Degenerate Transesterification of Dimeric Lithium 2,4,6-Trimethylphenolate and a Further Observation on the Reaction of Tetramers[1]

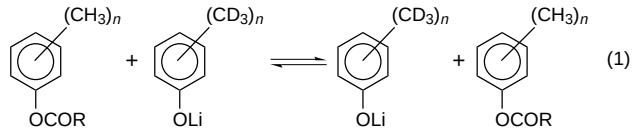
Lloyd M. Jackman* and Xian Chen

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received January 10, 1997. Revised Manuscript Received May 1, 1997[⊗]

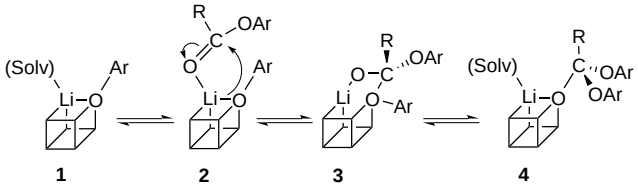
Abstract: The rates of exchange of the 2,4,6-trimethylphenolate ion between dimeric lithium 2,4,6-trimethylphenolate-d_9 and a series of 2,4,6-trimethylphenyl esters [2,4,6-$(CH_3)_3C_6H_2COOCH_2R$; R = CH_2CH_3, CH_3O, Ph, 4-CH_3Ph, 4-CF_3Ph, 4-ClPh, 4-CH_3OPh, 2-pyridyl, and 4-pyridyl] have been determined in dioxolane, THF, 1,2-dimethoxyethane, and pyridine. The reactions are first order in the lithium phenolate showing that the dimer reacts without dissociation. The rates of transesterification increase with increasing solvent donicity in contrast to the reaction of tetrameric lithium 3,5-dimethylphenolate. For all the esters, except R = 2-pyridyl, the rates of transesterification exhibit a linear correlation with their rates of hydrolysis. The 2-pyridyl ester exhibits an abnormally high rate of transesterification, which is attributed to a complex-induced proximity effect. Tetrameric lithium 3,5-dimethylphenolate undergoes transesterification less rapidly in the presence of hexamethylphosphoric triamide (0.25−1.6 equiv), a result consistent with a mechanism involving initial coordination of the ester to a lithium ion in the tetramer.

As part of an investigation of the role of aggregates of organic lithium compounds in their reactions with electrophiles in weakly polar aprotic solvents, we reported a study of the degenerate transesterification (eq 1) of lithium 3,5-dimethylphenolate.[2]

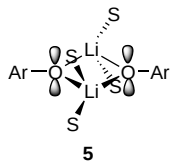


In solution this salt forms a hexamer, tetramer, or dimer, or mixtures thereof, depending on the solvent and temperature. We showed that each of these species can function as a true reactant in transesterification, and we studied reactions of the tetramer in detail. The principal features of the transesterification of the tetramer are that the reactions are first order in tetramer and their rates decrease with increasing Lewis basicity of the solvent. This led us to suggest the mechanism outlined in Scheme 1 in which the first step is the replacement of a solvent molecule of the tetramer **1** by the carbonyl oxygen atom of the ester. The tetrahedral intermediate in esterification, **3**, can then be formed intramolecularly from the new solvate **2**. Interchange of the aryloxy groups probably occurs through collapse of **3** to the hemiorthoester **4**. The concept that the ester cannot directly attack the putative phenolate ion in the tetramer is further supported by the observation of substantial complex-induced proximity effects[3] (CIPE) that we observed for esters having an additional Lewis base center in proximity to the ester group. It appears that the cubic structure of the tetramer is strongly preserved in this system and that more open structures (e.g., ladder structures), which would allow direct attack by an oxygen lone pair of electrons on the carbonyl carbon atom of the ester, are kinetically insignificant.

Scheme 1



We now consider the transesterification of a dimeric lithium phenolate. In a dimer, one electron lone pair on oxygen is exposed and is thus available to directly attack the carbonyl carbon atom of the ester. We have therefore studied the transesterificaton of lithium 2,4,6-trimethylphenolate, which exists almost exclusively as a dimer **5** in the solvents of interest, with a series of esters of the type 2,4,6-$(CH_3)_3C_6H_2COOCH_2R$, **6**.[4] We present evidence that prior coordination of the ester to lithium is of considerably less importance in the reactions of the dimer than in that of the tetramer.



