

Structure and Reactivity of Mixed Alkali Metal Alkoxide/Aryloxy Catalysts

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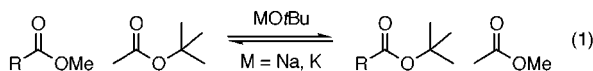
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Received September 10, 2001

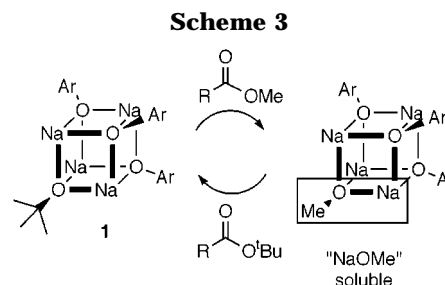
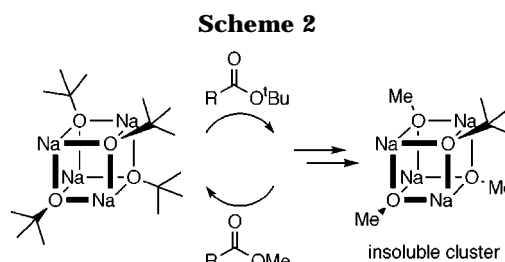
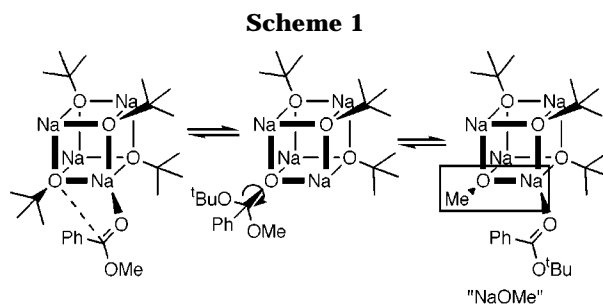
The average solution aggregation state of the ester interchange catalyst **1**, obtained by mixing 1 equiv of NaOt-Bu and 3 equiv of NaOC₆H₄-4-*t*-Bu, was determined to be 4.0 by vapor pressure osmometry (VPO) in THF. Low-temperature ¹H NMR spectra of **1** indicated that the THF solution contained a mixture of tetrameric clusters. On the basis of symmetry arguments and the sensitivity of the different species to the alkoxide/aryloxy ratio, the compounds were determined to be mixed clusters with 0:4, 1:3, 2:2, and 3:1 mixtures of the NaOt-Bu and NaOC₆H₄-4-*t*-Bu components. On a per -Ot-Bu basis, each cluster has a similar absolute activity, though the aryloxy-rich catalysts are significantly longer-lived. Unlike **1**, catalysts containing ortho-substituted aryloxides, **2**, do not give a strictly statistical distribution of clusters, and the activities of these catalysts depend on steric and electronic factors, though the absolute rate differences are not large.

Introduction

Alkali metal alkoxides such as KOt-Bu and NaOt-Bu are excellent catalysts for the ester interchange reaction, with some turnover frequencies (TOF) approaching 10⁷ h⁻¹ for eq 1.¹ In aprotic donating solvents (typical reaction conditions), KOt-Bu and NaOt-Bu form cubelike tetramers² that provide the framework for kinetically facilitating alkoxide/ester interchange while solubilizing a form of "NaOMe", an otherwise insoluble material,³ Scheme 1. Although these catalysts effectively convert methyl to more easily hydrolyzed *tert*-butyl esters (5–8 mol % KOt-Bu), the catalyst eventually precipitates from solution as methoxide builds up in the catalyst cluster, Scheme 2.^{3c}



The problem of over-methoxylation and precipitation of these catalysts was solved by the addition of an aryloxy salt cocatalyst, which was presumed to form a soluble mixed NaOt-Bu/NaOAr catalyst, Scheme 3;⁴ aryloxy additives were chosen as they do not productively interchange with alkyl esters. Our optimized catalyst combination was a 1:3 NaOt-Bu/NaOC₆H₄-4-*t*-Bu mixture, **1**, which had a significantly longer lifetime and was milder and more robust than its alkoxide-only parents. This new catalyst formulation enabled one-step



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(3) NaOMe forms infinite two-dimensional sheets and is virtually insoluble in aprotic solvents. See: (a) Weiss, E.; Aldorf, H. Z. *Anorg. Allg. Chem.* **1970**, *572*, 206–213. (b) Weiss, E.; Aldorf, H. Z. *Anorg. Allg. Chem.* **1964**, *332*, 197–203. (c) Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 658–660.

