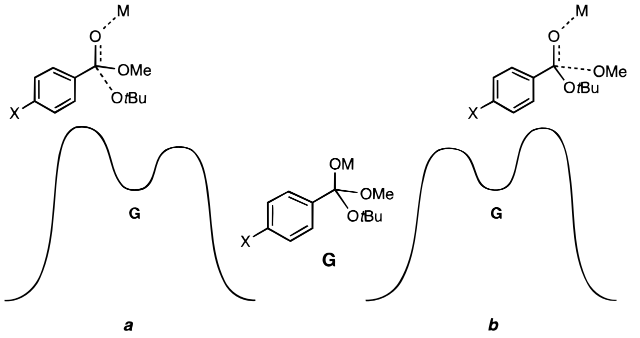
	<u>X</u>		<u>X</u>
1a	-OMe	**1e**	-Cl
1b	-*t*Bu	**1f**	$-CF_3$
1c	-Me	**1g**	-CN
1d	-H		

Discussion

A series of experiments probing the mechanistic details of the alkali-metal alkoxide-cluster-catalyzed ester interchange reaction have been performed. Kinetic evidence points to rates that are highly sensitive to the identity of the metal counterions in the catalyst and to both steric and electronic effects in the substrates. A rate-determining addition of *tert*-butoxide to MeBz is implicated by the orders in ester and the simplistic scenario in Scheme 3. The involvement of MeBz in the turnover-limiting step is also consistent with the linear free energy (LFE) relationship for para-substituted methyl benzoates ($\rho = +2.35$).

Although kinetic and LFE relationships point to the notion that MeBz is involved in the rate-limiting step, the putative involvement of tetrahedral intermediate **G** suggests two mechanistic possibilities, where the slow step is (a) addition of *tert*-butoxide to form **G** (***a***, Scheme 4) or (b) its breakdown (***b***, Scheme 4). We favor the former scenario for two reasons: (1) the magnitude and sign of ρ ($+2.35$) is most consistent with the *addition* of a nucleophile to the electrophilic carbonyl carbon and (2) the large and negative entropy of activation ($-32(3)$ eu) argues for substantial entropic reorganization, a scenario most easily reconciled by a rate determining *formation* of the tetrahedral intermediate **G**.

Scheme 4



While interpretation of these data is relatively straightforward using the simple model in Scheme 4, the analysis becomes more complex with cluster catalysts. A reasonable chain of events for a cluster-mediated transesterification has previously been proposed by Jackman.[17] A slightly modified version of this process is shown in Scheme 5 and highlights (1) the degree of reorganization that accompanies the addition/elimination sequence and (2) the number of potential intermediates that could be present along the reaction coordinate.

A typical transesterification reaction as shown in Scheme 5 requires three different charged oxygen atoms through the sequence. The fact that the rates of these reactions are not accelerated by polar solvents (the opposite is true) suggests that, despite the shuttling of negative charge, little charge buildup occurs during the transformation. It is therefore tempting to speculate that one role of the cluster in accelerating the rate of this reaction is to provide multiple points of attachment for neutralizing (i.e., stabilizing) developing negative charge in the transition state. Such a scheme would not be accessible in a mononuclear ion pair and thus provides a reasonable rationale for why clusters are exceptionally reactive. A second role for the cluster may be that the architecture of the aggregate ensures that alkoxide delivery to the carbonyl π^*-orbital occurs through a six-membered transition state that delivers the nucleophile along the stereoelectronically preferred approach trajectory (**H**, Scheme 5).[31]

The rate law, Eyring, and LFE relationships confirm a rate-determining addition of the metal alkoxide to MeBz. However, the exact role of the alkoxide nucleophile's structure and nuclearity on the reaction energetics is less clear. It has been established that NaO*t*Bu exists as a tetramer in ether, THF, and *tert*-butyl isobutyrate, and a mixture of hexamers and nonamers in cyclohexane and benzene. The aggregation state of the clusters in solutions that are 1.6 M in ester is unknown; however, the rather basic nature of esters[28] should tend to destabilize the higher (>4) aggregates found in nonpolar solvents. Our working model thus assumes that the major catalyst structure in solution is a tetrameric cube.

