Degenerate Transesterification of 3,5-Dimethylphenolate/3,5-Dimethylphenyl Esters in Weakly Polar, Aprotic Solvents. Reactions of Aggregates and Complex-Induced Proximity Effects

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Abstract: The rates of exchange of the 3,5-dimethylphenolate ion between lithium 3,5-dimethylphenolate-d_6 and a series of 3,5-dimethylphenyl esters have been determined in the weakly polar, aprotic solvents dioxolane, dimethoxyethane (DME), tetrahydrofuran (THF), and pyridine. The esters include the propionate, butyrate, methoxyacetate, β-methoxypropionate, 4-methoxybutyrate, 2-tetrahydrofuroate, 2-furoate, (*N*,*N*-dimethylamino)acetate, (methylthio)acetate, 2- and 4-pyridinecarboxylates, 2-pyridylacetate, 4-pyridylacetate, phenylacetate, and *p*-methoxy-, *p*-chloro-, and *p*-(trifluoromethyl)phenylacetates. The rates and kinetic orders of the reactions of 3,5-dimethylphenyl propionate in various solvents at 35 °C gave the following second-order rate constants (10^4k_2, L mol^{-1} sec^{-1}) for the following major aggregate species: THF tetramer, 6.5; DME tetramer, 3.3 (40 °C); dioxolane, 13, hexamer, 71; pyridine tetramer, 2.2, dimer, 29. For 3,5-dimethylphenyl β-methoxypropionate, the order of reactivity is dioxolane > DME > THF. These results are interpreted in terms of a preequilibrium in which a solvent on lithium in the tetramer is replaced by the ester. The rates of transesterification have been compared with the rates of hydrolysis in 30% aqueous ethanol for the above series of esters. Those esters that have a second Lewis base center proximal to the ester function show significantly increased reactivity in transesterification, which is attributed to a complex-induced proximity effect.

There is a growing body of evidence indicating that, in nonpolar and weakly polar solvents (ethers, tertiary amines), organolithium compounds[1,2,3] and lithium enolates,[3,4] phenolates,[5] and their nitrogen analogues[2,6] usually exist as aggregated contact ion pairs (dimers, tetramers, hexamers, and even higher oligomers). What is less well understood is the extent to which aggregates are primary reactants in reactions with electrophiles. This problem is especially significant in the nucleophilic reactions of organolithium compounds, dimeric lithium amides, and the cubic tetramers of lithium enolates and phenolates since, in these systems, all p orbitals containing lone pairs of electrons are directed toward

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Li cations and cannot take part in the accepted transition states of processes such as S_N2 displacements, additions to carbonyl groups, etc. Thus, identification of the nature of the primary reactant is the crucial step in all mechanistic studies in this area.

The question of the primary reactant has most frequently been addressed for reactions of lithium alkyls and aryls in nonpolar and weakly polar solvents. In hydrocarbon solvents in which hexamers and tetramers often prevail, dissociation to monomers appears to be involved,[7] although, in the case of additions to carbonyl groups[8] and α'-lithiation of carboxamides,[9] the kinetic form of the reactions is complicated by prior complexation between the two substrates and the mechanistic picture is less clear. Similarly, reactions of butyllithium in both diethyl ether and tetrahydrofuran (THF) with a variety of substrates are fractional-order with respect to the butyllithium, indicating they involve a predissociation step,[10] an exception being the addition to methyl trifluoroacetate, which is first-order.[10a] Other organolithium compounds, which are known to be aggregated under the reaction conditions, exhibit similar behavior.[11] McGarrity and his coworkers,[12] however, have produced unequivocal evidence that both tetrameric and dimeric butyllithium in THF at −85 °C can react with either benzaldehyde (addition) or cyclopentadiene (proton transfer) without prior dissociation. These workers, using a rapid-injection NMR technique,[13] were able directly to observe the simultaneous reactions of the two aggregates because both processes occur faster than the interaggregate exchange. With benzaldehyde, the tetramer reacts ~10 times slower than the dimer.

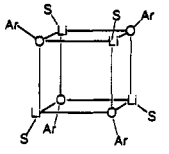
The only studies of nitrogen derivatives are those of Collum and his co-workers.[6n] They have shown that lithium diphenylamide in benzene/THF forms a mixed dimer with LiBr, which at low THF concentrations undergoes N alkylation more rapidly than $(Ph_2NLi)_2$ itself. As the ratio of THF is increased, both species dissociate to the more reactive, monomeric Ph_2NLi. Ultimately, at high enough THF ratios, the free anion becomes the reactant. Dissociation of oligomers to monomers appears to be involved in the mechanism of alkylation of the lithiated *N,N*-dimethylhydrazone of cyclohexanone in benzene/2-methyltetrahydrofuran mixtures.[14]

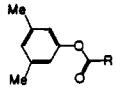
Although there are many studies that indicate that ion pairing and/or aggregation in weakly polar aprotic solvents can dramatically affect both the regio- and stereochemistry of the reactions of lithium enolates with electrophiles, in general little or nothing is known about the structures of the actual species undergoing reaction with the electrophile. Seebach,[4e] for example, has clearly demonstrated the involvement of mixed amide/enolate aggregates in enantioselective aldol reactions and Michael additions of lithium enolates in the presence of an optically active lithium amide, but it is not known whether the reactive species is a tetramer or a dimer. Similarly, aggregates and mixed aggregates are implicated in the control of regiochemistry in the alkylation of simple lithium enolates, but again the identities of the reacting species have not been established.[4a,f]

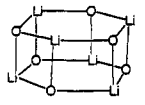
A number of factors complicate the study of kinetics of reactions of lithium enolates. These include changes in aggregation during the reaction, formation of mixed aggregates with product salts,[4f] and the concurrent formation of products from reactions at the C and O termini. In this paper, we describe studies of a model system that avoids these complications. The model consists of the degenerate transesterifications of lithium 3,5-dimethylphenolate (**1**) with a variety of 3,5-dimethylphenyl esters (**2**) in weakly polar, aprotic solvents, reactions that can be conveniently followed by isotopic exchange (eq 1). Carbon acylation of the

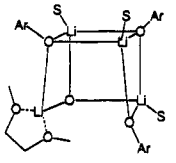
(1)

phenolate is completely repressed, and no change of the state of aggregation or formation of mixed aggregates can occur. The phenolate exists predominantly as the tetramer **3** in this class of solvent, and the transesterification is therefore a good model for O acylation of lithium enolates. While this latter reaction is not a particularly important one in synthetic organic chemistry, the results of our studies have some bearing on the mechanisms of aldol-type reactions. In particular, we report observations in-









dicating that the transesterification involves an initial coordination of the ester to the lithium cations in the tetrameric phenolate. Interaction between the lithium cation and carbonyl oxygen atom has been postulated as being responsible for the observed stereoselectivities in the aldol reactions of lithium enolates,[15] under conditions for which these reagents are expected to be aggregated. We will also show that the presence of another Lewis base center in the substituent R of the ester **4** can profoundly influence the rates of transesterification.

Experimental Section

NMR spectra were obtained with Bruker WP200 or AM360 spectrometers, the latter being used for all the kinetic studies of transesterification. UV spectra and rates of hydrolysis were obtained with a Perkin-Elmer Lamda 4C spectrophotometer.

