

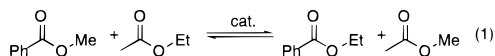
The Remarkable Catalytic Activity of Alkali-Metal Alkoxide Clusters in the Ester Interchange Reaction

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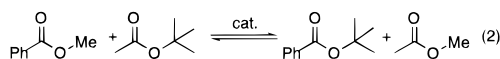
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Despite the fact that the transesterification reaction stands out as one of the most fundamental reactions in organic chemistry, there are no general methods for carrying out this transformation under mild conditions. We wish to report that a variety of alkali-metal alkoxides show high activity as catalysts for the ester interchange reaction—a coupled transesterification process (eq 1). These alkoxide clusters are at least 10^6 times more active than the known lanthanide isopropoxide catalysts recently reported by Okano ($M(OiPr)_3$; $M = La, Nd, Gd, Yb$).¹ Although alkali-metal alkoxides have been used for decades as strong bases,² to our knowledge, these complexes have been overlooked as catalysts for the ester metathesis reaction. We present herein preliminary experiments which document the remarkable rate-accelerations that alkali-metal alkoxides ($M = Li^+, Na^+, K^+, Rb^+$) affect on the ester metathesis reaction.



The high activity of these complexes became evident as we attempted to measure the rate at which the substrates in eq 1 reached equilibrium. In the presence of 5 mol % NaOtBu, this reaction reaches equilibrium in <10 s. *To establish equilibrium this catalyst completes at least 400 turnovers in <10 s!!* Such fast rates make aliquot quenching techniques coupled with GC analysis inappropriate for kinetic studies. However, more convenient rates were observed with *tert*-butyl acetate, and thus the process in eq 2 was adopted for more detailed mechanistic studies.³



Since *Mtert*-butoxides are soluble in common organic solvents and are easily purified by sublimation, they serve as ideal catalyst precursors. At a first-order level of analysis, the mechanism for the equilibration undoubtedly involves a series of coupled transesterification reactions (Scheme 1). This scenario invokes the intermediacy of NaOMe or NaOEt, suggesting that these materials should be equally competent catalysts for this process. Control experiments, however, show that, in fact, NaOEt is a poor catalyst for eq 2, presumably due to its insolubility in the reaction medium. Careful studies of the reaction in eq 2 using 5 mol % of NaOtBu as catalyst show that clean first-order relaxation kinetics are observed for at least a single half-life (~ 10 – 20 turnovers).⁴ However, the solutions begin to cloud after this period of time, and the reaction rates speed up despite precipitation of the catalyst. Clearly, such an

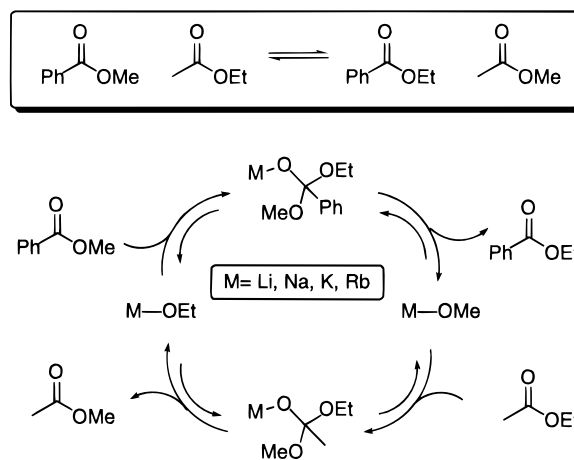
(1) Okano, T.; Hayashizaki, Y.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1993**, 1863–1864.

(2) *Encyclopedia of Organic Reagents*; Paquette, L. A., Ed.; potassium *tert*-butoxide; John Wiley and Sons: 1995; Vol. 6, pp 4189–4195.

(3) Using methyl alkanoates and *tert*-butyl acetate as substrates also sufficiently slows down the rate of reaction that comparisons of different alkyl groups are possible. In these studies, the relative reactivities are $nPr(100) > Ph(36) > iPr(6) > tBu(<1)$.

(4) Reaction kinetics were determined by monitoring the conversion (by GC) of methyl benzoate to a $\sim 50:50$ mixture of methyl benzoate and *tert*-butyl benzoate. The rate constants $k_{obs} = (k_1 + k_{-1})$ were obtained from a plot of $\ln([tert\text{-butyl benzoate}]_{equil} - [tert\text{-butyl benzoate}])$ versus time—the slope of the line is $-k_{obs}$.