Since the experimentally determined reaction orders in NaO*t*Bu are close to unity (Figure 3) and structures with an aggregation state of four are the major solution species, they point to tetrameric primary reactants. A reasonable explanation for the deviations from unity in catalyst order focuses on the equilibrium between the major tetrameric cube and a smaller or larger cluster reacting at a different rate (on a per alkoxide basis). When two active species are in equilibrium, the order in that catalyst is not, strictly speaking, defined. However, if the rates of catalysis are similar or one is present in a small concentration, then a perturbation in the log−log plot is

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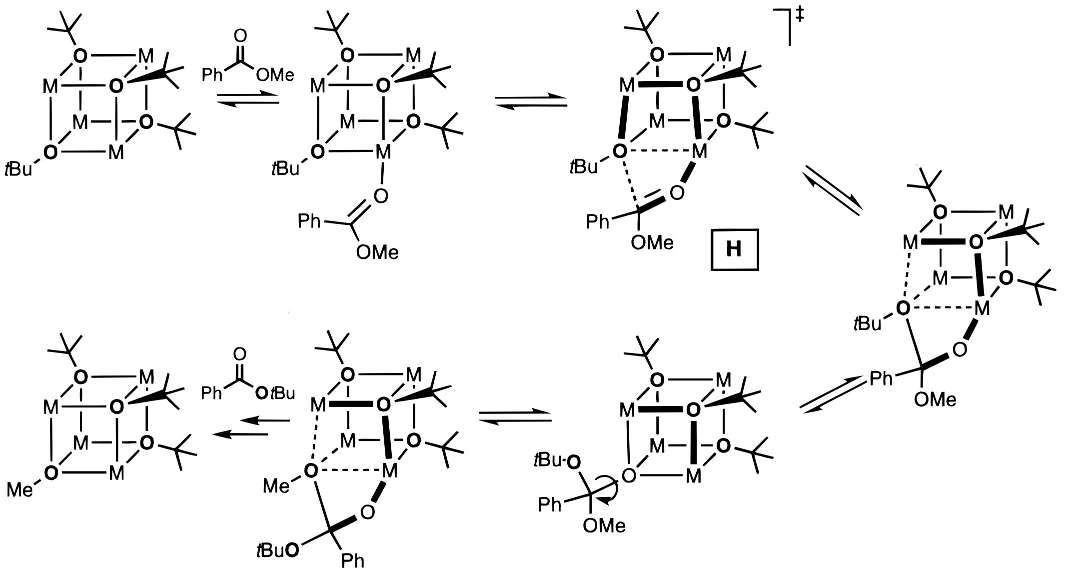
(29) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.

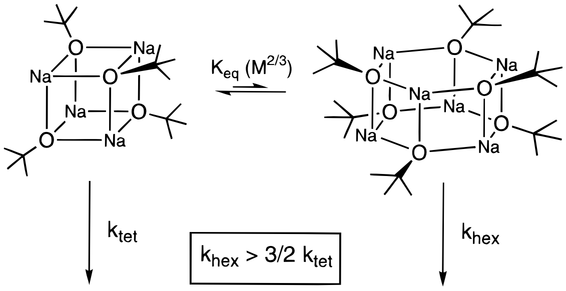
(30) Pregel, M. J.; Dunn, E. J.; Nagelkerke, R.; Thatcher, G. R. J.; Buncel, E. *Chem. Soc. Rev.* **1995**, 449−455.

(31) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

Scheme 5



Scheme 6



observed. For example, the reaction in hexane gives a catalyst order of 1.2(1) (Figure 3), consistent with a tetramer in equilibrium with a small concentration of a more reactive hexamer. As the catalyst concentration increases, the equilibrium shifts toward the more reactive aggregate and a higher than expected rate ensues (Scheme 6). This is a reasonable scenario since hexameric lithium aryl oxides have been previously shown to be up to 5.5 times more reactive than their tetrameric counterparts.[17] Similarly, the higher order in ether (1.4(1)) suggests that the hexamer/tetramer reactivity ratio is higher than in hexane. In THF, the order of 0.85(2) is consistent with two scenarios, equilibrium of the tetramer with (a) a more reactive dimer or (b) a less reactive hexamer. Both are possible as precedence for a more reactive dimer exists in lithium aryl oxide clusters.[17] As shown in Figure 3, the log−log plot for eq 7 is decidedly nonlinear in toluene. While this is most likely due to relative aggregation and kinetic effects, the structural data to deconvolute these contributions is not yet available and we include it for completeness.

