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The Role of Aggregates in Claisen Acylation Reactions of Two Lithium Enolates in THF[1]

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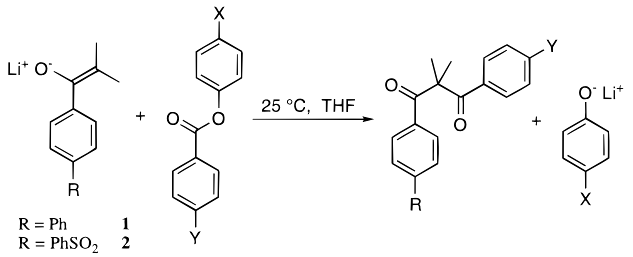
Lithium enolates are known to be generally aggregated in ethereal solvents,[2] and such aggregates have been assumed to be involved in reaction.[3] Several studies have provided some evidence for this assumption.[3c,e,j,4] Recent studies in our group have involved quantitative measurements of the aggregation equilibria of several lithium enolates in THF and their kinetic role in reactions. Thus, the lithium enolate of *p*-phenylisobutyrophenone, **1**, forms a monomer−tetramer equilibrium with $K_{1,4} = 5.0 \times 10^8$ M^{-3}, but alkylation reactions involve dominantly the monomer even when the tetramer is present in large excess.[5] The lithium enolate of *p*-phenylsulfonylisobutyrophenone, **2**, forms a monomer−dimer equilibrium with $K_{1,2} = 5.0 \times 10^4$ M^{-1}; the monomer is 3000 times more reactive than the dimer toward *p*-*tert*-butylbenzyl bromide.[6] Similarly, the lithium enolate of 2-(*p*-biphenylyl)cyclohexanone forms a monomer−dimer equilibrium with $K_{1,2} = 4.3 \times 10^3$ M^{-1} and again the monomer is the sole reactive species in alkylation reactions.[7] Clearly, in alkylation reactions lithium enolate monomers are much more reactive than aggregates; nevertheless, the extension of this generalization to other reactions is not clear.

Aldol-type additions of enolates to carbonyl compounds are among the most important and common carbon−carbon bond formation reactions in modern organic synthesis.[8] Understanding the role of enolate aggregates in this type of addition should have synthetic significance. Initial attempts by our group to study aldol additions of lithium enolates to aldehydes have been unsuccessful because of high reaction rates and subsequent reactions.[9] We now report, however, that the kinetics of analogous Claisen reactions of lithium enolates with phenyl esters can be studied by our procedures and dissected into the relative reactivities of monomers and aggregates. Ester carbonyls are more stable and inherently less reactive than aldehyde carbonyls, but their reaction mechanisms should be comparable.

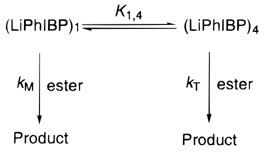
Scheme 1



R = Ph **1**
R = PhSO$_2$ **2**

X = H, Y = H **3**
X = Cl, Y = H **4**
X = H, Y = Cl **5**
X = Cl, Y = Cl **6**

Scheme 2



$$\text{Rate} = k_{\text{M}}\,[\text{Monomer}]\,[\text{Ester}] + k_{\text{T}}\,[\text{Tetramer}]\,[\text{Ester}] \qquad (1)$$

$$\text{Rate} / [\text{Tetramer}]\,[\text{Ester}] = k_{\text{M}}\,[\text{Monomer}] / [\text{Tetramer}] + k_{\text{T}} \qquad (2)$$

The reactions of **1** and **2** with phenyl benzoate are irreversible and proceed exclusively to the β-diketones (Scheme 1).[10] Initial rates (ca. 10% reaction) were measured by following the decrease in the absorption at 385 nm of **1** and 390 nm of **2** after addition of the esters in THF at 25 °C. Reactions were followed only in the early stages of reaction to avoid possible complications and interference from potential mixed aggregates between the lithium enolate and lithium phenolate.