Scheme 1



observation is not consistent with the simple scenario in Scheme 1 since NaOMe should be immediately generated and precipitated from the solution. Isolation of this slowly precipitated solid and quenching with DCl/D₂O followed by ¹H NMR analysis indicates that the aggregate is composed of a 3:1 ratio of NaOMe and NaOtBu.

An examination of the known solution^{5,6} and solid-state⁷ structures of *Mtert*-butoxides suggests that higher order clusters (tetramers or hexamers) are reasonable intermediates and may be intimately involved in catalyst turnover. In a related transesterification reaction, Jackman has clearly demonstrated that tetrameric and/or hexameric aggregates are the primary reactants in THF and dioxolane.⁸

Literature precedence coupled with the reported data leads to the preliminary hypothesis that our catalysts are also alkoxide clusters, perhaps tetramers (A–C), and that high reactivity (relative to NaOEt) is at least partially due to the enhanced solubility imparted by the *tert*-butoxy ligands in organic solvents. In essence, the *in situ*-derived clusters are solubilized forms of NaOMe and NaOEt resulting from the partial replacement of the *tert*-butoxy groups in the cluster B.⁹ As *tert*-butoxy groups continue to be substituted by methoxy or ethoxy substituents, the clusters lose their solubility and precipitate from solution.¹⁰ In hexane/ester mixtures, the insolubility of the trimethoxy/mono-*tert*-butoxy cluster suggests that for the process in eq 2, A, B, and the cluster derived from 2-OMe and 2-*tert*Bu groups constitute the active catalysts.¹¹ The presence of more than one active catalyst may also be responsible for the apparent

(5) For a partial list of references to the solution structures of alkali-metal alkoxides, see: (a) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, 113, 7288–7293. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, 110, 3829–3835, and references therein. (c) Schmidt, P.; Lochmann, L.; Schneider, B. *J. Mol. Struct.* **1971**, 9, 403–411. (d) Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, 114, 7482–7489. (e) Hartwell, G. E.; Brown, T. L. *Inorg. Chem.* **1966**, 5, 1257–1259.

(6) For general references on the solution and solid-state structures of metal-enolates, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 1624–1654. (b) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, 33, 2737–2769.

(7) (a) Chisolm, M. H.; Drake, S. R.; Nairni, A.; Streib, W. E. *Polyhedron* **1991**, 10, 337–345. (b) Davies, J. E.; Kopf, J.; Weiss, E. *Acta Crystallogr.* **1982**, B38, 2251–2253. (c) Weiss, E.; Alsdorf, H.; Kühn, H. *Angew. Chem., Int. Ed. Engl.* **1967**, 6, 801–802.

(8) Jackman, L. M.; Petrei, M. M.; Smith, B. D. *J. Am. Chem. Soc.* **1991**, 113, 3451–3458.

(9) Consistent with this proposal is the detection (GC) of substoichiometric quantities of *tert*-butyl esters (eq 1) from the addition of *tert*-butoxide to the starting esters.

(10) Alkali-metal methoxides form highly insoluble sheet-like structures, see: (a) Weiss, E.; Alsdorf, H. *Z. Anorg. Allg. Chem.* **1970**, 206–213. (b) Weiss, E.; Alsdorf, H. *Z. Anorg. Allg. Chem.* **1964**, 197–203.

(11) It is certainly reasonable to suggest that aggregates of higher order than four may characterize materials with high OMe/OtBu ratios. Our experiments have not addressed this issue as of yet.

Table 1. Effect of Alkali-Metal Cation on the Approach to Equilibrium of Eq 2^a

metal	ionic radii (Å) ¹²	k_{obs} (s ⁻¹)	$t_{1/2}$ (s)
Li ⁺	0.76	$<3.2 \times 10^{-4}$ ^b	>2100
Na ⁺	1.02	1.3×10^{-3}	535
K ⁺	1.38	3.2×10^{-2}	22
Rb ⁺	1.52	$\geq 9 \times 10^{-2}$ ^c	~8

^a Reaction conditions: 0.8 M in each ester, 40 mM in MO*t*Bu (5 mol %) under nitrogen atmosphere. See Supporting Information for experimental details. ^b Ill-behaved kinetics—reaction never reached equilibrium. ^c Lower limit—reaction rates were too fast to accurately measure (equilibrium in ~15–30 s).