Comparison of second-order rate constants for the addition of metal alkoxides to esters is instructive. In a closely related system, Jackman measured rate constants that varied from 2 × $\mathrm{M^{-1}\,s^{-1}}$ to 13 × 10^{-4} $\mathrm{M^{-1}\,s^{-1}}$ in various solvents at 35 °C for the process in eq 2. Rates as high as 2.9 × 10^{-3} $\mathrm{M^{-1}\,s^{-1}}$ at 35 °C for dimers were also observed.[17] Buncel has measured rate constants for the addition of alkali-metal ethoxides to aryl benzoates in ethanol and found that the metal effect on rate was not large (0.31 (Li^+), 0.55 (Na^+), 0.58 (K^+), and 0.48 (Cs^+) $\mathrm{M^{-1}\,s^{-1}}$; 25 °C).[30] Under these conditions, monomeric contact ion pairs are in equilibrium with reactive free ethoxide (0.13 $\mathrm{M^{-1}\,s^{-1}}$) and the metal enhances the rate of transesterification. Using equilibration rates (eq 7), apparent second-order rate constants of ∼0.03 (Li^+), 0.13 (Na^+), 3.2 (K^+), 9 (K^+), and 14 (Cs^+) $\mathrm{M^{-1}\,s^{-1}}$ at 25 °C are obtained assuming a *tetrameric* alkoxide catalyst. Clearly a stronger alkali-metal effect exists in the nonpolar to weakly polar aprotic solvents studied herein as compared to polar protic solvents.

The observation that donor solvents slow the rates of reaction is consistent with a competitive inhibition for the ester preequilibrium binding site on the cluster (Scheme 5).[26] The central tenet to this analysis further suggests that prebinding of the carbonyl oxygen of the ester to the alkali metal is necessary to ensuring intermediates (charged) of reasonable stability.[32] Conventional wisdom would also add that the metal acts as an electrophilic activator of the carbonyl group, thereby enhancing the rate of alkoxide addition.[26,33] However, the putative role of the alkali metal as a Lewis acid is less clear in the present case as rates run opposite the cations' inherent Lewis acidity, i.e. lithium, the strongest Lewis acid (size/charge), is the poorest catalyst while cesium is the best.[34]

An explanation for the ordering in metal reactivities evolves from considering the relative interaction of two metal cations with a single negative charge. From the ion-exchange and ion-selective electrode literature, a theory formulated by Eisenman describes the interaction of two ions in solution as an interplay between electrostatics and solvation. In the case of low electric field strength anions (charge diffuse), the electrostatic terms diminish and cation solvation strength becomes more important. This leads to weakly solvated cations (Cs^+) being more strongly attracted. In the case of high electric field strength anions (concentrated charge), the electrostatic terms dominate and the cation with the smallest size is most strongly attracted.[35]

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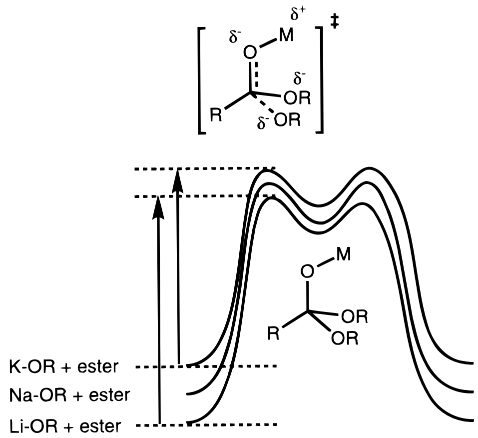
(32) While such a scenario has been assumed (reasonably) for many years, clear evidence for a prebound ester was found in the case of organolanthanide catalysts for the ring opening of lactones. In this case, the intermediate bound lactone could be isolated and spectroscopically characterized (NMR) and its conversion to a new alkoxide via alkoxide migration monitored. Yamashita, M.; Takemoto, Y.; Ihara, E.; Yasuda, H. *Macromolecules* **1996**, *29*, 1798−1806.

(33) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256−272. (b) Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597−2605.

(34) A further complication is the unkown effect on reactivity of the structural consequences (on the cluster) of a change in ionic radius in the cations (Li^+ (0.76 Å), Cs^+ (1.67 Å)).[25]

Scheme 7



In the present case, the solvation terms in the Eisenman equation are expected to be minimal for two reasons: (1) use of a relatively nonpolar solvent and (2) the aggregation of the metal alkoxides which shield the cations from solvation effects. The equation for the competition of two monovalent cations with a single anion thus reduces to $\Delta G°_{1/2} \approx 1/(r_a + r_1) - 1/(r_a + r_2)$, where r_a is the radius of the anion and r_1 and r_2 are the radii of cations 1 and 2, respectively (Coulomb's law). The concentrated (small) charge in the alkoxide anion maximizes the difference between the smallest and largest cations and leads to strong ground-state stabilization by the smaller metals (Scheme 7).