Materials. Dioxolane, THF, and dimethoxyethane were refluxed over sodium benzophenone ketyl and removed by distillation immediately prior to use. Pyridine (Fischer) was stored over sodium hydroxide and then fractionated, immediately before use, from calcium hydride with use of a 20-in. Fenske column packed with glass rings.

Lithium 3,5-Dimethylphenolate. Stock solutions were prepared by the previously described vacuum-line method.[5c]

3,5-Dimethylphenol-d_6. The following procedure was adapted from the work of Macdonald and Shannon.[16]

The 3,5-dimethylphenol was rigorously purified by recrystallization from hexane followed by sublimation. Under a nitrogen atmosphere, a heterogeneous mixture of the phenol (12 g, 0.1 mol), 60% nickel on kieselguhr (5.0 g, Aldrich Chemical Co.), and D_2O (100 mL) was heated to just below reflux with constant agitation. After 48 h, the reaction was stopped, the phenol separated via continuous extraction with diethyl ether, and the extent of deuteration determined by ^1H NMR. This procedure was repeated four times to afford complete deuteration of the methyl positions. The ^1H NMR also showed evidence of partial ring deuteration, particularly at the ortho positions. These positions were

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effectively exchanged back to hydrogen by dissolving the phenol in 5% aqueous NaOH (100 mL) and heating the solution to just below reflux for 24 h. The recovered phenol (8.3 g) was then purified by sublimation. The final levels of deuteration were determined by comparing the ^1H NMR intensities with an equimolar amount of 2,6-dimethylphenol. The methyl positions were greater than 99% deuterated, the ortho positions 8% deuterated, and the para position less than 5% deuterated.

Synthesis of 3,5-Dimethylphenyl Esters. 3,5-Dimethylphenyl Propionate. 3,5-Dimethylphenol (15 g, 0.12 mol) was dissolved in 10% aqueous KOH (150 mL) and the solution cooled in an ice bath. Propionyl chloride (10 g, 0.11 mol) was added dropwise with stirring and the mixture stirred for 1 h. After extraction with diethyl ether, the extracts were washed with 5% NaOH and dried ($MgSO_4$), and the solvent was removed to leave an oil, which upon distillation (57 °C (0.1 mmHg)) yielded 3,5-dimethylphenyl propionate (5 g, 23%) as a colorless liquid: IR 1762 cm^{-1}; ^1H NMR ($CHCl_3$) δ 6.87 (1 H, s), 6.71 (2 H, s), 2.58 (2 H, q, J = 7.0 Hz), 2.32 (6 H, s), 1.27 (3 H, t, J = 7.0 Hz). Anal. ($C_{11}H_{14}O_2$) C, H.

3,5-Dimethylphenyl Butyrate (4a). 3,5-Dimethylphenol (12.0 g, 0.1 mol) was dissolved in 10% aqueous KOH (100 mL). The resulting solution was cooled, butyryl chloride (8.2 g, 0.077 mol) was added dropwise with stirring, and the resulting solution was stirred for 1 h more. The solution clouded as it was allowed to warm to room temperature and was stirred for 1 h more. The solution was extracted with diethyl ether and the extract washed with cold aqueous NaOH (5%) and brine solutions. After the solution had dried ($MgSO_4$), the solvent was removed, leaving an oil, which on distillation (117 °C (0.9 mmHg)) gave 3,5-dimethylphenyl butyrate (7.0 g, 47%) as a colorless liquid: IR 1764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (1 H, s), 6.71 (1 H), 2.53 (2 H, t, J = 7.0 Hz), 2.33 (6 H, s), 1.80 (2 H, m), 1.06 (3 H, t, J = 7.0 Hz). Anal. ($C_{12}H_{16}O_2$) C, H.

3,5-Dimethylphenyl Methoxyacetate (4b). Methoxyacetyl chloride (6.0 g, 0.055 mol) was treated with aqueous potassium 3,5-dimethylphenolate, yielding after workup and distillation 3,5-dimethylphenyl methoxyacetate (4.2 g, 39%) as a white solid: mp 29–30 °C; IR 1774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1 H, s), 6.74 (2 H, s), 4.28 (2 H, s), 3.56 (3 H, s), 2.32 (6 H, s). Anal. ($C_{11}H_{14}O_3$) C, H.

3,5-Dimethylphenyl 3-Methoxypropionate (4c). 3-Methoxypropionitrile was hydrolysed in 20% aqueous KOH to give 3-methoxypropionic acid (bp 95 °C (6 mmHg), lit.[17] bp 126 °C (30 mmHg)). To the acid (5.0 g, 0.05 mol) and 3,5-dimethylphenol (6.0 g, 0.05 mol) in anhydrous ether (20 mL) was slowly added dicyclohexylcarbodiimide (10.0 g, 0.05 mol). The solution was stirred for 4 h and then filtered and the ethereal filtrate washed with 5% NaOH and brine solutions. After the solution had dried ($MgSO_4$), the solvent was stripped and the residue purified by flash chromatography (CH_2Cl_2 eluent) to give 3,5-dimethylphenyl 3-methoxypropionate (4.1 g, 39%) as a colorless oil: bp 127 °C (0.4 mmHg); IR 1762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (1 H, s), 6.71 (2 H, s), 3.78 (2 H, t, J = 6.0 Hz), 3.42 (3 H, s), 2.81 (2 H, t, J = 6.0 Hz), 2.31 (6 H, s). Anal. ($C_{12}H_{16}O_3$) C, H.

3,5-Dimethylphenyl 4-Methoxybutyrate (4d). 4-Methoxybutyric acid was prepared from sodium 4-hydroxybutyrate according to Reppe.[18] To an ethereal solution of the acid (6.0 g, 0.05 mol) and 3,5-dimethylphenol (6.0 g, 0.05 mol) was slowly added dicyclohexylcarbodiimide (10.0 g, 0.05 mol). The solution was stirred overnight and filtered and the filtrate washed with cold 5% NaOH and brine solutions. After the solution had dried ($MgSO_4$) the solvent was stripped, leaving an oil, which on flash chromatography (CH_2Cl_2 eluent) gave 3,5-dimethylphenyl 4-methoxybutyrate (3.2 g, 29%) as a colorless liquid: bp 102 °C (0.15 mmHg); IR 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (1 H, s), 6.70 (2 H, s), 3.50 (2 H, t, J = 6.2 Hz), 3.75 (3 H, s), 2.64 (2 H, t, J = 6.2 Hz), 2.32 (6 H, s), 2.02 (4 H, m). Anal. ($C_{13}H_{18}O_3$) C, H.

3,5-Dimethylphenyl 2-Tetrahydrofuroate (4e). 3,5-Dimethylphenyl 2-furoate (4.0 g, 0.019 mol) was dissolved in cyclohexane (100 mL) and catalytically hydrogenated in the presence of 10% Pd on charcoal (1.0 g). After 24 h, the theoretical uptake of hydrogen was reached. The catalyst was filtered, the solvent stripped, and the remaining liquid distilled (110 °C (0.15 mmHg)) to give 3,5-dimethylphenyl 2-tetrahydrofuroate (4.0 g, 98%) as a colorless oil: IR 1774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (1 H, s), 6.72 (2 H, s), 4.69 (1 H, dd, J = 6.0, 8.0 Hz), 4.06 (2 H, m), 2.32 (6 H, s), 2.35–2.00 (4 H, m). Anal. ($C_{13}H_{16}O_3$) C, H.

