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Role of Aggregates in Claisen Acylation Reactions of Imidazole, Pyrazole, and Thioesters with Lithium Enolates in THF[1]

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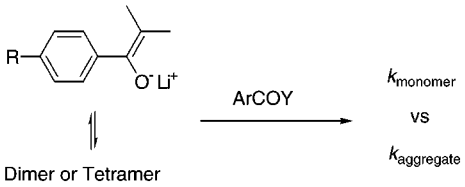
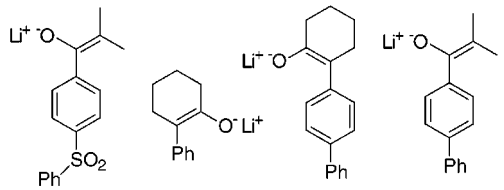
ABSTRACT



Although phenyl esters react with both monomers and dimers or tetramers of two lithium enolates in THF, the reactions of phenyl thiobenzoates are relatively much faster with the monomers. Similarly, imidazole esters react primarily with the monomers but pyrazole esters react with monomers and aggregates. The results are rationalized by a mechanism in which coordination with two lithium cations within an enolate aggregate is required for the reaction of aggregates to compete with monomers.

We have recently reported the aggregation and alkylation kinetics of several lithium enolates in THF. The lithium enolates of *p*-phenylsulfonylisobutyrophenone, **1**,[2] α-phenylcyclohexanone, **2**,[3] and α-*p*-biphenylylcyclohexanone, **3**,[4] form monomer−dimer mixtures in dilute solution, whereas that of *p*-phenylisobutyrophenone, **4**,[5] is a monomer−tetramer mixture, but in all cases alkylation reactions are much faster with the monomers than with the aggregates. For example, for the reaction of **1** with a benzylic bromide $k_{monomer}$ is 3000 times greater than k_{dimer}.[2] At concentrations typical of synthesis reactions, these enolates are dominantly aggregated yet the alkylation reactions are primarily with the monomers. These results were rationalized on the basis that the enolate oxygen in an aggregate is close to two or more lithium cations and is electrostatically, therefore, effectively less nucleophilic. As shown in Scheme 1, the same principles should apply to the Claisen reactions of lithium enolates with esters. Consequently, it is remarkable that in reactions of the lithium enolates **1** and **4** with aryl benzoates the aggregates are relatively much more reactive than in alkylation reactions.[6] For example, in reaction with phenyl benzoate, the tetramer of **4** is 1.3-fold as reactive as the monomer, whereas for **1**, k_{dimer} is 0.09 that of $k_{monomer}$. The Claisen reactions at synthesis concentrations are now dominantly with the aggregates.



1 **2** **3** **4**

One way to rationalize these results is to involve both oxygens in the ester in coordination with lithium cations in

(1) Carbon Acidity. 111.
(2) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−9.
(3) Wang, D. Z.-R.; Streitwieser, A. *Can. J. Chem.* **1999**, in press.
(4) Streitwieser, A.; Wang, D. Z.-R. *J. Am. Chem. Soc.* **1999**, in press.
(5) Abbotto, A.; Leung, S. S.-W.; Streitwieser, A.; Kilway, K. V. *J. Am. Chem. Soc.* **1998**, *120*, 10807−13.
(6) Leung, S. S.-W.; Streitwieser, A. *J. Am. Chem. Soc.* **1998**, *120*, 10557−8.

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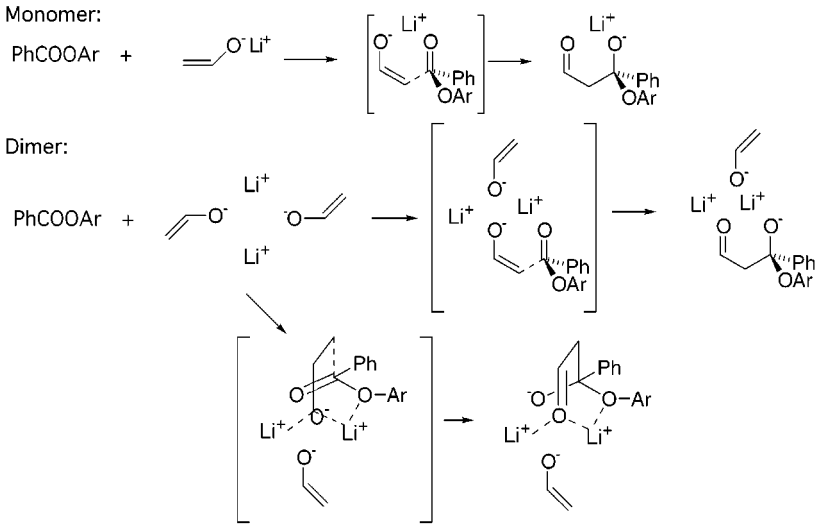
Scheme 1. Mechanisms for Claisen Reactions of Lithium Enolates with Esters

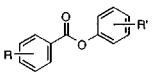
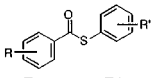
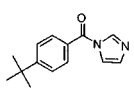
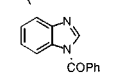
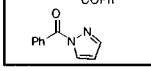


an aggregate such as in the proposed bicyclic intermediate or transition structure shown as the last reaction in Scheme 1. Such dual coordination provides an additional pathway that could be more competitive with the monomer reaction than the normal reaction of an aggregate with coordination of only the carbonyl oxygen.