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transformations with lower catalyst loadings (0.5–3 mol % **1**), enhanced functional group tolerance (e.g., nitro groups), and interchange of epimerizable α -amino esters.⁴

During catalyst development, experiments were designed under the reasonable assumption that, like [KOt-Bu]₄ and [NaOt-Bu]₄, these mixed cluster catalysts were also tetrameric, though little data were available to

directly support this notion. While many lithium⁵ and sodium⁶ aryloxide clusters have been characterized, to our knowledge, no mixed alkoxide/aryloxide clusters of sodium have been reported. However, a Cambridge Structural Database search revealed several relevant structure types that result from the aggregation of mixtures of anionic components, and these include a mixed lithium bis-aryloxide/alkoxide (hexamer),⁷ an aryloxide/alkyl (tetramer),⁸ a mixed alkoxy/chloride (dimer of tetramers),⁹ an aryloxy/iodide (tetramer),¹⁰ an enolate/halide (dimers),¹¹ an enolate/amido (dimers),¹² an alkoxide/alkyl (tetramers),¹³ and a Li/K enolate/alkoxide (octamer).¹⁴ As a general rule, sodium aryloxides preferentially crystallize as tetramers in the presence of a highly polar aprotic solvent^{6a,e,k,m} or coordinating aryloxide substituent.^{6a,f,1} As a result, the catalyst was similarly expected to be a tetramer under reaction conditions.¹⁵

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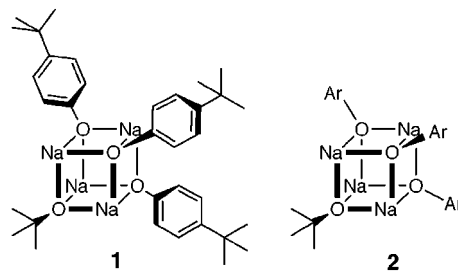
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Table 1. Vapor Pressure Osmometry Results for **1** and Its Components

	molarity (M)	molarity by VPO (M) ^a	aggregation state
NaOt-Bu	0.080	0.020	4.0
NaOC ₆ H ₄ -4- <i>t</i> -Bu	0.120	0.028	4.3
(NaOt-Bu)(NaOAr) ₃ (1)	0.120	0.029	4.0

^a Dry THF at 23 °C.

Since little relevant data were available, we initiated and report herein experiments that probe the structure, longevity, and activity of mixed sodium aryloxy/alkoxy ester interchange catalysts.



Ar =
2-Me, 2-H, 2-Et, 2-*i*Pr, 2-*t*-Bu, 2-OMe, 2-F, 2-NH₂,
2-Cl, 3-Cl, 3-CF₃, 3-Br, 3-F, 4-OMe, 4-F, 4-Cl
phenoxide, 2-naphthoxide and 6-Br-2-naphthoxide

Results and Discussion

Preparation of Mixed Alkoxide/Aryloxide Catalysts. Mixed cluster catalyst **1** was prepared for each experiment by dissolving 1 equiv of NaOt-Bu and 3 equiv of NaOC₆H₄-4-*t*-Bu in THF. This protocol provided a catalyst with optimum activity and reproducibility for kinetic studies. However, **1** could also be prepared and stored for later use by dissolving the alkoxide and aryloxide salts in THF as described above. Solvent removal provided **1** as a white powder that was stable in the glovebox for several months. Alternatively, a third, somewhat more convenient method for the large-scale preparation or storage of **1** was to combine 4 equiv of NaOt-Bu and 3 equiv of 4-*t*-Bu-phenol in THF. This solution could be used as prepared or concentrated in vacuo to remove the THF and the *t*-BuOH; although for careful kinetic studies we preferred the first method, the activity of **1** was independent of the manner of preparation. For screening purposes, the generic catalysts **2**, [NaOt-Bu/3NaOAr], were prepared in situ using the NaOt-Bu and aryloxide salt method.

