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# Effect of Solvent on Aggregation and Reactivity of Two Lithium Enolates[1]

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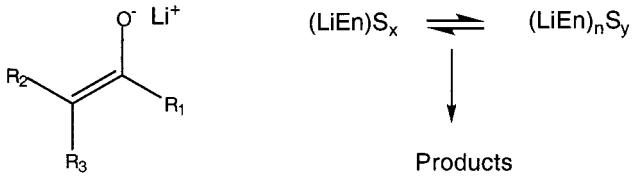
## ABSTRACT




**Studies with two lithium enolates show that aggregation varies from comparable to lower in dimethoxyethane (DME) compared to tetrahydrofuran (THF) but that aggregation is much higher in methyl *tert*-butyl ether (MTBE). Alkylation reactions, which occur dominantly with the enolate monomers, are exceptionally slow in MTBE, but even acylation reactions that can occur with aggregates are orders of magnitude slower in MTBE. These reactions apparently require additional solvation of the lithium cation, and MTBE is ineffective at such solvation.**

Lithium enolates are among the important reagents in modern organic synthesis.[3] These organolithium reagents are usually generated in ethereal solvents, where they are known to exist as a variety of ion pair aggregates.[4−6] Understanding the role of the different aggregates in enolate reactivity remains an important goal in physical organic chemistry.[7] Recently, we have reported equilibrium constants for different aggregates of the lithium enolates of several ketones in THF by spectroscopic and equilibrium studies.[8−12] In this paper, we compare the aggregation states of the lithium enolates of *p*-phenylisobutyrophenone (LiPhIBP) and 2-phenyl-α-tetralone (LiPhAT) in methyl *tert*-butyl ether (MTBE) and dimethoxyethane (DME) with those in THF. The kinetics of reaction of LiPhIBP and LiPhAT with various electrophiles in THF, DME, and MTBE are also reported. These studies show that alkylation and acylation reactions are much slower in MTBE; the alkylation reactions occur dominantly via the enolate monomers that are in exceptionally low concentration in MTBE, but even acylation reactions that can occur with aggregates are much slower in MTBE.

Important studies by Collum et al.[13] have established that the coordination ability of ethers toward lithium cation is MTBE < THF < DME. This generalization agrees well with results for LiPhIBP, which in dilute THF solutions is a mixture of monomer ($\lambda_{max}$ = 352 nm) and tetramer (($\lambda_{max}$ = 329 nm) with $K_{1,4} = 5.0 \times 10^8$ M$^{-3}$.[10] The $\lambda_{max}$ of LiPhIBP in MTBE ($c = 6.9 \times 10^{-4}$ to $5.2 \times 10^{-3}$ M) is constant at 331 ± 1 nm, which corresponds to the tetramer. In contrast,

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**Table 1.** Aggregation of Two Lithium Enolates in Three Ethereal Solvents

| | solvent | | |
|---|---|---|---|
| | THF | DME | MTBE |
| | LiPhIBP | | |
| $\lambda_{max}$ (nm) | 333−352[a] | 348 | 331 |
| concn range (M) | $4 \times 10^{-3}$ to $7 \times 10^{-5}$ | $8 \times 10^{-4}$ to $3 \times 10^{-3}$ | $7 \times 10^{-4}$ to 5 × 10−3 |
| aggregation state | M−T | monomer | tetramer |
| $K_{1,4}$ ($M^{-3}$) | $5.0 \times 10^{8}$ | | |
| | LiPhAT | | |
| $\lambda_{max}$ (nm) | 366−378[b] | 362.5−369.5 | 350 |
| concn range (M) | $1 \times 10^{-3}$ to $6 \times 10^{-5}$ | $1 \times 10^{-3}$ to 6 × 10−5 | $1 \times 10^{-3}$ to $5 \times 10^{-5}$ |
| aggregation state | M−D | M−D | tetramer |
| $K_{1,2}$ ($M^{-1}$) | 1930 | 3700 | |

[a] Reference 10. [b] Reference 14.

in DME solutions ($8.4 \times 10^{-4}$ to $4.5 \times 10^{-3}$ M) $\lambda_{max} = 348 \pm 2$ nm, corresponding to the monomer. For comparison, Jackman and Szeverenyi[4a] concluded from an NMR study at higher concentrations that the lithium enolate of isobutyrophenone in DME is a mixture of tetramer and a lower aggregate that they considered to be the dimer.