5

We take this opportunity to further emphasize the crucial role of coordination in the transesterification of tetrameric lithium 3,5-dimethylphenolate by showing that the reaction is inhibited by the addition of hexamethylphosphoric triamide (HMPA). This cosolvent is generally expected to dissociate aggregates to more

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

(1) Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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

(3) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *11,* 356.

(4) The differences between ^{13}C chemical shifts of the phenolate and those of the corresponding anisole are very similar to those observed for lithium 2,6-dimethylphenolate, which is firmly established as existing as the dimer in the solvents of interest.[5] The latter phenol was not used because competitive C-acylation at the *para* position became a problem with more reactive esters.

(5) Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105,* 4177.

S0002-7863(97)00087-5 CCC: $14.00

reactive species, but for this particular system we showed[6] that it fully solvates the tetramer and stabilizes it relative to lower aggregates. Since the ester competes unfavorably with HMPA for the lithium sites of the tetramer, the transesterification is retarded.

Experimental Section

NMR spectra were obtained with a Bruker AM360 spectrometer, which was also used for all the studies of the kinetics of tranesterification. UV spectra and rates of hydrolysis were obtained with a Perkin-Elma Lambda 4C spectrophotometer.

Materials. Dioxolane, THF, and dimethoxyethane (DME) were refluxed over sodium containing sodium benzophenone ketyl and removed by distillation immediately prior to use. Pyridine (Fischer) was stored over sodium hydroxide and then fractionated from calcium hydride immediately prior to use.

[$^2H_9$]-Trimethylphenol. A previously described adaptation[2] of a general method of deuteration developed by MacDonald and Shannon[7] was used. 2,4,6-Trimethylphenol was rigorously purified by recrystallization from hexane followed by sublimation. A heterogeneous mixture of the phenol (8 g, 0.058 mol), 60% nickel on kieselguhr (3 g, Aldrich Chemical Co.), and D_2O (80 mL) was heated at 95 °C in a nitrogen atmosphere with constant agitation for 48 h. The phenol was extracted with diethyl ether and the extent of deuteration of the methyl groups was checked by ^{1}H NMR. After four such treatments, the deuterium content of the methyl groups was >99%. The recovered phenol (6 g) was sublimed before use.

Synthesis of 2,4,6-Trimethylphenyl Esters. 2,4,6-Trimethylphenyl Butyrate (6a). 2,4,6-Trimethylphenol (13.0 g, 0.095 mol) was dissolved in a 1:3 mixture (40.0 mL) of anhydrous pyridine and diethyl ether. Butyryl chloride (10.0 g, 0.094 mol) was added dropwise with stirring to this solution at 0 °C. The yellowish solution was stirred for 1 h, then water (100 mL) and ether (100 mL) were added. The aqueous layer was separated, and the ethereal layer was extracted by cold 5% NaOH (3 × 30 mL). The resulting ethereal layer was washed by water (2 × 30 mL). After drying ($MgSO_4$), the solvent was removed by evaporation. The remaining oily product was distilled (79 °C/0.1mmHg), giving 2,4,6-trimethylphenyl butyrate (9.1 g, 46% yield) as a colorless liquid: IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.87 (2H, s), 2.58 (2H,5), 2.28 (3H, s), 2.12 (6H, s), 1.82 (2H, q), 1.08 (2H, t). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.66: H, 8.73. Found: C, 75.80; H, 8.64.

2,4,6-Trimethyphenyl Methoxyacetate (6b). Methoxyacetyl chloride (5.0 g, 0.046 mol) was treated with 2,4,6-trimethlyphenol (10.0 g, 0.073 mol) in a 1:3 mixture (40 mL) of anhydrous pyridine and diethyl ether. After workup and distillation, 2,4,6-trimethylphenyl methoxyacetate (9.8 g, 87.5%) was obtained as white solid (mp 42−44 °C). The solid was recrystallized from anhydrous hexane (10 mL) to afford white crystals: mp 44 °C; IR 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.66 (2H, s), 4.31 (2H, s), 3.52 (1H, s), 2.24 (3H, s), 2.10 (6H, s). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.86; H, 7.82. Found: C, 70.12; H, 8.01.