Vapor Pressure Osmometry (VPO). As a first step to determining the structure of catalyst **1**, we measured its solution aggregation state by vapor pressure osmometry. VPO enables average molecular weights to be measured, from which average aggregation states can be calculated. Table 1 outlines the results for this study. By

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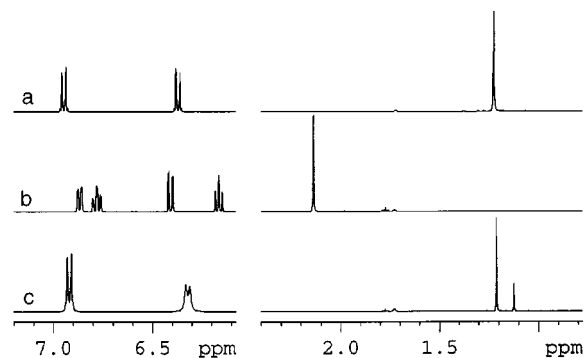


Figure 1. Room-temperature ^1H NMR (400 MHz, $\text{THF-}d_8$): (a) $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$; (b) $\text{NaOC}_6\text{H}_4\text{-2-CH}_3$; and (c) **1** (vertical scale in aryl region has been increased for clarity).

VPO, the molecular weight of a 0.080 M solution of NaOt-Bu is 383 g/mol (nominal MW = 96 g/mol), i.e., the average aggregation state is 4.0, a value consistent with previous reports.² Similarly, a 0.12 M solution of $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$ (172.2 g/mol) has a molecular weight of 738 g/mol (0.028 M) and an aggregation of 4.3.^{5k,16} A 0.030 M solution of catalyst **1** that was predicted to have a composition corresponding to $(\text{NaOt-Bu})(\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu})_3$ (612.6 g/mol) was then tested and found to have a molecular weight of 633 g/mol (0.029 M). While not an unambiguous structural identification, the VPO measurements support the assertion that mixed clusters such as **1** are tetramers in THF.

Cluster Characterization by ^1H NMR. The aryl region of the room-temperature ^1H NMR spectra of $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$ (0.40 M, $\text{THF-}d_8$, Figure 1a) revealed well-resolved signals, with a characteristic upfield 2-H doublet (6.95 ppm, $J = 8.4$ Hz) and a *tert*-butyl signal (1.25 ppm) that is slightly downfield of NaOt-Bu (1.08 ppm). Ortho-substituted aryloxides had similar spectral patterns in the aryl region ($\text{NaOC}_6\text{H}_4\text{-2-CH}_3$ is provided as an example, Figure 1b). In the room-temperature ^1H NMR spectrum of **1** (Figure 1c), the signals for the ortho (LWHH = 20 Hz, at 400 MHz) and meta to O^- hydrogens are broadened and shifted somewhat upfield ($\Delta\delta \sim 0.06$ ppm) from the all-aryloxy case; a similar trend was observed with catalysts **2**. Broadening of the aryl signals suggested a dynamic process that was investigated by variable-temperature ^1H NMR experiments.

As shown in Figure 2, cooling a $\text{THF-}d_8$ solution of **1** resulted in further broadening of the aryl signals, but more quickly in the ortho position, which ultimately loses coupling information at 268 K (Figure 2b), broadening further (LWHH = 40 Hz) and becoming unsymmetrical by 253 K, Figure 2c. Further cooling to 223 K decoalesces this signal into a set of four sharp doublets in a 46:39:13:2 ratio at 6.37, 6.30, 6.25, and 6.21 ppm, respectively (Figure 2d). The 3-H signal is less informative, and further cooling does not help to resolve the overlap, Figure 2e. Clearly, several environments are accessible, most reasonably suggesting that (1) multiple species are present in solution, (2) these equilibrate on the NMR time scale, and (3) that more than one catalyst may be involved in turnover.