Kinetic studies with both enolates gave rate orders in the esters of unity. For the reaction of **1** with 4-chlorophenyl benzoate, **4**, 21 kinetic runs were carried out. In the concentration range studied, $(1.0-7.4) \times 10^{-3}$ M in enolate, the equilibrium aggregation number ranges from 2.1 to 3.5 and the rate order of the enolate changes from 0.67 to 0.63. These results lead to an average kinetic aggregation number of 1.9 ± 0.3.[11] Similarly, for the reaction of **2** with 4-chlorophenyl benzoate, **4**, 20 kinetic

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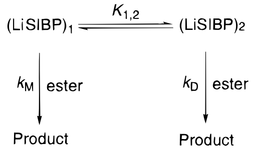
(10) **1** was prepared in THF solution with the lithium salt of 9,9,10-trimethyldihydroanthracene as a base; **2** was prepared in THF solution with the lithium salt of 9-benzylfluorene as a base. Both bases were obtained from the corresponding neutrals and sublimed LDA.

(11) The slope of a plot of log(rate/[ester]) vs log{enolate} is $n_{\text{agg}}/n_{\text{k}}$ where n_{agg} is the average aggregation number of the enolate and n_{k} is the corresponding number of the kinetically active species. Krom, J. A.; Streitwieser, A. *J. Am. Chem. Soc.* **1992**, *114*, 8747−8.

S0002-7863(98)02360-9 CCC: $15.00

Scheme 3



$$\text{Rate} = k_M\,[\text{Monomer}]\,[\text{Ester}] + k_D\,[\text{Dimer}]\,[\text{Ester}] \quad (3)$$

$$\text{Rate} / [\text{Dimer}]\,[\text{Ester}] = k_M\,[\text{Monomer}] / [\text{Dimer}] + k_D \quad (4)$$

Table 2. Bimolecular Rate Constants of the Claisen Acylation Reactions

	enolate **1**		enolate **2**	
ester	$10^3 k_M$, $M^{-1}\,s^{-1}$	$10^3 k_T$, $M^{-1}\,s^{-1}$	$10^3 k_M$, $M^{-1}\,s^{-1}$	$10^3 k_D$, $M^{-1}\,s^{-1}$
3	10.1 ± 0.8	13 ± 3	19.6 ± 0. 9	1.7 ± 0.2
4	35.5 ± 1.4	33 ± 4.3	91.1 ± 3.9	5.3 ± 0.8
5	33.1 ± 1.6	41 ± 4	68.3 ± 5.3	8.3 ± 0. 9
6	146 ± 5	105 ± 17	329 ± 14	34 ± 2

experiments led to the average kinetic aggregation number of 1.27 ± 0.02 (Table S1, Supporting Information). These results clearly indicate that monomer is not the only reactive species and that higher order aggregates of the lithium enolates are involved in the rate-determining addition process.

For the reactions formulated as in Schemes 2 and 3, the total rate of reaction can be written as eq 1 or 3 and rearranged to eq 2 or 4, respectively. Plotting the kinetic results as in eq 2 or 4 gives straight lines in which the slopes are k_M and the intercepts are k_T and k_D, respectively (Figures 1 and 2). The kinetic rate constants for several reactions of the two enolates with several substituted phenyl benzoates are summarized in Table 2 (Figures S3−S8, Tables S3 and S4, Supporting Information).[12]

In general, monomers are still more reactive than higher order aggregates. After statistical correction, for **1**, the monomer is about 4 times faster than the tetramer with all of the phenyl esters studied. In the case of **2**, the monomer is about 20 times faster than the dimer. Compared with alkylation reactions, in which monomer is at least 1000 times more reactive than higher order aggregates,[5−7] the difference in reactivities of the monomer and aggregates toward ester carbonyls is surprisingly small. In particular, under synthesis conditions of several tenths molar, in which monomer is present to the extent of only about 1% of the total enolate concentration, addition of enolate to the ester carbonyl occurs dominantly via the aggregates, a conclusion that is just the reverse of that for alkylation reactions. Clearly, the relative roles of aggregates can change for different reactions.