2,4,6-Trimethyphenyl 4-Pyridylacetate (6i). 4-Pyridylacetyl chloride hydrochloride (5.0 g, 0.029 mol) and 2,4,6-trimethyphenol (3.9 g, 0.028 mol) were dissolved in anhydrous pyridine (200 mL), and dicyclohexylcarboxydiimide (DCC) (6.0 g, 0.029 mol) was added to the stirred solution. After the mixture was stirred for 24 h under a nitrogen atmosphere, diethyl ether (200 mL) was added and the mixture filtered. The filtrate was extracted repeatedly with cold 5% NaOH solution (6 × 50 mL), then wash with water (4 × 50 mL). After drying ($MgSO_4$), the solvent was evaporated and the crude yellowish oily residue (3.2 g) was purified by flash chromatography (100% diethyl ether as a eluent). The recovered product (2.5 g) crystallized as a light-yellow solid on standing at −15 °C Two recrystallizations from petroleum ether (bp 60−80 °C) afforded the pure ester (1.8 g, 21%) as light yellow crystals: mp 52.4−53 °C; IR 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$) d (2H, d), 7.35 (2H, d), 3.86 (2H, s), 2.22 (3H, s), 1.97 (6H, s). Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.68; H, 6.64.

2,4,6-Trimethylphenyl 2-Pyridylacetate (6h). A solution of 2-pyridylacetic acid hydrochloride (5 g, 0.029 mol) and 2,4,6-trimethylphenol (3.9 g, 0.023 mol) in anhydrous pyridine (200 mL) was added dropwise to DCC (6.0 g, 0.029 mol). After 24 h of stirring the mixture was worked up as for **6i** to give a crude oily product (2.9 g, 34.5% yield). Purification by flash chromatography (100% diethyl ether), followed by recrystallization from petroleum ether, afforded the 2-pyridylacetate as pale yellow crystals (1.8 g, 21.4%): mp 51 °C; IR 1767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.62 (1H, d), 7.80 (1H, t), 7.50 (1H, d), 7.30 (1H, 5), 6.81 (2H, s), 4.20 (2H, s), 2.25 (3H, s), 2.02 (6H, s). Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.29; H, 6.95.

2,4,6-Trimethylphenyl Phenylacetate (6e). Dicyclohexylcarbodiimide (DCC, 4.5 g, 0.022 mol) was slowly added to an anhydrous diethyl ether (50 mL) solution of phenylacetic acid (3.0 g, 0.022 mol) and 2,4,6-trimethylphenol (3.0 g, 0.022 mol). The solution was stirred for 24 h, The white precipitate of the urea was removed by filtration, and the ether solution was washed with cold, aqueous NaOH (4 × 50 mL; 5% w/v) followed by water (3 × 59 mL). The solvent was removed by evaporation and the solid residue was triturated with petroleum ether (20 mL). A further quantity of the urea was removed by filtration. After removal of solvent from the filtrate, distillation of the residue afforded a colorless liquid (bp 125 °C/15 mmHg; 4.0 g, 78% yield) that solidified on standing (mp 34−36 °C). Recrystallization from hexane (5 mL) gave the pure ester (3.5 g, 68%): mp 36−37 °C; IR 1761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (5H, m), 6.60 (1H, s), 2.22 (3H, s), 1.94 (6H, s). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.56; H, 7.18.

2,4,6-Trimethylphenyl 4-Methoxyphenylacetate (6g). 4-Methoxyphenylacetic acid (3.0 g, 0.018 mol), 2,4,6-trimethylphenol (2.6 g, 0.019 mol), and DCC (3.7 g, 0.018 mol) were reacted by following the procedure used for **6g**. After the reaction was complete, the solvent was evaporated and the solid residue was washed with cold acetone. The acetone-insoluble urea was removed by filtration. After removal of the solvent from the filtrate the residue was recrystallized from hexane to give the ester as colorless crystals (2.0 g, 38.5%): mp 48−49 °C; IR 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41 (2H, d), 6.89 (2H, d), 6.79 (2H, s), 3.79 (2H, s), 3.78 (3H, s), 2.20 (3H, s), 1.95 (6H, s). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.92; H, 7.10.