3,5-Dimethylphenyl 2-Furoate (4f). 2-Furoyl chloride was treated with aqueous potassium 3,5-dimethylphenolate, yielding after workup and distillation 3,5-dimethylphenyl 2-furoate as a colorless liquid: bp 100 °C (0.1 mmHg); IR 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (1 H, dd, J = 0.7, 1.6 Hz), 7.37 (1 H, dd, J = 0.8, 3.6 Hz), 6.91 (1 H, s), 6.84 (2 H), 6.60 (1 H, dd, J = 1.8, 3.6 Hz), 2.35 (6 H, s). Anal. ($C_{13}H_{12}O_3$) C, H.

3,5-Dimethylphenyl (*N*,*N*-Dimethylamino)acetate (4g). A reaction apparatus consisting of a 250-mL round-bottom flask with a Dean–Stark water trap was charged with a solution of 3,5-dimethylphenol (5.0 g, 0.041 mol) in dry toluene (150 mL). A small aliquot (1 mL) of butyllithium (1.6 M) in hexane was added via a syringe followed by *N*,*N*-dimethylglycine ethyl ester (5.0 g, 0.038 mol). The resulting solution was then heated to reflux, and every few hours a small aliquot was drained from the Dean–Stark trap. This was continued until all the toluene had been drained. The remaining liquid was cooled, taken up in ether (200 mL), and repeatedly extracted with cold aqueous 5% NaOH solution. After the solution had dried ($MgSO_4$), the ether was stripped, leaving an oil, which upon fractional distillation gave unreacted ethyl ester (1.8 g) and 3,5-dimethylphenyl (*N*,*N*-dimethylamino)acetate: 5.2 g (61%); bp 90 °C (0.2 mmHg); IR 1768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (1 H, s), 6.72 (2 H, s), 3.43 (2 H, s), 2.46 (6 H, s), 2.32 (6 H, s). Anal. ($C_{12}H_{17}NO_2$) C, H.

3,5-Dimethylphenyl (Methylthio)acetate (4h). This compound was prepared from the corresponding ethyl ester by the same transesterification procedure used for **4g**: bp 98 °C (0.1 mmHg); IR 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1 H, s), 6.73 (2 H, s), 3.41 (2 H, s), 2.32 (6 H, s), 2.31 (3 H, s). Anal. ($C_{11}H_{14}SO_2$) C, H.

3,5-Dimethylphenyl 2-Pyridinecarboxylate (4i). This compound was prepared from the ethyl ester by the transesterification procedure for **4g**: mp 47–48 °C; IR (Nujol) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.86 (1 H, d, J = 3.6 Hz), 8.27 (1 H, d, J = 7.9 Hz), 7.92 (1 H, t, J = 8.0 Hz), 7.56 (1 H, t, J = 4.0 Hz), 6.93 (1 H, s), 6.88 (2 H), 2.35 (6 H, s). Anal. ($C_{14}H_{13}NO_2$) C, H.

3,5-Dimethylphenyl 4-Pyridinecarboxylate (4j). Isonicotinoyl chloride hydrochloride (7.0 g, 0.04 mol), 3,5-dimethylphenol (10.0 g, 0.08 mol), and anhydrous pyridine (100 mL) were refluxed for 4 days. The solution was then poured into cold 5% aqueous NaOH (300 mL), and ether (200 mL) was added. The organic layer was separated and washed repeatedly with 5% aqueous NaOH and finally with brine solution. After the solution had dried ($MgSO_4$), the organic layer was evaporated, leaving an oil, which crystallized on the addition of petroleum ether. Repeated recrystallization afforded 3,5-dimethylphenyl 4-pyridinecarboxylate (5.2 g, 29%) as white needles: mp 60–61 °C; IR (Nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.84 (2 H, d, J = 3.9 Hz), 7.98 (2 H, d, J = 3.9 Hz), 6.93 (1 H, s), 6.83 (2 H, s), 2.35 (6 H, s). Anal. ($C_{14}H_{13}NO_2$) C, H.

3,5-Dimethylphenyl 2-Pyridylacetate (4k). This compound was prepared from the corresponding ethyl ester by the same transesterification procedure used for **4g**. The product readily hydrolyzed upon distillation; therefore, the ethyl ester was removed by vacuum distillation and the residue stored in a refrigerator overnight, where it crystallized. Repeated recrystallization from petroleum ether gave 3,5-dimethyl 2-pyridylacetate as a pale yellow solid, which slowly darkened upon standing: mp 73–74 °C; IR (Nujol) 1752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (1 H, d, J = 4.4 Hz), 7.71 (1 H, t, J = 7.6 Hz), 7.39 (1 H, d, J = 7.8 Hz), 7.24 (1 H, t, J = 7.6 Hz), 6.86 (1 H, s), 6.72 (2 H, s), 4.09 (2 H, s), 2.30 (6 H, s). Anal. ($C_{15}H_{15}NO_2$) C, H.

3,5-Dimethylphenyl 4-Pyridylacetate (4l). To an anhydrous solution of 4-pyridylacetic acid hydrochloride (6.0 g, 0.035 mol) and 3,5-dimethylphenol (4.25 g, 0.035 mol) in pyridine (150 mL) was added, dropwise, dicyclohexylcarbodiimide (7.14 g, 0.035 mol). After the solution was stirred for 24 h, ether (200 mL) was added and the mixture filtered. The filtrate was washed repeatedly with 5% NaOH and brine solutions. After the solution had dried ($MgSO_4$), the solvent was evaporated and the residue purified by flash chromatography (diethyl ether eluent) to give a solid product. Recrystallization from petroleum ether yielded 3,5-dimethylphenyl 4-pyridylacetate (2.2 g, 26%) as a white solid: mp 73–74 °C; IR (Nujol) 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.65 (2 H, d, J = 5.0 Hz), 7.43 (2 H, d, J = 5.0 Hz), 6.89 (1 H, s), 6.68 (2 H, s), 3.90 (2 H, s), 2.27 (6 H, s). Anal. ($C_{15}H_{15}NO_2$) C, H.

3,5-Dimethylphenyl Phenylacetate (4m). Phenylacetyl chloride (2.0 g, 0.013 mol) was treated with aqueous potassium 3,5-dimethylphenolate to yield, after workup and distillation (110 °C (0.01 mmHg)), 3,5-dimethylphenyl phenylacetate: 1.9 g (61%); IR 1762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (5 H, m), 6.87 (1 H, s), 6.70 (2 H, s), 3.86 (2 H, s), 2.32 (3 H, s). Anal. ($C_{16}H_{16}O_2$) C, H.