On the other hand, the negative charge in the transition state for *tert*-butoxide addition will be spread among the three oxygen atoms and result in a larger, more diffuse anion as compared to the ground-state alkoxides. The effect of the larger anion in the transition state is to compress the energy difference between the smallest and largest cations (Scheme 7). This transition-state compression hypothesis is consistent with the observed cation reactivities ($Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$) and moreover predicts the linear correlation between log k_{obs} and $1/r_{ionic}$ (Figure 4).[36] While this correlation has been observed by several groups,[37] it was Buncel who first applied the Eisenman theory to the concept of transition-state stabilization.[30,38]

Summary

We have shown that alkali-metal alkoxide clusters function as highly active catalysts for the ester interchange reaction. Mechanistic investigations implicate a stepwise process for our test reaction wherein *tert*-butoxide addition to methyl benzoate is turnover limiting and is sensitive to para substituents. Reaction orders in catalyst and the known aggregation behavior of these alkoxides implicate tetrameric clusters as the primary reactants. These clusters have been shown to be modified under the reaction conditions to clusters containing mixed *tert*-butoxy and methoxy substituents which appear to have enhanced activities compared to the tetrameric all-*tert*-butoxide cluster. The good correlation between log(rate) and $1/r_{ionic}$ suggests a scenario wherein strong electrostatic interactions occur in the ground state and are diminished in the transition state, leading to the observed ordering in rate ($Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$).

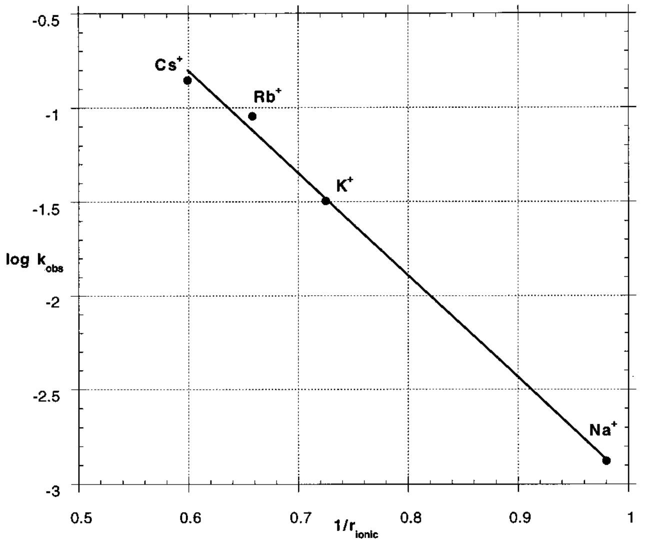


Figure 4. log k_{obs} (one half-life) for eq 7 vs reciprocal six-coordinate ionic radius of the metal cation[25] (0.8 M in each ester, 40 mM MO*t*Bu (5 mol %), THF).

We propose that the roles of the cluster in facilitating the rate of transesterification, are

(1) To supply multiple cations within the cluster framework to serve as charge neutralizing sites. These sites stabilize developing negative charge in the transition state.

(2) To provide scaffolding for first precoordinating the ester, potentially activating it, and then delivering the alkoxide nucleophile via a six-membered transition state along the stereoelectronically preferred Bürgi−Dunitz angle.

Our efforts are currently focused on identifying and structurally characterizing cluster intermediates. These results will be reported in due course.

Experimental Section

Materials and Methods. All solvents were prepared by first purging reagent grade solvents with dry nitrogen and then dried by passing over a column of activated alumina,[39] with the exception of DME, *t*BuOMe, 2-Me-THF, and 2,5-Me$_2$-THF, which were dried and vacuum distilled from purple sodium/benzophenone ketyl solutions. Esters were purchased from Aldrich and distilled over CaH$_2$. Alkali-metal alkoxide catalysts were prepared from the corresponding metal and *tert*-butyl alcohol, purified by sublimation, and stored in an inert atmosphere glovebox. Potassium *tert*-butoxide solutions (1 M in THF) were purchased from Aldrich. Reactions were carried out in an inert argon atmosphere using standard Schlenk line techniques. Para-substituted *tert*-butyl benzoates for GC calibration were synthesized as described in ref 3b.