2,4,6-Trimethylphenyl 4-methylphenylacetate (6f). 4-Methylphenylacetic acid (7.0 g, 0.047 mol), 2,4,6-trimethylphenol (6.3 g, 0.047 mol), and DCC (9.6 g, 0.047 mol) were reacted by following the procedure used for **6g**. Recrystallization of the crude product from hexane afforded the ester as a colorless crystal: mp 36−37 °C; IR 1762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (2H, d), 7.20 (2H, d), 3.81 (2H, d), 2.33 (3H, s), 2.21 (3H, s), 1.96 (6H, s). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.56; H, 7.40.

2,4,6-Trimethylphenyl 4-Chlorophenylacetate (6d). 4-Chlorophenylacetic acid (7.6 g, 0.045 mol), 2,4,6-trimethylphenol (6.0 g, 0.044 mol), and DCC (9.0 g, 0.044 mol) were coupled by using the same procedure as for **6g**. After workup and distillation, 2,4,6-trimethylphenyl 4-chlorophenylacetate was obtained as a colorless liquid (bp 153 °C/0.2 mmHg) that solidified on standing. Recrystallization from hexane gave the ester as colorless crystals (7.0 g, 54% yield): mp 84−86 °C; IR 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (2H, s), 7.24 (2H, s), 6.81 (2H, s), 3.82 (2H, s), 2.22 (3H, s), 1.95 (6H, s). Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.71; H, 5.93. Found: C, 70.64; H, 5.87.

2,4,6-Trimethylphenyl 4-Trifluoromethylphenylacetate (6c). 4-Trifluoromethylphenylacetic acid, 2,4,6-trimethylphenol, and DCC were reacted by using the same procedure as for **6e** in anhydrous diethyl ether and hexane (1:5; 100 mL). After workup and distillation (140 °C/0.15 mmHg), recrystallization from hexane afforded the ester as colorless crystals: mp 66−67 °C; IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61 (2H, d), 7.51 (2H, d), 6.62 (2H, s), 3.92 (2H, s), 2.22 (3H, s), 1.96 (6H, s). Anal. Calcd for $C_{18}H_{17}F_3O_2$: C, 67.04; H, 5.28. Found: C, 67.12; H, 5.21.

Rates of Transesterification by Deuterium Exchange. The general procedure described in an earlier paper[2] has been used throughout this study. The reactions were followed by integration of the proton NMR signals of the 2(6)-methyl group.

(6) Jackman, L. M.; Xian Chen *J. Am. Chem. Soc*. **1992**, *114*, 403.

(7) MacDonald, C. G.; Shannon, J. S. *Aust. J. Chem*. **1965**, *18*, 1009; **1967**, *20*, 297.

(8) (a) Maria, P.-C.; Gal J.-F. *J. Phys. Chem*. **1985**, *89*, 1296. (b) Maria, P.-C. Private communication.

Table 1. Second-Order Rate Constants for the Transesterification of Lithium 2,4,6-Timethylphenolate with 2,4,6-Trimethylphenyl 4-Trifluoromethylphenylacetate (0.25 M)

solvent	$-\Delta H(BF_3)$,[a] kcal mol^{-1}	temp,°C	[phenolate], M	10^4k_2, L mol^{-1} s^{-1}
dioxolane	16.5[b]	60	0.50	3.6
		60	0.30	4.3
		60	0.25	2.6
		60	0.20	3.5
		60	0.10	3.0
		40	0.25	0.26
THF	21.6	60	0.54	5.3
		60	0.26	4.6
DME		60	0.50	13
		60	0.20	14
		60	0.13	14
		60	0.050	13
		40	0.26	0.54
pyridine	30.6	40	0.50	6.5
		40	0.25	5.0
		40	0.13	5.2

[a] Reference 8a. [b] Reference 8b.

Rates of Ester Hydrolysis and Ethanolysis. Hydrolyses were carried out by using sodium hydroxide in aqueous ethanol (33% v/v) and ethanolyses with potassium hydroxide in anhydrous ethanol.

In a typical experiment, an aliquot (1.00 mL) of an aqueous NaOH (or anhydrous ethanolic KOH) stock solution (0.045 M) was added to a solution of the ester in ethanol (2.0 mL; 4.5×10^{-4} M) in a 1-cm cuvette at 42 °C. The large excess of alkali ensured pseudo-first-order kinetics. The production of the phenolate ion was followed by monitoring the absorbance at 298 nm. The pseudo-first-order rate constants were obtained by fitting the absorbance *vs* time data to the equation $A_t = A_0 + A_\infty(1 - e^{-kt})$ by the method of nonlinear least squares.