3,5-Dimethylphenyl 4-Methoxyphenylacetate (4n). To an anhydrous solution of 4-methoxyphenylacetic acid (16 g, 0.1 mol) and 3,5-dimethylphenol (12 g, 0.1 mol) in ether (150 mL) was added dicyclohexylcarbodiimide (20 g, 0.1 mol). After it was stirred for 3 h, the mixture was filtered and the filtrate washed with 5% NaOH and brine solutions. After the solution had dried ($MgSO_4$), the solvent was evaporated and the residue purified by flash chromatography (5:1 hexane/diethyl ether), yielding 3,5-dimethylphenyl 4-methoxyphenylacetate as a white solid, which was recrystallized from hexane: mp 63–64 °C; IR (Nujol) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (2 H, d, J = 8.5 Hz), 6.92

(17) Jones, L. W.; Powers, D. H. *J. Am. Chem. Soc.* **1924**, *51*, 2530.
(18) Reppe, v. W.; Mitarbeitern *Justus Liebigs Ann. Chem.* **1956**, *596*, 191.

(2 H, d, J = 8.5 Hz), 6.85 (1 H, s), 6.67 (2 H, s), 3.83 (3 H, s), 3.79 (2 H, s), 2.30 (6 H, s). Anal. ($C_{17}H_{18}O_3$) C, H.

3,5-Dimethylphenyl 4-Chlorophenylacetate (4o). 4-Chlorophenylacetic acid and 3,5-dimethylphenol were coupled by the same procedure for **4n**: bp 140 °C (0.05 mmHg); IR 1762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (4 H, s), 6.86 (1 H, s), 6.67 (2 H, s), 3.82 (3 H, s), 2.31 (6 H, s). Anal. ($C_{16}H_{15}ClO_2$) C, H.

3,5-Dimethylphenyl 4-(Trifluoromethyl)phenylacetate (4p). 4-(Trifluoromethyl)phenylacetic acid and 3,5-dimethylphenol were coupled with use of the same procedure for **4n**: mp 35–36 °C; IR 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (2 H, d, J = 8.2 Hz), 7.51 (2 H, d, J = 8.2 Hz), 6.87 (1 H, s), 6.68 (2 H, s), 3.91 (2 H, s), 2.31 (6 H, s). Anal. ($C_{17}H_{15}F_3O_2$) C, H.

Rates of Transesterification by Deuterium Exchange. The general procedure used for determining the rates of transesterification is illustrated for the ester **4l** (R = CH_2(4-pyridyl)) with lithium 3,5-dimethylphenolate-d_6 in dimethoxyethane.

A stock solution (0.50 M, 10.0 mL) of lithium 3,5-dimethylphenolate-d_6 in dimethoxyethane was prepared via a previously described vacuum-line technique.[5c] This solution was transferred to a dry septum-capped bottle and was stable enough for use up to 5 days after preparation. A stock solution (0.50 M, 3.0 mL) of **4l** (R = CH_2(4-pyridyl)) in dimethoxyethane, containing 10% C_6D_{12} lock, was prepared immediately before use. An oven-dried 5-mm NMR tube was capped with a rubber septum and flushed with nitrogen for 10 min. An aliquot of the ester solution (0.50 mL) was syringed into the NMR tube, the sample placed in the spectrometer (already equilibrated to 303 K), and the magnetic field shimmed. The tube was then removed, and an aliquot of the lithium phenolate solution (0.50 mL) was added via a syringe. The tube was inverted twice to achieve good mixing and then placed in the spectrometer. After the magnetic field was quickly locked and shimmed, a computer program was activated that took a spectrum every 30 + 30n s (10 + 10n for the faster reactions), n being appropriate for the rate of the particular reaction. The spectra were acquired with use of a very small pulse width (0.3 μs, 5°) and low receiver gain in order to prevent distortions arising from the strong solvent signals. Eight or sixteen transients were collected, depending on the solute concentrations, with use of AP phase cycling. A sweep width of 5 kHz and a data length of 16 K, corresponding to an acquisition time of 1.64 s, was used without an additional relaxation delay. Writing the FID to disk and preparation for the next spectrum required 4.5 s. As the transesterification proceeded, the CD_3 groups exchanged with the CH_3 groups and the sample time corresponding to each measurement was taken to be the beginning of each spectrum acquisition.

Rates of Ester Hydrolysis. A typical experiment involved adding an aliquot (1.00 mL) of aqueous NaOH stock solution (0.020 M) to a solution of ester in ethanol (2.00 mL, 4.50 × 10^{-4} M) in a 1-cm-wide silica cell. The alkali was kept in large excess to ensure first-order kinetics. The reaction was followed spectrophotometrically at 32.0 °C with a Perkin-Elmer Lambda 4C instrument. The rate of phenolate production was monitored via its absorbance at 295 nm. Pseudo-first-order rate constants were obtained by fitting the absorbance vs time curves to the equation $A_t = A_0 + A_\infty(1 - e^{-kt})$ by the method of nonlinear least squares. The values obtained could be reproduced to ±5%.

Results

Determination of the Rates of Exchange. In order to minimize errors associated with fluctuations in the spectrometer output, the extent of deuterium exchange at time t is expressed as

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

where I_{ester} and $I_{phenolate}$ are the peak intensities of the respective ^{1}H methyl resonances and x_t is the fraction of unlabeled ester at time t.

Assuming that the isotope effect is negligible, the rate of exchange of the phenolate residue between lithium phenolate and ester, i.e., the transesterification rate (R), is constant throughout any given experiment since the concentrations of reactants do not change. The transesterification does, however, result in isotopic exchange, causing the initial value of x_0 (~1) to decay to a final value (x_e), which depends on the relative concentrations of lithium phenolate and ester in that experiment. The rate of redistribution

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

$$x_t = (x_0 - x_e)e^{-k't} + x_e \quad (2)$$

$$-(dx_t/dt)_{t=0} = R = (x_0 - x_e)k' \quad (3)$$

$$R = k[E]^m[P]^n \quad (4)$$

Table I. Rates of Transesterification of 3,5-Dimethylphenyl Propionate (0.50 M) with Lithium 3,5-Dimethylphenolate in Several Solvents at 35 °C

	10^5R (mol L^{-1} s^{-1})			
[P] (M)	THF	DME[a]	dioxolane	pyridine
0.050				0.92
0.075	0.537	0.550		1.38
0.100	0.835	0.633	1.78[b]	1.52
0.150	1.23	0.972[c]	3.14[b]	1.85
0.175		1.09[b]	3.38	
0.200	1.55	1.23	4.30	2.23
0.225			4.36	
0.250	2.03	1.37[b]	5.60[b]	2.58
0.300	2.47	1.57	6.58	2.65
0.350		2.02[c]	7.37	3.17
0.400	3.43	2.08	9.45	3.27
0.450		2.10	10.35	3.83
0.500	4.42	2.29[b]	12.1[d]	3.60
0.600		2.90		
0.650			14.5	
0.750				5.60
0.800		4.42	20.0	

[a] 40 °C. [b] Average of two results. [c] Average of three results. [d] Average of four results.

of the isotopic label must, and does, follow the simple exponential rate equation (2), where k' is a first-order rate constant. Since at the *beginning* of the reaction the ester and lithium phenolate are entirely present as the ^{1}H and ^{2}H isotopomers, respectively, each phenolate exchange is also an isotopic exchange so that $(dx_t/dt)_{t=0}$ must be *equal in magnitude* to the rate of transesterification (R). Differentiating (2) and setting t = 0 then gives (3). The value of R from one experiment to another will depend on the concentrations of ester and lithium phenolate and on their kinetic orders (m and n, respectively). The rate constant for transesterification is therefore given by (4).