When differing concentrations of **1** (0.08–4.0 M) were cooled to 198 K ($\text{THF-}d_8$), the signal pattern and relative

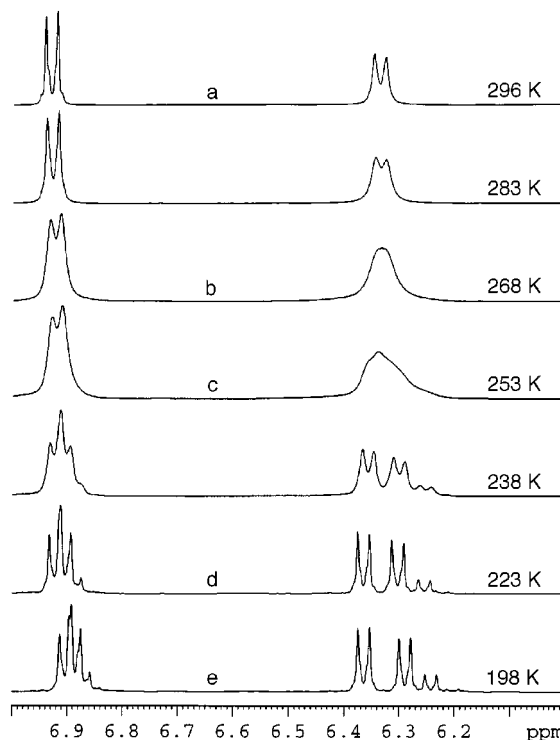


Figure 2. Variable-temperature ^1H NMR (400 MHz) of **1** (0.4 M in $\text{THF-}d_8$).

intensities were invariant, indicating that clusters of a single nuclearity are equilibrating rather than a tetramer/hexamer-type equilibria. Jackman previously observed that the transesterification activity of $(\text{LiOAr})_x$ clusters was described by an equilibrating mixture of tetramers ($x = 4$) and hexamers ($x = 6$), which react at different rates.¹⁷

Additional evidence for the identity of the compounds observed in the 198 K ^1H NMR spectrum of **1** was obtained by examining different $\text{NaOt-Bu}/\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$ ratios, Figure 3. The ortho hydrogen of the aryloxy-only cluster $[\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}]_4$ resonates at 6.37 ppm, the chemical shift of the most downfield of the resolved signals in the mixture, Figure 3a. Increasing the alkoxide content of the solution generates new species more upfield of the parent, presumably the expected mixed alkoxy/aryloxy clusters. To test the hypothesis that these were compositional isomers of a cubic tetramer, we systematically varied the $\text{NaOt-Bu}/\text{NaOAr}$ ratio from aryloxy rich (1:7) to aryloxy poor (7:1). Low-temperature ^1H NMR spectra, Figure 3, were consistent with this hypothesis, as the isomer ratio was sensitive to the salt ratio, though not on the absolute concentration. For example, increasing the alkoxide/aryloxy ratio from 1:3 to 2:2 shifts the peak populations upfield from pure $[\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}]_4$, Figure 3d. An aryloxy-rich mixture, on the other hand, shifts this distribution downfield toward the all-aryloxy component, Figure 3b.¹⁸

The mixture of compounds that give rise to four distinct 2-H proton signals is most easily explained by a mixture of tetrameric cubes made up of 0:4, 1:3, 2:2, 3:1, and 4:0 combinations of NaOt-Bu and $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$. When the integrated ratio of clusters is corrected for the number of aryloxides in each cluster type, the normalized ratio

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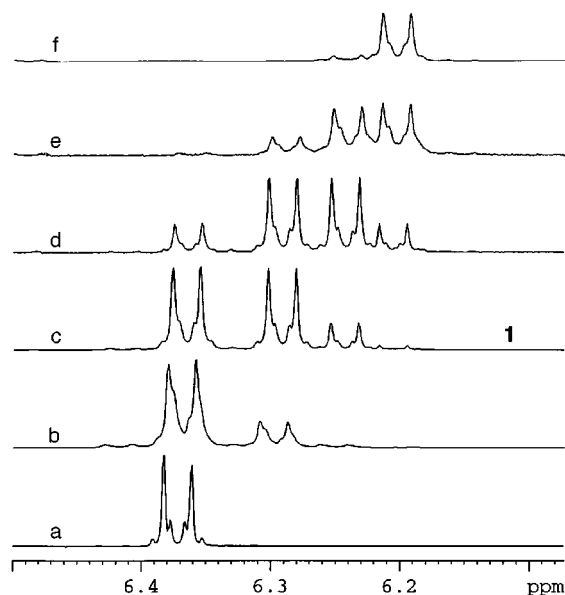


