

Equilibrium Constants and Alkylation Kinetics of Two Lithium Enolates/LiHMDS Mixed Aggregates in THF

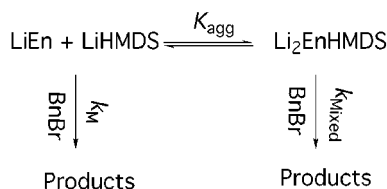
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ABSTRACT



Mixed aggregates between lithium enolates and lithium hexamethyldisilazide (LiHMDS) have been studied in THF using UV–vis spectroscopy. The equilibrium constants (K_{agg}) between monomeric LiEn and monomeric LiHMDS are 760 and 560 M^{-1} when LiEn are LiSIBP and LiBnPAT, respectively. The alkylation kinetics of the reactions with benzyl bromide were studied at 25 °C. The rate constants for the mixed aggregates, k_{Mixed} , are substantially smaller than those of the monomeric enolates.

Lithium amides such as lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS) are frequently used to deprotonate ketones to form lithium enolates. The product lithium enolates are generally aggregated and could form mixed aggregates with the lithium amide. The importance of such mixed aggregates and their possible role in subsequent reactions has been inadequately addressed. Mixed aggregates between lithium amides and lithium enolates have been reported both in the crystal state^{1–3} and in solution.^{4,5} Such mixed aggregates have been the subject of theoretical study,^{6,7} but there has been virtually no quantitative study of their equilibrium constants for formation and their reactivities. In this paper we report the formation constants of mixed aggregates in THF of LiHMDS with two lithium

enolates, LiSIBP and LiBnPAT, from *p*-phenylsulfonyl-isobutyrophenone (SIBP) and 6-phenyl-2-benzyl- α -tetralone (BnPAT), respectively, and a kinetics study of their reactivities in an alkylation reaction. Lithium hexamethyldisilazine (LiHMDS) is widely used because it combines the properties of a strong base with weak nucleophilicity and it also has the advantage of solubility in both hydrocarbon and polar solvents. We reported previously the use of UV–vis spectroscopy for determining the equilibrium constants and alkylation kinetics of a lithium enolate/lithium bromide mixed aggregate in THF.⁸ This approach was applied in the present cases. We have also reported that LiSIBP and LiBnPAT in THF solution are mixtures of monomer and dimer ($K_{1,2} = 5.0 \times 10^4 \text{ M}^{-1}$ for LiSIBP⁹ and $K_{1,2} = 3.8 \times 10^3 \text{ M}^{-1}$ for LiBnPAT).¹⁰

Incremental addition of LiHMDS to THF solutions of LiSIBP causes a blue shift in the UV–vis spectra from $\lambda_{\text{max}} = 391 \text{ nm}$ to $\lambda_{\text{max}} = 370.5 \text{ nm}$ as shown in Figure 1. An

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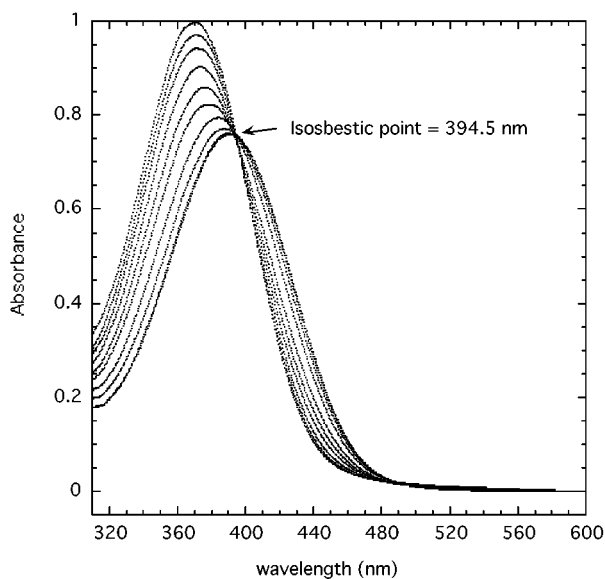


Figure 1. Effect of incremental addition of LiHMDS to a solution of 0.00208 M LiSIBP in THF at 25 °C. The plot with lowest absorbance is without addition of LiHMDS. The plot with highest absorbance is from addition of 0.077 M LiHMDS. The net effect is a shift in λ_{max} from 391 to 370.5 nm.

isosbestic point at 394.5 nm indicates the formation of a single mixed aggregate species. A similar blue shift (λ_{max} = from 361 to 345 nm) and isosbestic point at 363 nm were observed for the addition of LiHMDS to a THF solution of LiBnPAT (Figure 2). Since these enolates form dimers at