In practice, the disappearance of the ^{1}H isotopomer of the ester was followed to >80% completion. Although x_0 and x_e are in principle known, they have been obtained, together with k', by fitting x_t vs t data (30–50 points) to (2) via the method of nonlinear least squares. This procedure allows the determination of k' from data obtained after the sample has reached thermal equilibrium in the spectrometer. Furthermore, by including x_e as an adjustable parameter, uncertainties in its value arising from small errors in initial concentrations, isotope effects, and small amounts of hydrolysis could be largely eliminated. The last source of error is probably the most serious, particularly for the slower reactions, because the resulting phenol equilibrates with the phenolate at a rate that is rapid on the NMR time scale and can lead to apparent phenolate to ester ratios that are higher than predicted from their initial concentrations. However, if the above experimental procedure is carefully followed, the predicted and found values of x_e agree to within better than 10%. The estimated values of x_0 were 1.00 ± 0.015.

The initial rates of transesterification of lithium 3,5-dimethylphenolate with 3,5-dimethylphenyl propionate in several solvents are presented in Table I. Since the tetramer of the lithium phenolate is the major or sole species present in these solvents, the rate constants (k, apparent or true) have been obtained by replacing [P] by [P]/4 in (4) (e.g., in Tables II, III, V, and VI and Figure 1).

Transesterification with 3,5-Dimethylphenyl Propionate. i. Kinetic Order in Ester. The second-order rate constants for two different esters at constant phenolate concentration and varying ester concentration are given in Table II. As expected, the transesterification is first-order in ester.

ii. Kinetic Order in Phenolates. a. In Tetrahydrofuran. The rates of transesterification with 3,5-dimethylphenyl propionate were determined for phenolate concentrations in the range 0.075–0.5 M. The kinetic order in phenolate was found from the least-squares fit of log R vs log [P], which gives n = 1.06 ± 0.03. The second-order rate constants, calculated assuming that tetrameric lithium phenolate is the reactant, are listed in Table III.

Table II. Effect of Ester Concentration on the Apparent Second-Order Rate Constants for Two Transesterifications of Tetrameric Lithium 3,5-Dimethylphenolate (0.125 M)

	10^3k (L mol^{-1} s^{-1})	
[E] (M)	propionate in dioxolane[a]	3-methoxypropionate in DME[b]
0.25		2.20
0.30	1.96	
0.35		2.20
0.40	1.90	
0.50	1.94	2.12

[a] At 35 °C. [b] At 30 °C.

Table III. Second-Order Rate Constants for the Transesterification of *Tetrameric* Lithium 3,5-Dimethylphenolate with 3,5-Dimethylphenyl Propionate (0.50 M)

	10^4k (L mol^{-1} s^{-1})	
tetramer concn (M)	THF[a,b]	DME[c,d]
0.019	5.7	5.9
0.025	6.7	5.1
0.037	6.6	5.2
0.044		5.0
0.050	6.2	4.9
0.062	6.5	4.4
0.075	6.6	4.2
0.087		4.6
0.100	6.9	4.2
0.112		3.7
0.125	7.1	3.7
0.150		3.8
0.200		4.4

[a] At 35 °C. [b] Average 6.5 ± 0.4. [c] At 40 °C. [d] Average 4.5 ± 0.6.

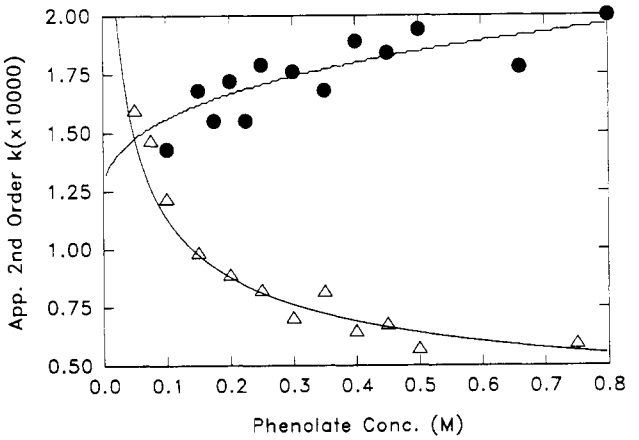


Figure 1. Apparent second-order rate constants for the transesterification of 3,5-dimethylphenyl propionate with lithium 3,5-dimethylphenolate at 35 °C in pyridine (△) and dioxolane (●). The solid lines correspond to the values calculated from the parameters given in the text.

b. In Pyridine. As illustrated in Figure 1, the reaction in pyridine exhibits a marked departure from second-order kinetics, with the apparent second-order rate constants increasing with decreasing phenolate concentration. We have previously shown, by ^{13}C NMR spectroscopy, that lithium 3,5-dimethylphenolate coexists as tetramer and dimer in this solvent and have determined ΔH and ΔS for the equilibrium between the two species.[5b,c] It is therefore probable that the kinetic behavior is the result of simultaneous reactions of the dimer and tetramer as outlined in Scheme I.

The transesterification rate (R) for a given concentration can be explicitly expressed in terms of the three parameters k_T, k_D, and K_{eq}. Nonlinear least-squares analysis of the data (Table I) gives K_{eq} = 330 M^{-1} (ln K_{eq} = 5.8), k_D = 2.9 × 10^{-3}, L mol^{-1} s^{-1}, and k_T = 2.2 × 10^{-4} L mol^{-1} s^{-1} at 35 °C, which reproduce the observed values of R_0 with an accuracy of ±6%. A value of ln K_{eq} = 5.8 (±0.8) at 35 °C is obtained from ΔH and ΔS for the dimer/tetramer equilibrium, which were previously determined

Scheme I

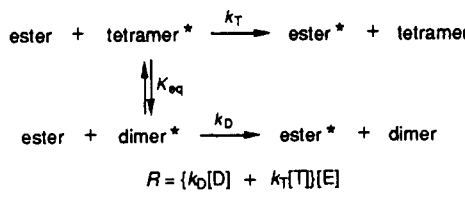


Table IV. Rate Constants for the Transesterification of Lithium 3,5-Dimethylphenolate at 35 °C with 3,5-Dimethylphenyl Propionate

	$-\Delta H_{BF_3}$ (kcal mol^{-1})	10^4k (L mol^{-1} s^{-1})		
		dimer	tetramer	hexamer
dioxolane	16.4[a]		13	71
THF	21.6[b]		6.5	
DME[c]		23	3.3	
pyridine	30.8[b]	29	2.2	

[a] Reference 23b. [b] Reference 23a. [c] At 40 °C.

from ^{13}C NMR spectra in the temperature range −40 to +1 °C.[5c] The agreement between the two estimates of the equilibrium constant provides strong evidence that Scheme I is correct.