Results

Determination of the Kinetic Order in Lithium Phenolate. Deuterium-labeled lithium 2,6-dimethylphenolate was used for all experiments. The details of the kinetic analysis have been presented previously.[2] Briefly, the extent of exchange (x_t) at time t is given by eq 2, where $I_{phenolate}$ and I_{ester} are intensities of the proton resonances of the 2(6) methyl groups of the phenolate and ester, respectively. The first order rate constant for exchange (k′) is obtained from eq 3 from x_t *vs* t data by evaluating x_0, x_e (the value of x_t at equilibrium), and k', using the method of nonlinear least squares. The rate of transesterification is then given by eq 4, and k_2 is the second-order rate constant assuming that dimeric lithium phenolate is the reactant. The errors in the values of k_2 are <10%.

$$x_t = I_{phenolate}/(I_{phenolate} + I_{ester}) \quad (2)$$

$$x_t = (x_t - x_e)/(x_0 - x_e)e^{-k't} \quad (3)$$

$$\text{rate} = (x_0 - x_e)k' = k_2[\text{ester}][\text{phenolate}]/2 \quad (4)$$

The apparent second-order rate constants for the transesterification in four different solvents are presented in Table 1. Since their values are independent of lithium phenolate concentration and since the overwhelming predominant lithium phenolate species is the dimer,[4] we conclude the dimer reacts without prior dissociation to less aggregated species. If the reaction involved initial dissociation, the rates would be proportional to [phenolate]$^{1/2}$ and the apparent rate constants calculated by eq 4 would vary by a factor of 2.2 for a change in phenolate concentration from 0.5 to 0.1 M and by 3.2 for a change of 0.5 to 0.05 M.

Solvent Effects on Rates of Transesterification. In our study of the transesterification of lithium 3,5-dimethylphenolate we showed the rates of the tetrameric species increased with *decreasing* Lewis basicity of the solvent (Table 2). We interpreted this result as indicating that the first step in the reaction involves a rapid, reversible displacement of one of the lithium-bound solvent molecules of the tetramer by the carbonyl oxygen atom of the ester (Scheme 1). The effect of the change in Lewis basicity of the solvent is probably attenuated by the presence of the solvent molecules on the other two lithium atoms attached to the phenolate oxygen atom, the assumption being that better donor solvents will enhance the nucleophilicity of the phenolate.

Table 2. Effects of Solvents on the Relative Rates of Transesterification of Tetrameric and Dimeric Lithium Phenolates

	3,5-dimethylphenolate		2,6-dimethylphenolate		$\Delta H(BF_3)$,
solvent14	tetramer	dimer	40 °C	60 °C	kcal mol^{-1}
Dioxolane	3.9		0.5	0.3	16.4
THF	2.0			0.4	21.6
DME	(1.0)	(1.0)	(1.0)	(1.0)	
Pyridine	0.7	1.3	9.2		30. 8

Table 3. Second-Order Rate Constants, k_2 (L mol^{-1} s^{-1}), and Relative Rate Constants, k_{rel}, for the Transesterification with 2,4,6-$(CH_3)_3C_6H_3OLi$ in Dioxolane and Hydrolysis in 33% Aqueous Ethanolic NaOH of the Esters, 2,4,6-$(CH_3)_3C_6H_2COOCH_2R$, **6**

		transesterification		hydrolysis	
compd	R	10^4k_2	k_{rel}	10^4k_2	k_{rel}
6a	(CH_2CH_3)	0.10	(1.0)	19 ± 4	(1.0)
6b	(CH_3O)	31	310	2370 ± 16	125
6c	(4-CF_3Ph)	2.6	26	335 ± 9	18
6d	(4-ClPh)	1.8	18	210 ± 8	11
6e	(Ph)	0.72	7.2	69 ± 3	3.6
6f	(4-CH_3Ph)	0.51	5.1	61 ± 1	3.2
6g	(4-CH_3OPh)	0.29	2.9	57 ± 3	3.0
6h	(2-Pyridyl)	17	170	264 ± 16	14
6i	(4-pyridyl)	3.2	32	636 ± 18	34