Figure 3. ^1H NMR spectra for different ratios of NaOt-Bu and $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$ ($\text{THF-}d_6$, 198 K): (a) pure $\text{NaOC}_6\text{H}_4\text{-4-}t\text{-Bu}$ (NaOAr); (b) 1:7 NaOt-Bu/NaOAr (ratio of ortho protons = 74:23:3:0); (c) 1:3 NaOt-Bu/NaOAr (catalyst **1**); (d) 2:2 NaOt-Bu/NaOAr (ratio of ortho protons = 14:38:35:13); (e) 3:1 NaOt-Bu/NaOAr ; (f) 7:1 NaOt-Bu/NaOAr .

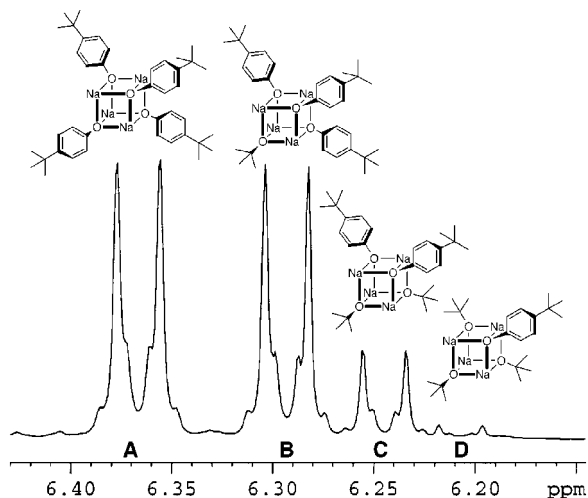


Figure 4. Assignment of clusters present in **1** from the ortho-OAr proton signals.

of tetramers is 35:40:19:6 for **A**, **B**, **C**, and **D** respectively in **1** (Figure 4). These values closely match those expected by a purely statistical analysis (32:42:21:5).¹⁹ The tetramer corrected integral values for the 2:2 and 3:1 mixtures also agree with a statistical treatment and further support the mixed tetramer hypothesis.

Aryloxide Effects on Cluster Distributions. Like the 4-*tert*-butylphenyl-substituted case discussed above, the measured and calculated cluster ratios were similar for different ratios of NaOt-Bu with NaOC_6H_5 , $\text{NaOC}_6\text{H}_4\text{-4-Cl}$, and $\text{NaOC}_6\text{H}_4\text{-4-OMe}$, indicating that electronic perturbations in the aryloxide component do not affect

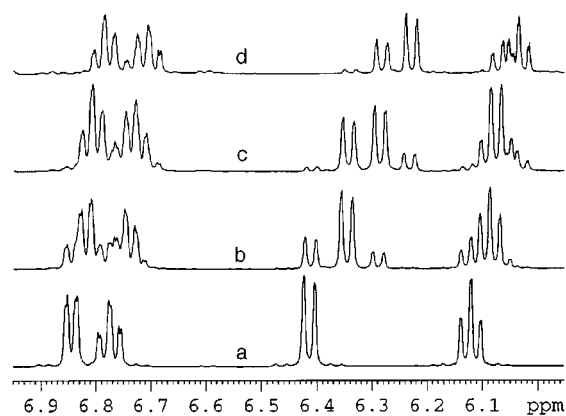
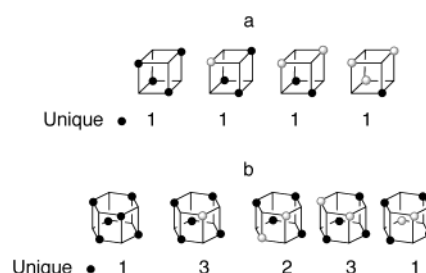


Figure 5. Low-temperature ^1H NMR ($\text{THF-}d_6$, 198 K) of different mixtures of NaOt-Bu and $\text{NaOC}_6\text{H}_4\text{-2-Me}$: (a) pure $\text{NaOC}_6\text{H}_4\text{-2-Me}$ (NaOAr); (b) 1:3 NaOt-Bu/NaOAr ; (c) 2:2 NaOt-Bu/NaOAr ; (d) 3:1 NaOt-Bu/NaOAr . The ratio of uncorrected ortho signals for b and c are 27:59:14:0 and 3:39:46:12, respectively.