c. In Dimethoxyethane (DME). The transesterification in this solvent, in which the predominant species is the tetramer,[5b] exhibits small deviations from second-order kinetics (Table III) and a fractional order of 0.84 ± 0.04. It is therefore possible that the pathway involving the dimer may make a minor contribution at low phenolate concentrations, although this species has not been detected in DME by NMR. Fitting the rate vs phenolate concentration data through a simplex search yielded $K_{eq} \approx 5 \times 10^4$ M^{-1} at 40 °C and k_D and k_T equal to 2.3 × 10^{-3} and 0.33 × 10^{-3} L mol^{-1} s^{-1}, respectively. These parameters fit the observed data with an accuracy of ±2.8%. The minimum in the error surface is, however, very shallow, and the contribution of the dimer to the observed rates could, in fact, be negligible.

d. In Dioxolane. In this solvent, lithium 3,5-dimethylphenolate in dioxolane is known to coexist as a tetramer and hexamer, which exchange slowly on the ^{13}C NMR time scale below −40 °C. ΔH and ΔS for the tetramer/hexamer equilibrium have also been determined[19] and afford $K_{eq}(T \rightleftharpoons {}^2/_3H)$ = 0.57 M$^{-1/3}$ at 35 °C. The apparent second-order rate constants for transesterification exhibit an *upward* drift (Figure 1) with increasing phenolate concentration, which can be attributed to a greater reactivity of the hexamer. The data were submitted to a grid search with use of the above value of K_{eq}. This yielded values for 10^4k of 13 and 71 L mol^{-1} s^{-1} for the transesterification of the tetramer and hexamer, respectively, values that reproduce the observed rates to ±5.8%. A further search in which K_{eq} was also varied located the global minimum at K_{eq} = 0.51 M$^{-1/3}$, which is gratifyingly close to the extrapolated value. We therefore conclude that both tetramer and hexamer are reactants in dioxolane.

The second-order rate constants for all these systems are summarized in Table IV.

Transesterification with Other 3,5-Dimethylphenyl Esters. In order to examine the effect of the structure of the carbonyl moiety of the ester on the rates of transesterification, it was necessary to decide on a common solvent for the experiments. THF is the obvious choice since the phenolate is completely tetrameric in this solvent. Unfortunately, the experiments are more difficult in this solvent because of the proximity of the resonances of its β-protons to those of the aromatic methyl groups of the 3,5-dimethylphenyl esters. DME was therefore chosen since the reaction of the propionate is mainly, if not completely, through the tetramer. However, since we were particularly interested in the effects of R groups in **2**, which have Lewis base centers, we established the kinetic order in phenolate for a system (R = $CH_2CH_2OCH_3$) of this type in DME. The apparent second-order rate constants,

(19) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, in press.

Scheme II

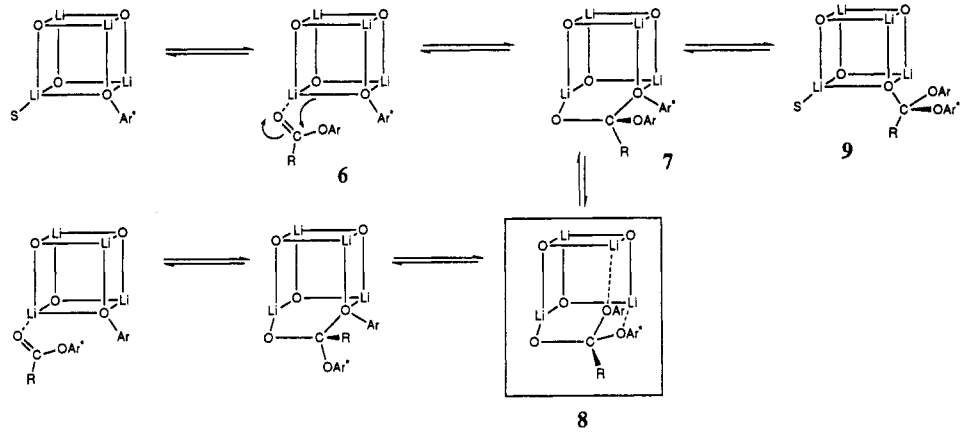


Table V. Second-Order Rate Constants (k) for the Transesterification of 3,5-Dimethylphenolate with 3,5-Dimethylphenyl β-Methoxypropionate (0.25 M) at 30 °C

solvent	[P] (M)	10^4k (L mol^{-1} s^{-1})
DME	0.125	22.7
DME	0.15	21.2
DME	0.25	22.0
DME	0.35	22.0
dioxolane	0.25	45.0
THF	0.25	6.5

shown in Table V, indicate that the reaction is first-order in phenolate.

The second-order rate constants for transesterification with 16 3,5-dimethylphenyl esters in DME are in Table VI, together with those for the hydrolysis of these esters in 30% aqueous ethanol.

Discussion

Aggregates as Primary Reactants. The kinetic order of the transesterification with respect to lithium phenolate in both THF and DME is very close to unity, and since we have shown[5b,c] that lithium 3,5-dimethylphenolate is the tetramer in these solvents, the reaction must proceed through a tetrameric species, though not necessarily that having the structure **3**.

The fact that the rate data for the reaction of 3,5-dimethylphenolate in pyridine is well accounted for by Scheme I is strong evidence that both the tetramer and dimer are primary reactants, especially since the kinetic analysis yields a value of K_{eq} in good agreement with that estimated by extrapolation of the values of K_{eq} at low temperatures based on ^{13}C NMR spectroscopic determinations of the relative populations of the two species. The dimer reacts approximately 1 order of magnitude faster than the tetramer. This may be because the former has one lone pair of electrons on oxygen that is not directed toward a lithium cation. This explanation is not, however, available for the similar difference reported for the rates of reaction of dimeric and tetrameric butyllithium with benzaldehyde.[12]

It also seems certain that both the tetramer and hexamer, which coexist in dioxolane, are primary reactants. The hexamer is about 3.5 times as reactive on a per phenolate basis. The $^{13}C_{para}$ chemical shift[5c] of the hexamer and its ^7Li quadrupole splitting constant[20] are consistent with structure **5**, which like the tetramer has each oxygen attached to three lithium ions.[22] It is therefore reasonable

Table VI. Second-Order Rate Constants (k (L mol^{-1} s^{-1})) and Relative Rates (k_{rel}) for the Transesterification in DME at 30 °C and Hydrolysis in 30% Aqueous Ethanolic NaOH at 30 °C of the Esters **4**

	transesterification		hydrolysis	
R in **4**	10^4k	k_{rel}	10^2k	k_{rel}
a: $CH_2CH_2CH_3$	1.72	(1)	3.9	(1)
b: CH_2OCH_3	550	322	190	49
c: $CH_2CH_2OCH_3$	22	13	11	2.8
d: $CH_2CH_2CH_2OCH_3$	5.2	3	8.7	2.2
e: 2-tetrahydrofuryl	160	93	92	2.3
f: 2-furyl	2.4	1	4.7	1.2
g: $CH_2N(CH_3)_2$	64	37	28	7.1
h: CH_2SCH_3	18	10	140	36
i: 2-pyridyl	190	110		
j: 4-pyridyl	19	11		
k: CH_2(2-pyridyl)	380	220	39	9.8
l: CH_2(4-pyridyl)	31	18	138	35
m: CH_2Ph	7.7	4	21	5.4
n: CH_2(*p*-methoxyphenyl)	3.6	2	19	5.0
o: CH_2(*p*-chlorophenyl)	13	8	40	10
p: CH_2(*p*-(trifluoromethyl)phenyl)	18	10	88	23

that the rates of transesterification of the tetramer and hexamer are similar.