The rate constants in Table 1 allow an assessment of the effect of the Lewis basicity of the solvent for the reaction of a dimeric lithium phenolate and the findings are summarized in Table 2. In contrast to the findings for tetrameric lithium 3,5-dimethylphenolate, the rate of transesterification of the dimer is increased by increasing solvent Lewis basicity. A possible explanation for this behavior is that the putative phenolate ion in the dimer, in contrast to that in the cubic tetramer, has an exposed lone pair of electrons on oxygen and can therefore directly attack the carbonyl carbon atom without prior coordination of the ester to the lithium cation. The effect on increasing Lewis basicity is then confined to the weakening of the Li−OAr, resulting in increased nucleophilicity of the phenolate. This description neglects a possibly significant contribution of the interaction of the developing negative charge on the carbonyl carbon atom with the incipient positive charges of the two lithium cations. The importance of such a contribution would depend, among other factors, on the electronic and steric nature of the attached solvent molecules.

Complexed-Induced Proximity Effects (CIPE). The importance of the initial attachment of the ester to the cubic tetramer in the transesterification of lithium 3,5-dimethylphenolate was further substantiated by the observation that esters of the type RCH_2CO_2Ar, in which R has a Lewis base center in the vicinity of the carbonyl group, are abnormally reactive.[2] For esters lacking such centers, there is a linear free energy relation between their rates of transesterification and those for their hydrolysis by 30% aqueous ethanolic sodium hydroxide. Thus the deviations from this relationship observed for the R's with proximal Lewis base centers provided a measure of their CIPE. The largest CIPE's were observed for R = OCH_3 and 2-pyridyl, which were found to lower the free energy of activation by 1.7 and 2.2 kcal mol^{-1}, respectively. We have

Table 4. Comparison of the Rates of Hydrolysis in 33% Aqueous Ethanolic Sodium Hydroxide and Ethanolysis in Anhydrous Ethanolic Potassium Hydroxide for Two Substituted Acetates of 3,5-Dimethylphenol at 42 °C

ester	$10^4k(HO^-)$	$10^4k(EtO^-)$	$k(EtO^-)/k(HO^-)$
6b (−OCH_3)	2,370	3320	1.4
6d (−*p*-ClPh)	201	243	1.2

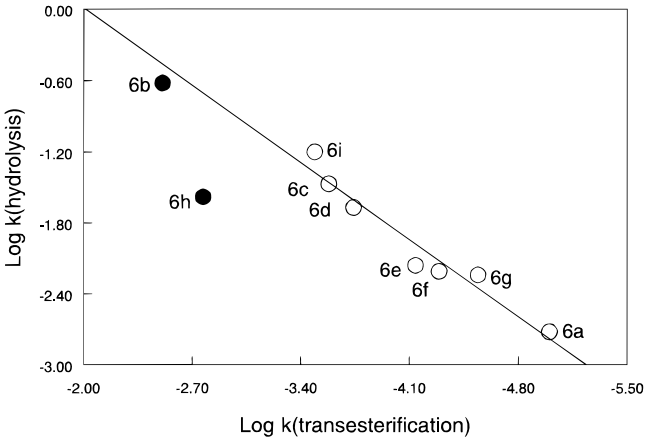
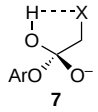


Figure 1. Relation between the rates of hydolysis and transesterification for the 2,4,6-trimethylphenyl esters listed in Table 3.

now considered the possibility that the apparent CIPE might, in fact, be due to the retardation of the rate of hydrolysis rather that accelerations of transesterification. The former could arise if the second Lewis base center becomes involved in hydrogen bonding to the hydroxyl proton in the tetrahedral intermediate formed in ester hydrolysis (e.g. **7**). Comparison (Table 3) of the rates of hydrolysis of the 4-chlorophenylacetate and 2-methoxypropionate esters of 3,5-dimethylphenol in aqueous ethanolic sodium hydroxide with those of their sodium ethoxide catalyzed ethanolysis in anhydrous ethanol, for which the intermediates have no hydroxyl group, indicates the absence of any special effect in the hydrolysis of the 2-methoxypropionate.