Scheme 4



the intercluster thermodynamics. On the other hand, cluster distributions in 2-substituted aryloxides do not follow a statistical model. For example, rather than the expected 32:42:21:5 mixture, a 1:3 $\text{NaOt-Bu/NaOC}_6\text{H}_4\text{-2-Me}$ mixture had a 20:58:22:<1 distribution of clusters (Figure 5b), which is disproportionately populated in the 1:3 cluster. This departure from a statistically controlled distribution is apparently due to heightened steric interactions between the ortho substituents in the all-aryloxide cube that are relieved in the alkoxide-diluted cases (Figure 5c,d). Like the 2-Me case, other 2-substituted aryloxides (e.g., 2-Et, 2-*Pr*, and 2-Cl phenoxide) have a slight thermodynamic bias for the 1:3 complex.

The combination of VPO measurements, the statistical analysis of low-temperature NMR for variable alkoxide/aryloxide ratios, and the concentration-independent NMR spectra, together, suggest that the observed equilibrating species are tetramers, a proposition that is also supported by symmetry arguments. Consider the four possible mixed tetramers in Scheme 4a; the symmetry of each cluster is such that only one \bullet or \circ environment results. Use of an aryloxide reporter ligand would then lead to four unique clusters, the ratio of which should be sensitive to the ratio of components in a predictable way. On the other hand, the inherently lower symmetry of the hexameric structure (another a priori reasonable structure)⁷ leads to many more combinations of two components, e.g., 1:5, 2:4, 3:3, 4:2, 5:1, and 0:6. Moreover, most of these combinations also have multiple configurational isomers in addition to multiple chemically distinct environments per cluster. Scheme 4b shows the possible isomers for the 0:6, 1:5, and 2:4 combinations along with the number of chemically distinct \bullet environments in

(18) Similar signal patterns and shifts in signal populations were observed in the ^{31}P NMR of HMPA-solvated lithium phenoxide clusters and have been assigned to mono-, di-, tri-, and tetrasolvated cubes. See ref 5e.

(19) For statistical methods and treatment of raw NMR data, see Supporting Information.

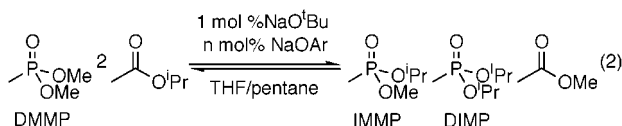
Table 2. Initial Rates (v_{initial}) and 2 h Conversions to DIMP (Eq 2) for Different Ratios of NaOt-Bu and NaOC₆H₄-4-*t*-Bu

NaOt-Bu/NaOAr ^a	v_{initial} (rel to 1) ^b	[DIMP] _{2h} , M ^c
4:0	1.13	0.05
7:1	1.02	0.07
3:1	0.87	0.085
1:1	0.93	0.13
1:3 (1)	1.00	0.17
1:7	0.80	0.17

^a Ar = -C₆H₄-4-*t*-Bu. ^b v_{initial} for **1** = 0.0155 M s⁻¹.
^c [DIMP]_{equilibrium} = 0.19 M.

each. Since the isomer ratio is statistically controlled (a flat isomer surface) and the number of observable isomers is described by a distribution of tetrameric mixed clusters, we consider these symmetry considerations to be additional evidence for describing catalysts **1** and **2** as equilibrating tetramers, although, as usual, the observed isomers may not be the catalytically active species.