Positive Hammett ρ values of about 2−3 are found in both benzoate and phenolate rings for both monomer and aggregates. Considering that the reactions were carried out in a solvent of low polarity, these values are quite reasonable.[13] Moreover, the substituent effects for both monomer and aggregate appear to be additive. For example, in the case of the monomer of **2**, 4-chlorophenyl benzoate **4** is about 4.65 times as reactive as phenyl benzoate **3** and phenyl 4-chlorobenzoate **5** is about 3.49 times as reactive as phenyl benzoate **3**. The combined effect should make 4-chlorophenyl 4-chlorobenzoate **6** about 16.2 times as reactive as phenyl benzoate **3**; the observed factor is 16.8. These studies are being continued with additional enolates and esters; preliminary results, for example, show that the same types of kinetic studies can be applied to thioesters.

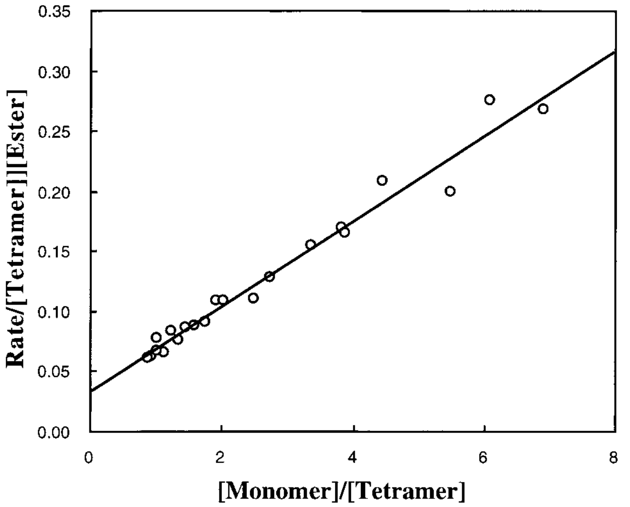


Figure 1. Plot for determining the bimolecular rate constants for the reaction of monomeric and tetrameric lithium enolate of **1** with 4-chlorophenyl benzoate **4**. The equation of the least-squares line shown is $y = (0.033 \pm 0.0043) + (0.0355 \pm 0.0014)x$.

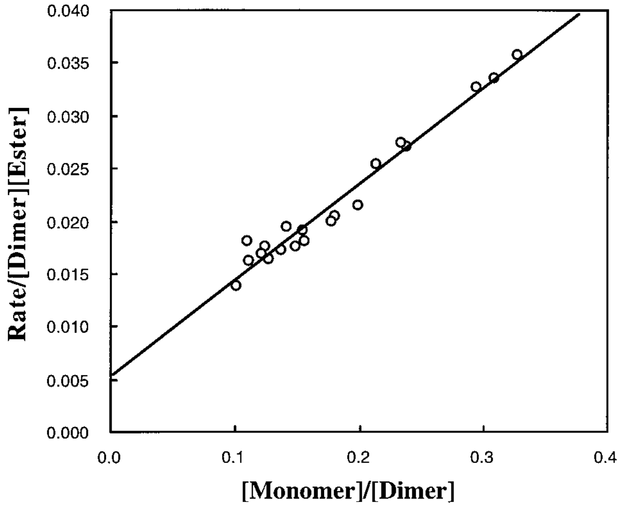


Figure 2. Plot for determining the bimolecular rate constants for the reaction of monomeric and dimeric lithium enolate of **2** with 4-chlorophenyl benzoate **4**. The equation of the line shown is $y = (0.0053 \pm 0.0008) + (0.0911 \pm 0.0039)x$.

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Supporting Information Available: Tables S1, S3, and S4 and Figures S3−S8 of kinetic data (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[12] Phenyl benzoate **3** and 4-chlorophenyl benzoate **4** were obtained from Aldrich and Lancaster, respectively. Phenyl 4-chlorobenzoate **5** and 4-chlorophenyl 4-chlorobenzoate **6** were prepared from the reaction of 4-chlorobenzoyl chloride and the corresponding phenols with triethylamine as a base.

[13] For the alkaline hydrolyses of substituted phenyl benzoates in 33% acetonitrile−water at 25 °C, Hammett ρ values of 2.0 and 1.3 were found in benzoate and phenolate rings, respectively. See: Kirsch, J. F.; Clewell, W.; Simon, A. *J. Org. Chem.* **1968**, *33*, 127−132.