The more conjugated LiPhAT is a less basic enolate (p$K$ = 11.14,[14] compared to 15.86[10] for LiPhIBP) and is present as a monomer ($\lambda_{max}$ = 381.5 nm)/dimer ($\lambda_{max}$ = 361.5 nm) equilibrium in THF with $K_{1,2}$ = 1930 $M^{-1}$.[14] In MTBE, LiPhAT also exists as a tetramer, as evidenced by a constant $\lambda_{max}$ = 350 nm ($c = 4.7 \times 10^{-5}$ to $1.2 \times 10^{-3}$ M), shorter than that of the dimer. By contrast, $\lambda_{max}$ for LiPhAT in DME ($c = 6.3 \times 10^{-5}$ to $9.8 \times 10^{-4}$ M) shifts from 369.5 to 362.5 nm. This is a relatively small variation for singular value decomposition (SVD) analysis, but the data indicate a monomer ($\lambda_{max}$ = 372.5 nm)/dimer ($\lambda_{max}$ = 359 nm) equilibrium with an equilibrium constant $K_{1,2}$ = 3700 $M^{-1}$, a number quite similar to that in THF.

Table 1 collects the aggregation data for LiPhIBP and LiPhAT in all three of these ethereal solvents. It is clear that lithium enolate monomers are stabilized by coordinating solvents. In the poorly coordinating MTBE the tetrameric species dominate. The effect of DME as solvent is more complex; it deaggregates LiPhIBP to the monomer relative to THF but is comparable to THF toward LiPhAT. In the equilibrium M ⇄ D ⇄ T, electrostatic forces move the equilibrium to the right and solvation moves the equilibrium to the left, but the solvation effects are opposed by entropy requirements for solvation. Both oxygens in DME through their mutual inductive effects are less basic than the THF oxygen, but DME is bidentate. The experimental results show that these opposing effects are finely balanced for LiPhIBP and LiPhAT.

Kinetics of reactions of LiPhIBP and LiPhAT with several electrophiles were studied at 25 °C in all three solvents, with results that are summarized in Table 2. We have reported previously that enolate monomers are much more reactive in alkylation reactions in THF than are dimers or tetramers.[8−12] This generalization is consistent with the lack of reactivity of both enolates in MTBE toward benzyl bromide. There is clearly very little monomer in MTBE solutions and MTBE is therefore unsuitable as a solvent for lithium enolate alkylations. In contrast, monomeric LiPhIBP and LiPhAT show comparable reactivity toward benzyl bromide in THF and in DME. Analysis of the rate data for LiPhAT in DME, making use of the observed $K_{1,2}$ in the manner we have used previously, shows that the observed rate is that of the monomer. The analysis is given in Supporting Information.

In the Claisen acylation reaction of lithium enolates with esters in THF aggregates react competitively with monomers, apparently because the two ester oxygens can coordinate to more than one lithium cation in the aggregate.[15] As summarized in Table 2, such reactions are also slower in MTBE by at least 2 orders of magnitude compared to THF. Similarly, *N*-benzoylpyrazole with two coordinating centers has been shown to react with lithium enolate aggregates as

**Table 2.** Reactivities of the Monomer (M) and Tetramer (T) of LiPhIBP and the Monomer (M), Dimer (D), and Tetramer (T) of LiPhAT with Various Electrophiles

| | | LiPhIBP | | LiPhAT | | |
|---|---|---|---|---|---|---|
| electrophile | solvent | $k_M$ | $k_T$ | $k_M$ | $k_D$ | $k_T$ |
| benzyl bromide | THF | 0.11[a] | | 0.036[b] | | |
| | MTBE | | ∼0[c] | | | ∼0[c] |
| | DME | 0.041 | | 0.038 | | |
| phenyl thiobenzoate | THF | 0.17[d] | | | | |
| | MTBE | | ∼0[c] | | | |
| | DME | 0.078 | | | | |
| benzoylpyrazole | THF | 3.7[d] | 2.9[d] | 0.57 | 0.7 | |
| | MTBE | | 0.3 | | | 0.06 |
| | DME | 0.9 | | | | |
| *p*-chlorophenyl *p*-chlorobenzoate | THF | 0.146[e] | 0.105[e] | 0.042 | 0.02 | |
| | MTBE | | ∼0[c] | | | 0.003 |
| *m*-chlorophenyl benzoate | MTBE | | ∼0[c] | | | |

[a] Reference 6. [b] Reference 14. [c] $k_2$ less than $10^{-3}$ $M^{-1}$ $s^{-1}$. [d] Reference 15b. [e] Reference 15a.

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well as monomers; it reacts in MTBE solution but more slowly than in THF. These reactions apparently require additional solvation at the transition state, which MTBE is ineffective in supplying. On the other hand, the sulfur in phenyl thiobenzoate does not coordinate effectively to lithium cation and this ester reacts dominantly only with monomers. Accordingly, it shows comparable reactivity in THF and DME but is not reactive in MTBE.

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**Supporting Information Available:** Extinction coefficient measurements of LiPhIBP and LiPhAT in DME and MTBE, several representative kinetic plots, and SVD analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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