A corollary of this scheme is that any structural change that inhibits coordination of the ether oxygen of the ester (such as ortho substitution) should interfere with this pathway and reduce the relative reactivity of the aggregate. Similarly, the sulfur of a thioester should be much less effective in coordination with a lithium cation, and this alternative pathway should also be unavailable. In the present paper, these corollaries are subjected to experimental test.

Kinetic measurements were made as in the previous work.[6] Excess ester was added to a solution of the lithium enolate and the initial rate of loss of the enolate absorbance was followed in the UV. These initial rates were divided by the concentrations of ester and aggregate and plotted against the [M]/[D] ratio of **1** and the [M]/[T] ratio for **4**; the slope gives

Table 1. Reactivities of the Monomer (M) and Dimer (D) of 1 and the Monomer (M) and Tetramer (T) of 4 with Various Esters, Thioesters, and Amides

	LiSIBP, **1**			LiPhIBP, **4**		
 R R'	$10^2 k_M$ $M^{-1}s^{-1}$	$10^2 k_D$ $M^{-1}s^{-1}$	k_D/k_M	$10^2 k_M$ $M^{-1}s^{-1}$	$10^2 k_T$ $M^{-1}s^{-1}$	k_T/k_M
m-Cl	19.7 ± 0.5	1.7 ± 0.1	0.086			
m-Cl o-Me	4.53 ± 0.41	0.07 ± 0.06	0.015			
m-Cl o-MeO	17.9 ± 1.2	0.59 ± 0.17	0.033			
p-CN	96 ± 3.7	4.2 ± 0.7	0.044	26.5 ± 1.0	25.8 ± 4.0	1.0
p-CN o-Me	24.7 ± 1.2	0.05 ± 0.2	0.002	6.57 ± 0.29	3.33 ± 0.7	0.5
 R R'						
H H	37.8 ± 1.0 31.5 ± 1.4	0 -0.6 ± 0.3	0	17.0 ± 0.2 13.8 ± 0.2	0 0.3 ± 0.3	0
H p-MeO	9.2 ± 0.3	0.1 ± 0.04	0.01			
p-MeO H	9.2 ± 0.5	-0.15 ± 0.06	0	3.8 ± 0.1	-0.07 ± 0.06	0
H o-MeO	10.8 ± 0.4	-0.02 ± 0.05	0	3.6 ± 0.1 4.1 ± 0.1	-1.2 ± 0.1 -1.1 ± 0.2	0
	297 ± 25	3.7 ± 4.1	0.01			
	160 ± 8	9.8 ± 1.1	0.06	71.9 ± 1.2 64.6 ± 2.1	6.8 ± 1.7 13.1 ± 2.9	0.09 0.2
	811 ± 76	136 ± 16	0.17	369 ± 7	286 ± 60	0.78

k_M and the intercept is k_D or k_T, respectively.[7] Several typical plots are given as Figures S1−S4 (Supporting Information). The results obtained are summarized in Table 1.

Ortho substituents on the phenyl esters do reduce the reactivities of the two enolate monomers as expected for any carbonyl reaction but only by a modest amount; the reduction is much greater for the dimer or tetramer in accord with expectations of a mechanism requiring additional coordination of the phenol oxygen. The effect with thioesters is even more striking. The reactivities of the aggregates are now essentially nil, comparable to the relative reactivities in alkylation reactions. The intercepts were occasionally negative, indicating a rate constant of zero within experimental error.

The results with some reactive amides have additional interest. Imidazole and benzimidazole esters are quite reactive with the lithium enolates but kinetics could be measured by working with dilute solutions. The aggregates do react but relatively more slowly than the monomers compared to phenol esters. The amide nitrogen is not basic and probably does not coordinate with lithium cation; the ring nitrogen probably does coordinate in an aggregate but not efficiently because of geometry. Benzoylpyrazole is also highly reactive and reacts equally effectively with enolate monomer or aggregate. The proximity of the ring nitrogen in the pyrazole clearly allows it to coordinate together with the carbonyl group with two different lithiums within an aggregate.

Conclusion. Claisen reactions of phenol esters with aggregates of lithium enolates can be competitive with monomers because both ester oxygens coordinate with lithium cations within the aggregate. When such coordination is inhibited, the reactions with the aggregates become less important. Reactions of thioesters occur only with the enolate monomers because sulfur does not coordinate with lithium. The ring nitrogen of pyrazole amides can coordinate with additional lithium cations, and its reaction with enolate aggregates is competitive with that of monomers. The further implication of these results is that aldol addition reactions of lithium enolates with simple ketones and aldehydes with a single oxygen must occur dominantly with the enolate monomers. Thus, the mechanism proposed by Seebach et al.,[8] for reaction of the cubic tetramer of a lithium enolate with an aldehyde, although eminently reasonable, clearly cannot normally compete with the simple addition of monomer even at synthesis concentrations.

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Supporting Information Available: Figures S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136−7.

(8) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622−6.