Influence of Aryloxide on Catalyst Activity. In addition to structural changes, we wished to know how the catalyst activity responded to the ratio of components or to the structure of the aryloxide. The phosphoryl-carbonyl interchange reaction in eq 2²⁰ is sufficiently challenging (does not reach equilibrium with 5 mol % NaOt-Bu) that it can be utilized to measure two performance parameters: initial rate (v_{initial} , M sec⁻¹) and catalyst longevity²¹ as expressed by [DIMP]_{2h}.²² Under the reaction conditions, the equilibrium concentration of DIMP is 0.19 M and is typically not achievable with only 1 mol % of NaO^tBu, measuring [DIMP] after 2 h provides a convenient measure of longevity. The progress of the reaction can be reliably assayed by aliquoting techniques and GC analysis, and [DMMP] decreases linearly to 0.2 M DMMP (10–35 s, ~120 turnovers). The negative slope of the plot of [DMMP] vs time thus yields the initial rate (v_{initial}) of the reaction.



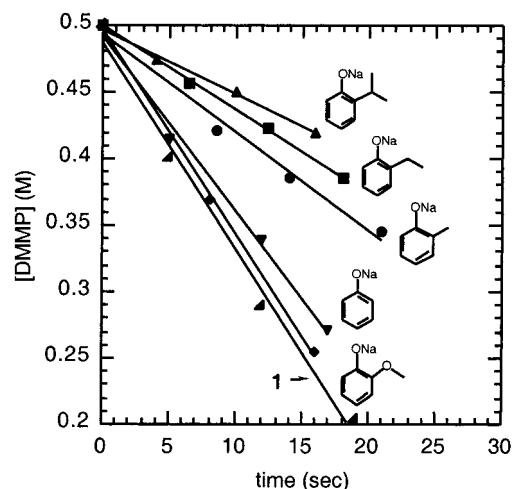
First, we determined the v_{initial} and longevity of different ratios of NaOt-Bu and NaOC₆H₄-4-*t*-Bu, with the goal of assessing the relative reactivity of the clusters that were observed in Figure 4 (Table 2). While the differences in initial rates are subtle and ultimately do not allow this distinction to be made, the differences in catalyst longevity are striking, as only the 1:3 and 1:7 alkoxide/aryloxide mixtures provide catalysts that significantly approach equilibrium (eq 2). On the basis of an analysis previously put forward,⁴ we ascribe this increased longevity to a shifting of the clusters to more soluble aryloxide-rich catalysts. Under aryloxide-poor conditions, the catalysts precipitate prior to establishing equilibrium.

We also wished to determine if electronic and steric variations in the aromatic additive led to systematic trends in catalyst activity. Overall, the aryloxide effect

(20) Initial reaction conditions are 0.5 M DMMP, 1.0 M isopropyl acetate in a 1:40 v/v mixture of tetrahydrofuran/pentane, and 1 mol % catalyst.

(21) Kissling, R. M.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 1585–1590.

(22) The concentration of diisopropyl methylphosphonate, DIMP, after 2 h of reaction time.

**Figure 6.** Initial loss of DMMP for the reaction in eq 2 with different **2**. Initial reaction conditions: 0.50 M DMMP, 1.00 M *t*-PrOAc, 1 mol % NaO^tBu, 3 mol % NaOAr, in 1:25 v/v THF/pentane.**Table 3.** Initial Reaction Rates (relative to **1**) and [DIMP]_{2h} for Catalysis of Eq 2 with Various **2**

catalyst, 1, 2 (Ar =)	v_{initial}^a (rel to 1)	[DIMP] _{2h} ^b (M)	catalyst, 1, 2 (Ar =)	v_{initial}^a (rel to 1)	[DIMP] _{2h} ^b (M)
1	1	0.17	3-Cl	1.25	0.17
2-Me	0.47	0.14	3-CF ₃	1.16	0.17
2-H	0.84	0.14	3-Br	1.13	0.16
2-Et	0.4	0.12	3-F	1.06	0.17
2- ⁱ Pr	0.31	0.07	2-Np ^c	0.84	0.14
2- <i>t</i> -Bu	0.35	0.05	6-Br-2-Np	1.19	0.16
2-OMe	0.99	0.09	4-OMe	1.08	0.17
2-F	0.99	0.11	4-F	1.11	0.18
2-NH ₂	0.81	0.15	4-Cl	1.05	0.16
2-Cl	0.56	0.13			