Gas chromatography was performed on a Hewlett-Packard 6890 GC equipped with an HP-5 column (30 m × 0.32 mm) and an HP 6890 series autosampler. ^{1}H NMR spectra were obtained at 200 MHz on a

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[35] The complete Eisenman equation for the competition of two cations for a single anion is $\Delta G°_{1/2} = e^2/(r_a + r_2) - e^2/(r_a + r_1) - (\Delta G_2 - \Delta G_1)$, where e is the electronic charge, r_a is the radius of the anion, r_1 and r_2 are the radii of cations 1 and 2, respectively, and ΔG_1 and ΔG_2 are the solvation energies of cations 1 and 2 (Coulomb's law).

[36] While $1/r_{ionic}$ is not mathematically equivalent to the simplified Eisenman equation, substituting various pairs of reasonable anion sizes into this expression yields families of curves which correlate closely to $1/r_{ionic}$ ($R \sim 0.99$).

[37] (a) Kurts, A. L.; Sakembaeva, S. M.; Reutov, O. A. *J. Org. Chem. USSR (Engl.)* **1974**, *10*, 1572−1580. (b) Powell, D. G.; Warhurst, E. *Trans. Faraday Soc.* **1962**, *58*, 953−956. (c) Mathias, A.; Warhurst, E. *Trans. Faraday Soc.* **1962**, *58*, 948−952.

[38] Attempts to fit log(k_{obs}) vs $[1/(r_{ionic} + r_{alkoxide}) - 1/(r_{ionic} + r_{TS})]$ (the rigorous anion size dependence in the electrostatic term) to extract information about the size of the alkoxide ($r_{alkoxide}$) and transition-state anions (r_{TS}) were unsuccessful. The flat potential energy surfaces were not sensitive to changes in anion sizes and did not satisfactorily converge on reasonable $r_{alkoxide}$ and r_{TS} values.

[39] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

Bruker WP 200 instrument. ^{13}C NMR spectra were obtained at 50 MHz on a Bruker WP 200 instrument.

Typical Kinetic Experiments. A typical kinetic measurement was run as follows: Methyl benzoate (5 mmol, 0.63 mL) and *tert*-butyl acetate (5 mmol, 0.67 mL) were combined in a round-bottomed flask and diluted with 2.5 mL of the desired solvent. In a separate flask, MO*t*Bu (0.025 mmol) was dissolved in 2.5 mL of the desired solvent. The esters (0.8 M in each ester) were transferred via syringe to the catalyst solution. Aliquots were withdrawn via syringe, quenched in saturated aqueous NH_4Cl solution, diluted with ethyl acetate, and analyzed by GC to monitor the conversion of methyl benzoate to *tert*-butyl benzoate. Integration percentages were corrected for response factor differences between *tert*-butyl benzoate and methyl benzoate, i.e. $\%PhCO_2Me$ (GC)/$\%PhCO_2tBu$ (GC) $= \mathbf{1.46} \times$ $\%PhCO_2Me$ (actual)/% $PhCO_2tBu$ (actual).

Solvent Effects on Rate. Experimental conditions for carrying out these measurements were identical to those described above except for the substitution of THF with the solvent of choice.

Determination of Activation Energies. Rate measurements were made as described above. The temperature of the reaction was controlled using a Neslab cryobath, and the kinetic data were extracted using the initial rate to 1 half-life and fitted to the linearized form of the Eyring equation.

Linear Free Energy Relationships. Rate measurements were as described in Typical Kinetic Experiment using sodium *tert*-butoxide (5 mol %) as catalyst, and initial rates were determined from the first half-life. Integration percentages were corrected for response factor differences between the substituted methyl benzoate and the corresponding *tert*-butyl benzoate using authentic samples of the substituted *tert*-butyl benzoates.[3b]

Acknowledgment. Support from the University of North Carolina at Chapel Hill is gratefully acknowledged. M.R.G. is an NSF CAREER Award recipient.

Supporting Information Available: Kinetic plot highlighting the deviations from linearity for a simple first-order relaxation analysis, log−log plot to determine the kinetic order in esters, Eyring plot for the process in eq 7, and a Hammett plot for the substrates in eq 8 (2 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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