7

The rates of transesterification of a similar series of esters of 2,4,6-trimethylphenol are given in Table 4, together with those of their hydrolysis in aqueous ethanolic sodium hydroxide. There is a linear free energy relationship between the two reactions for the compounds **6a,c**−**h** (Figure 1). In contrast to the transesterification of tetrameric lithium 3,5-dimethylphenolate, the *β*-methoxypropioniate, **6b**, falls close to the same straight line and therefore does not exhibit a CIPE. This result is also consistent with a mechanism involving direct attack on the carbonyl carbon atom of the ester by the available electron pair of the phenolate ion without prior association of the reacting entities. The 2-pyridyl derivative, **6h**, does exhibit an enhanced rate of transesterification corresponding to a lowering of $\Delta G^{\ddagger}$ of 1 kcal mol^{-1} compared to 2.2 kcal mol^{-1} for the reaction of the tetrameric system. Thus, only the reaction of **6h**, which has the strongest basic center, appears to involve prior coordination.

The Effect of Hexamethylphosphoric Triamide (HMPA) on the Rate of Transesterification of Tetrameric Lithium 3,5-Dimethylphenolate. It is well-known that the addition of even small amounts of HMPA often catalyzes the reactions of organic lithium salts with electrophiles in weakly polar aprotic solvents.[9,10] This may be attributed to deaggregation or ionization induced by the strongly cation solvating co-solvent. In the seminal paper on the importance of aggregation in lithium enolate chemistry, Seebach, Amstutz, and Dunitz[11] considered an alternative explanation (Scheme 2) for the increased rates and altered regiochemistry for reactions of tetrameric lithium enolates with electrophiles produced by the addition of HMPA. In this mechanism, the HMPA first replaces a solvent molecule attached to lithium and then switches place with a phenolate ion. The latter then has unencumbered lone pairs of electrons that, as in the case of the dimer discussed above, can interact directly with electrophiles. We now show that, at least for transesterification, this second mechanism is not operative.

Scheme 2

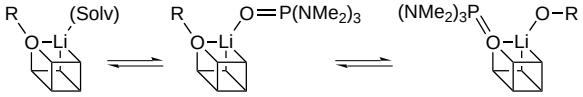


Table 5. Second-Order Rate Constants for the Transesterification of Lithium 3,5-Dimethylphenolate (0.25 M) with 3,5-Dimethylphenyl-2-furoate (0.25 M) in THF at 45 °C in the presence of HMPA

HMPA (equivalents)	10^4k_2, L mol^{-1} s^{-1}
0	2.21
0.25	1.98
0.75	0.9
1.6	0.73

We have demonstrated[6] that progressive addition of HMPA to tetrameric lithium 3,5-dimethylphenolate, in either diethyl ether or THF, first replaces the four solvent molecules attached to lithium. In THF observable (by NMR) dissociation of the tetramer occurs only with greater amounts (>2 equiv) of HMPA. The proposed mechanism for transesterification of the tetramer (Scheme 1) involves the initial coordination of the ester to lithium, and this will be energetically unfavorable for lithium with HMPA attached. Thus, unless the mechanism in Scheme 2 is available, the addition of small amounts of HMPA should retard rather than catalyze the reaction. The effects of the additions of HMPA on the rate of a typical transesterification of lithium 3,5-dimethylphenolate are shown in Table 5. Remarkably, *addition of HMPA retards transesterification*. We conclude that the mechanism in Scheme 2 is not operative. The results in Table 5 cannot be readily discussed in quantitative terms. Our earlier studies[6] showed that the addition of HMPA to lithium 2,4,6-dimethylphenolate in THF generates a series of solvated tetramers $Li_4(OAr)_4{\cdot}(HMPA)_n(THF)_{4-n}$, where n = 1 to 4. Even with 2 equiv of HMPA, some of the $n = 3$ species is still present. The ester can, of course, replace THF in the $n = 1$, 2, or 3 species. The resulting complexes possibly undergo the transesterification step more readily because the strong solvation of neighboring lithium cations by HMPA will make the phenolate ions more nucleophilic. We also found that, with more than 2 equiv of HMPA, dissociation of the tetramer to smaller and presumably more reactive aggregates occurs. For these reasons, the data in Table 5 only provide a qualitative demonstration that additions of small ratios of HMPA retard tranesterification.

Acknowledgment. We gratefully acknowledge support for this work by a grant (CHE-9102732) from the National Science Foundation.

JA970087X

(9) Normant, H. *Bull Soc. Chim. Fr*. **1968**, 761.
(10) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 285 and references cited therein.
(11) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.