^a v_{initial} for **1** = 0.0155 M sec⁻¹. ^b Concentration measured after 2 h; [DIMP]_{equilibrium} = 0.19 M. ^c Np = naphthyl.

was found to be modest (4-fold range in initial rates), though several stereoelectronic trends emerged. Figure 6 tracks DMMP loss for several 2-substituted catalysts. Not surprisingly, ortho substituents tended to slow the catalyst (H > Me > Et > *i*-Pr ~ *t*-Bu), although hetero-substituents such as OMe, F, or NH₂ partially or completely compensated for the size effect. Electron-donating substituents at the m- or p-position modestly improved the activity, while electron-withdrawing groups (e.g., 3-Cl, 3-CF₃, 3-Br) were more strongly activating. The most active catalysts were 3-Cl, 3-CF₃ phenol, and 6-Br-2-naphthol, each of these also achieving near-equilibrium conditions after 2 h. While the steric effect can most easily be ascribed to an inhibition of substrate prebinding, the electronic effect is less easily rationalized. The rate acceleration observed with 2-heterosubstituents is curious; for example, 2-OMe, 2-NH₂, and 2-F each have a v_{initial} that is comparable to **1** (only 2-OMe is shown in Figure 6).²³ The initial rate of 2-OMe is about twice that of the 2-ethyl and 2-Cl despite having an A-value²⁴ that

(23) While it is tempting to speculate that α -heteroatom chelation to the sodium center is the source of the rate enhancement, a chemically convincing kinetic role for such an event is speculative at best. Examples of ground-state chelation of the alkali metal can be found in refs 5c and 6f,l,n.

(24) (a) Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139–194. (b) Buchanan, G. W.; Webb, V. L. *Tetrahedron Lett.* **1983**, *24*, 4519. (c) Schneider, H.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579.

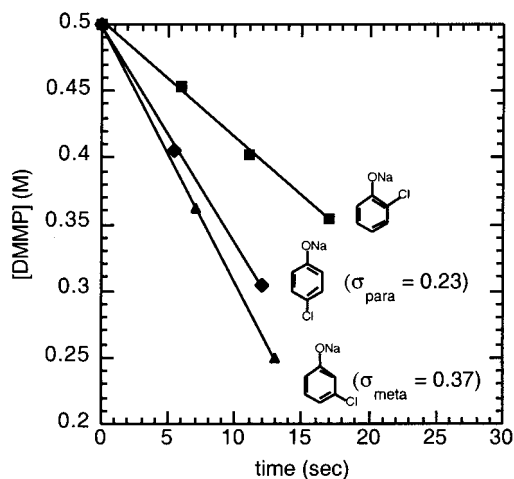


Figure 7. Initial loss of DMMP for the reaction in eq 2 for chloro-substituted **2**.

is intermediate between the two. Further evidence that the position of a given substituent impacts the initial rates is well illustrated by the 2-, 3-, and 4-chloro substituted catalysts (Figure 7).

Conclusions

Mixed alkali metal alkoxide/aryloxide catalysts for the ester interchange reaction exist as a mixture of tet-

rameric clusters under reaction conditions as evidenced by VPO and low-temperature NMR studies. For para- and meta-substituted aryloxides, the mixed cluster populations fit a statistical model of the possible two-component tetramers, while mixed catalysts with bulky ortho substituents do not. The activities of catalyst mixtures as described by ν_{initial} , both from the standpoint of alkoxide/aryloxide ratio and aryloxide structure, are similar, as the more aryloxide-rich catalyst mixtures are significantly more robust. Although mechanistic interpretation of electronic effects is complicated by a non-linear free energy relationship, a screening of aryloxide additives has identified several new catalysts with slightly improved performance.

Acknowledgment. Financial support from the Army Research Office (DAAD190110526) and Union Carbide (Innovation Recognition) is gratefully acknowledged. M.R.G. is a Camille Dreyfus Teacher Scholar (2000). R.M.K. is a GAANN Fellow (2000/2001).

Supporting Information Available: Experimental details, statistical methods, and treatment of NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO016105H