Solvent Effects and Mechanism. The fact that the tetramer can undergo transesterification without dissociation poses an interesting problem because its cubic structure **3** is such that the three lone pairs of the phenolate oxygen atom are directed toward three lithium cations, and it is therefore not obvious as to how the reaction with an electrophile, in this case the ester carbonyl group, can occur. One possibility is that the cubic tetramer is in equilibrium with other tetramer structures such as tricyclic ladder, bicyclic, or monocyclic forms in which one of the oxygen lone pairs is unattached to lithium and is able to exercise its nucleophilic function. The formation of such structures would presumably involve additional solvation of lithium and should be favored by increasing solvating power of the solvent. The data in Table IV show the opposite trend; i.e., transesterification is favored by weaker Lewis basicity of the solvent as judged by its enthalpy of reaction with BF_3. This evidence appears to rule out the direct participation of tetramers that have more open structures than the usual cubic array.

The observed effect of the Lewis basicity of the solvent is, however, consistent with a preequilibrium step in which the carbonyl oxygen of the ester displaces a solvent molecule from a lithium cation at one corner of the tetramer cube **6**, (Scheme II). Breaking of a Li–O bond with concomitant formation of a C–O bond with the carbonyl carbon atom leads to the expected tetrahedral intermediate **7** in transesterification. This is a sterically reasonable intermediate since it involves the formation of two six-membered rings. The actual interchange of phenolate residues can then occur through a transition state (**8**) in which the two residues are bound to separate lithium atoms. Alternatively, **7**

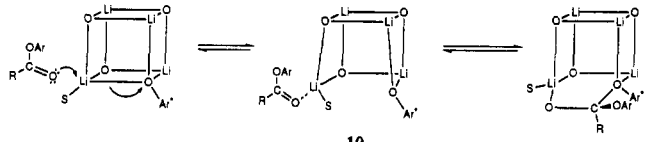
(20) The relatively low value of 74 kHz for QSC of this species[19] is best accommodated by a structure with a nearly tetrahedral array of ligands, three of which being anions, around the Li cation.[21]

(21) Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355.

(22) Williard[3g] has shown that the unsolvated lithium enolate of methyl *tert*-butyl ketone is a hexamer having an approximately hexagonal prismatic structure with each oxygen atom attached to three lithium atoms and vice versa.

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

Scheme III



10 11

could undergo reversible collapse to the hemiortho ester **9**, which also effects the exchange of the OAr groups. An analogy for the formation of **9** is provided by the observation of the mixed alkoxide, which is formed directly in the addition of butyllithium to benzaldehyde in THF.[12]

There is, of course, strong precedence for the preequilibrium step in the organic chemistry of lithium. As well as the frequent invocation of such interactions as a rationale for stereoselectivities in such processes as the aldol reaction[15] (Zimmerman–Dubois transition state[24]) and the α-deprotonation of carbonyl compounds by lithium amides,[25] direct observation of lithium–carbonyl oxygen complexes have been made in several important systems. Beak and Smith[26] used stopped-flow infrared spectroscopy to demonstrate preequilibrium formation of such a complex between *sec*-butyllithium and the amide carbonyl oxygen during the α′-deprotonation of *N,N*-dialkylamides and have implicated the complex as an intermediate in the reaction.[26b] Similarly, Meyers, Rieker, and Fuentes[27] have shown, again by stopped-flow IR, that *tert*-butyllithium complexes with formamidines prior to α-deprotonation of the latter. It is noteworthy that these investigators were led to postulate complex formation because the ease of α-deprotonation increased dramatically with the decreasing cation-solvating power of the solvent. Smith[8] has also detected prior complexation in the addition of alkyllithium compounds to ketones in hydrocarbon solvents.[8b] It may well be that complex formation is always necessary for addition and deprotonation reactions of carbonyl, imine, and similar groups when the anionic nucleophile is an aggregate in which all lone pairs of electrons of the anionic center are bonded to lithium cations.

There is a variant of Scheme II that must be considered (Scheme III). It is possible that attack on lithium by the carbonyl oxygen atom can, either directly or through the intermediacy of a pentacoordinate lithium cation, give rise to the species **10** as an intermediate, which then collapses to **11**, a solvated analogue of the species **7** in Scheme II. This mechanism cannot readily be distinguished from that in Scheme II since **10** can also be reached by attack of solvent on **6**. A mechanism involving **11** will presumably attenuate the role of solvent Lewis basicity and may, in fact, be in better accord with the magnitude of the solvent effect found in Table IV. On the other hand, there is no precedence for an open structure such as **11**, and it may be of too high an energy to occur even as a reaction intermediate. We note that a direct observation of the species **7** would not distinguish between the two schemes.

Complex-Induced Proximity Effects (CIPE). In both Schemes II and III, the essential role of the preequilibrium step is to attach the ester to the tetramer in order to effect electrophilic attack of the putative phenolate ion on the carbonyl carbon atom. There is no reason to believe that the carbonyl group and the phenolate residue can assume a spatial relationship that allows the anion to approach the carbonyl carbon atom along the preferred pathway, which is defined by the Bürgi–Dunitz angle.[28] It is therefore possible that the presence of other Lewis base centers in the acid moiety of the esters might provide more effective means of attachment, even though the electrophilic activation of the carbonyl group associated with coordination of its oxygen to lithium would be lost. Rate enhancements of transesterification associated with a second Lewis base center can be considered as a manifestation of CIPE, which Beak and Myers[29] have shown to play an important role in a number of reactions of organic compounds of lithium.

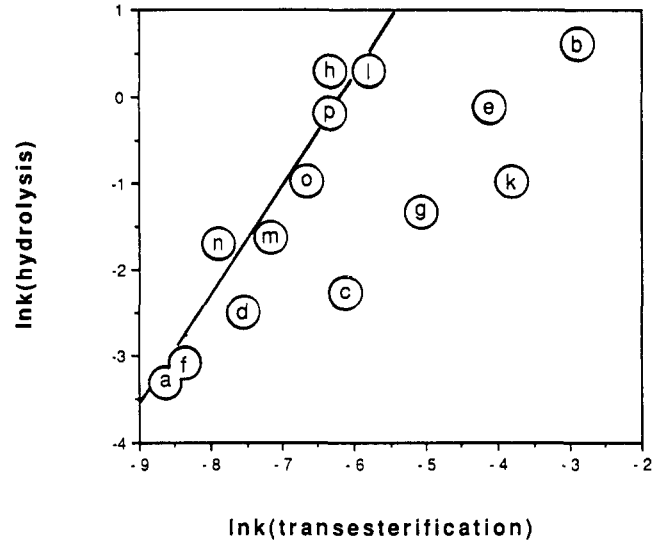


Figure 2. Relation between the rates of hydrolysis and transesterification for the 3,5-dimethylphenyl esters listed in Table VI.