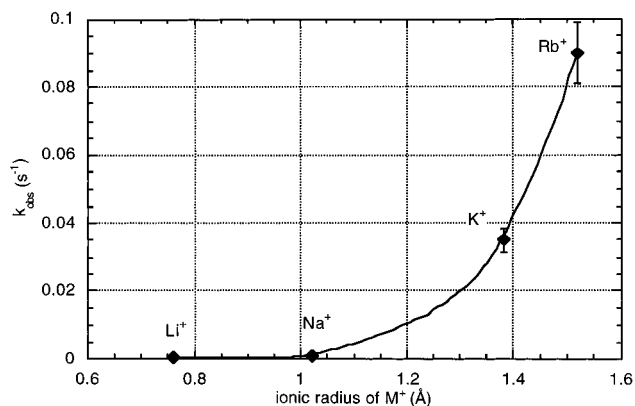
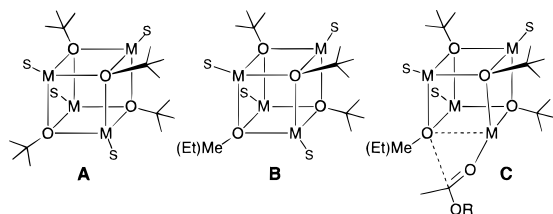


Figure 1. Observed first-order relaxation rate constants for eq 2 vs ionic radius of the MO*t*Bu catalyst (0.8 M in each ester, 40 mM in catalyst monomer (5 mol %), see Supporting Information for experimental details). The line represents a smooth curve through the data points.

rate increases after the first 1–1.5 half-lives. Despite this gradual precipitation of catalyst, most reactions reach equilibrium long before complete precipitation of catalyst occurs.



We have also determined the influence of the cation on the rates of reaction and observed that rate increases dramatically upon descending the periodic table (Table 1, Figure 1). It is not clear whether this effect is a result of greater ionicity in the metal-oxygen bond (electronic), structural changes imparted by the larger metals on the cluster framework (steric), or both.¹²

We have also observed a curious solvent effect on the reactivity of NaO*t*Bu. Again, using eq 2 as our test reaction

(12) For representative six-coordinate ionic radii, see: Shannon, R. D. *Acta Crystallogr.* **1976**, 751–767.

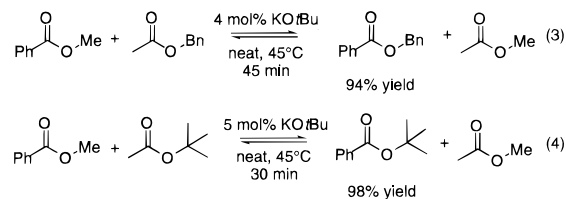
Table 2. Effect of Solvent on the Rate of Approach to Equilibrium for Eq 2^a

solvent	k_{obs} (s ⁻¹ ($\times 10^{-3}$))	$t_{1/2}$ (s)
hexanes	7.0 ± 0.9	100
toluene	3.6^b	195
<i>t</i> BuOMe	3.4^b	205
ether	3.4 ± 0.2	205
CH ₂ Cl ₂	1.6^b	435
THF	1.3 ± 0.3	535

^a Reaction conditions: 0.8 M in each ester, 40 mM NaO*t*Bu (5 mol %), under nitrogen. The reaction was monitored to 20% conversion by GC and analyzed using standard approach to equilibrium kinetic expressions. See Supporting Information for full experimental details. ^b Single measurement.

we find that well-behaved relaxation kinetics are observed over at least 1 half-life (Table 2). These studies reveal that the reactions are more rapid in nonpolar solvents with turnover in hexanes being ~5× faster than that in THF. Such a trend has been previously observed by Jackman for the transesterification of aryl esters mediated by a well-characterized lithium-aryloxide tetramer and was attributed to reduced competition by the solvent for the ester preequilibrium metal binding site (C).⁸ Such a mechanism may also be operative in the present metal clusters.

In addition to the above mechanistic studies we have also begun investigating the synthetic utility of the ester interchange reaction. Using a protocol wherein an aspirator vacuum is applied to the reaction to remove a volatile byproduct (methyl acetate), it was possible to synthesize benzyl benzoate and *tert*-butyl benzoate in >94% yield using up to 5 mol % of a commercially available solution of KO*t*Bu in THF (eqs 3–4).



In summary, a new class of remarkably active ester metathesis catalysts have been identified and their reactivity associated with higher-order aggregates. Current efforts are directed toward an understanding of the relationship between the catalysts solution structure and activity. Coupled to such efforts are studies aimed at catalyst optimization and development of this reactivity into a viable synthetic methodology for both small molecule and polyester synthesis.

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Supporting Information Available: Experimental details for kinetic measurements and a representative relaxation to equilibrium plot; synthetic procedure for the synthesis of benzyl benzoate and *tert*-butyl benzoate (4 pages). See any current masthead for ordering and Internet access instructions.

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