Table VII. Observed and Predicted Free Energies of Activation for the Transesterification, at 30 °C in DME, of 3,5-Dimethylphenyl Esters Possessing a Second Lewis Base Center

R in **4**	$\Delta G^{\ddagger}$ (kcal mol^{-1}) obsd	pred	diff
b: CH_2OCH_3	19.6	21.3	1.7
c: $CH_2CH_2OCH_3$	21.6	22.7	1.1
d: $CH_2CH_2CH_2OCH_3$	22.5	22.8	0.3
e: 2-tetrahydrofuryl	20.4	21.7	1.3
g: $CH_2N(CH_3)_2$	20.9	22.2	1.3
k: CH_2(2-pyridyl)	19.9	22.1	2.2

The substantial dependence of the rates of transesterification on the structures of some of the esters in Table VI may be associated with the CIPE but must also include contributions from the usual electronic and steric effects that influence the rate-controlling formation of the tetrahedral intermediate in carbonyl addition reactions. These latter contributions can be assessed by examining the rates of hydrolysis of the esters in solvent systems for which the cation plays no role. We therefore determined the second-order rate constants for the hydrolysis of the esters **4a–4p** in 30% aqueous ethanolic sodium hydroxide (Table VI).

A comparison of the rate constants of transesterification and hydrolysis is conveniently presented by plotting the logarithms of the rate constants (Figure 2). It can be seen that the points for the butyrate **4a**, the phenylacetates **4m–4p** and the 4-pyridylacetate **4l** give a reasonable straight line (r = 0.9708). The furoate **4f** and the (methylthio)acetate **4h** also fall on this line, indicating the absence of CIPE in their transesterification. It is expected that the furan oxygen in **4f** is much less basic than the solvent oxygen atoms since delocalization of the aromatic π-electrons leave an appreciable net positive charge on oxygen. It is also expected that the "soft" sulfur atom in **4h** will show little affinity for the "hard" lithium cation. Inclusion of **4f** and **4h** affords the straight line (r = 0.9663) shown in Figure 2.

Those esters in which the acid moiety contains an available Lewis base center exhibit significantly higher rates of transesterification over the values predicted from their rates of hy-

(24) Zimmerman, H.; Traxler, M. *J. Am. Chem. Soc.* **1957**, *79*, 1920. DuBois, J. E.; DuBois, M. *J. Chem. Soc., Chem. Commun.* **1968**, 1567. DuBois, J. E.; DuBois, M. *Bull. Soc. Chim. Fr.* **1969**, 3120, 3553.

(25) Evans, D. A. In *Asymmetric Sythesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 1–110 and references cited therein.

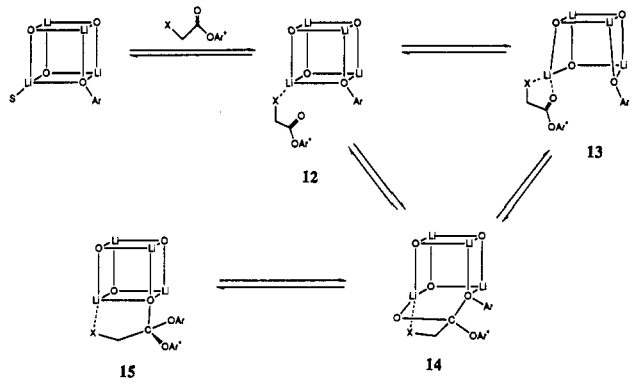
(26) (a) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. (b) Hay, D. R.; Zhiguo Song; Smith, S. G.; Beak, P. *Ibid.* **1988**, *110*, 8145.

(27) Meyers, A. I.; Rieker, W. F.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *110*, 2082.

(28) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1536.

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

Scheme IV



drolysis. The differences between the predicted and observed free energies of activation for the transesterification are given in Table VII. The largest increase is found for the 2-pyridylacetate and corresponds to a rate enhancement of 40. The magnitude of the CIPE will depend on the cation-solvating ability of the second Lewis base center and on the ease with which the Bürgi–Dunitz approach of the carbonyl group to the phenolate ion can be achieved.

The first three entries in Table VII show the effect of increasing the length of the chain between the carbonyl group and the second base center. The result is a decrease in the CIPE, presumably because the adoption of the correct conformation for the Bürgi–Dunitz approach is expected to become more difficult by approximately 1 (kcal mol^{-1})/methylene group due to the negative entropy associated with the loss of 1 degree of internal rotational freedom. Separation of the CIPE into the two contributing terms for the series **4b**, **e**, **g**, and **k** is not feasible in view of the small range (1.3–2.2 kcal mol^{-1}) of the differences between the observed and predicted values of $\Delta G^{\ddagger}$, except perhaps to note that the effect is greatest for the 2-pyridylacetate because the pyridyl residue is the best cation-solvating ligand in this series. The rates of hydrolysis of the 2- and 4-picolinates were not determined because the esters interfered with the spectrophotometric method used. However, it is clear from the relative rates for the two esters that CIPE is operating in the case of the 2-isomer.

Possible CIPE pathways are shown in Scheme IV. The initial step is the replacement of solvent by the second Lewis base center of the ester to give the intermediate **12**. This intermediate may allow the carbonyl group to be positioned for a favorable attack by the phenolate ion, but presumably this would also require an incipient interaction with the lithium cation, as indicated in **12**, during the formation of the tetrahedral intermediate **14**. Alternatively, attack by the carbonyl group on the Li cation could occur first, leading to the "open" intermediate **13**, analogous to **9**, followed by the formation of **14**. Finally, exchange of the aryloxy groups can occur through the hemiortho ester **15**.

The inversion of the order of rates in THF and DME in going from the propionate to the β-methoxypropionate is significant. Although the Lewis basicity of DME as a monodentate ligand for BF_3 has not been reported, it presumably should lie between dioxolane and THF because of the inductive effect of the second oxygen two carbons removed from the first. This order (dioxolane > DME > THF) for the free energies of formation of **12** accords with the relative rates of transesterification of the β-methoxypropionate in the three solvents, given that the formation of **12** involves a direct competition between the solvent and the second Lewis base center for the lithium cation. If the reaction of the propionate involves only the intermediate **5**, the order of rates should be the same as for the β-methoxypropionate. If, however, the intermediate **9** is involved, the rate of its conversion to **10** could be influenced by steric factors associated with the solvent S. These should be similar for dioxolane, THF, and pyridine, but they may be different for DME. Alternatively, DME could exert a specific effect through the formation of **16**, in which it functions as a bidentate ligand. This process would be in direct competition with the formation of **10** and would lower the overall rate of transesterification.

Summary

i. Depending on the solvent, dimers, tetramers, and hexamers of lithium 3,5-dimethylphenolate are the primary reactants in its transesterification.

ii. Under the same conditions, the dimer reacts ~20 times faster than the tetramer on a per phenolate basis.

iii. Under the same conditions, the hexamer reacts 3–4 times faster than the tetramer on a per phenolate basis.

iv. The rate of transesterification decreases with increasing Lewis basicity of the solvent.

v. The presence of a Lewis base center in the ester, in the vicinity of the carbonyl group, results in increased rates of transesterification attributable to complex-induced proximity effects.

vi. For the tetramer, the observations are consistent with mechanisms involving the initial binding of the ester to the intact aggregate.

Acknowledgments. We gratefully acknowledge support for this work by a grant (CHE8801884) from the National Science Foundation. We also thank Ed Rakiewicz for his help in preparing the figures.