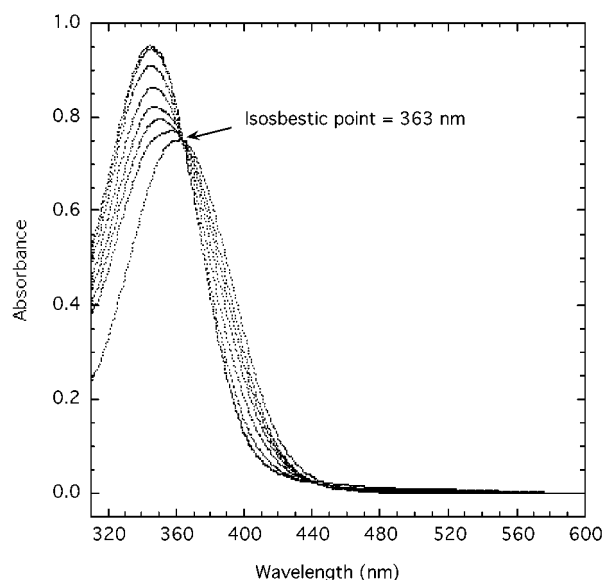
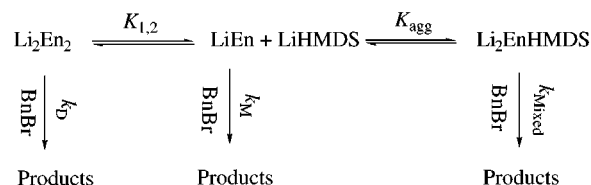


Figure 2. Effect of incremental addition of LiHMDS to a solution of 0.00064 M LiBnPAT in THF at 25 °C. The plot with lowest absorbance is without addition of LiHMDS. The plot with highest absorbance is from addition of 0.0509 M LiHMDS. The net effect is a shift in λ_{max} from 361 to 345 nm.

these concentrations and LiSIBP forms a 1:1 mixed aggregate with LiBr, we assume that the mixed aggregates in the present cases are also the 1:1 aggregates, (LiEn)(LiHMDS), Scheme 1.

Scheme 1



The value of K_{agg} is given by eq 1 where [LiEn] and

$$K_{\text{agg}} = \frac{[\text{Li}_2\text{-EnHMDS}]}{[\text{LiEn}][\text{LiHMDS}]} \quad (1)$$

[LiHMDS] are the concentrations of monomers in equilibrium. Since LiHMDS exists primarily as a monomer in THF,¹¹ its concentration is taken directly. Deconvolution of the UV-vis spectra of the mixtures, making use of previously determined spectra for the enolate monomers and dimers, gave the concentrations of monomer, dimer, and mixed aggregate for each mixture (Tables S1 and S2, Supporting Information).

Average values found for K_{agg} are taken as $560 \pm 90 \text{ M}^{-1}$ for LiBuPAT/LiHMDS and $760 \pm 55 \text{ M}^{-1}$ for LiSIBP/LiHMDS, with the errors taken as the standard deviations. The estimated errors are probably reasonable measures of the accuracy as well as the precision. The values found for the two K_{agg} are of similar magnitude and are somewhat lower than that found for LiSIBP/LiBr, $K_{\text{agg}} = 3600 \text{ M}^{-1}$.

There have been only a few reports of the reactivities of enolate-amide mixed aggregates and then only for proton-transfer reactions.⁴ In the present work we use the K_{agg} values found above in a quantitative kinetic study of alkylation reactions of the mixed aggregates. Reaction kinetics between LiEn and a large excess of benzyl bromide (BnBr) were measured in the presence of LiHMDS. Initial rates were determined by the decrease of absorbance of LiEn at the isosbestic point for the first 10–20% reaction. Since LiHMDS can also react with BnBr and complicate the reaction kinetics, the products were analyzed by GC-MS after quenching the first 10–20% reaction. The desired alkylation product was at least 2.5 times larger than the LiHMDS reaction product, *N,N*-bis(trimethylsilyl)benzylamine. Consequently, changes in concentration of BnBr due to reaction with LiHMDS are negligible during the initial stages of reaction.

The total rate expression is given by eq 2. In previous

$$\text{rate} = \frac{-d\{\text{LiEn}\}}{dt} = k_M [\text{LiEn}][\text{BnBr}] + k_{\text{Mixed}} [\text{Li}_2\text{EnHMDS}][\text{BnBr}] \quad (2)$$

work the dimers of LiSIBP and LiBuPAT were shown to be

much less reactive in alkylation reactions than the monomers;^{9,10} thus, the dimer reactions have been omitted from eq 2. Simple rearrangement gives eq 3 in which the rate

$$\frac{\text{rate}}{[\text{Li}_2\text{EnHMDS}][\text{BnBr}]} = k_{\text{Mixed}} + \frac{k_{\text{M}}}{K_{\text{agg}} [\text{LiHMDS}]} \quad (3)$$

function is now a linear equation in $1/[\text{LiHMDS}]$. From the initial rates and K_{agg} and $K_{1,2}$, the quantities were calculated for each kinetic point. The rate constants for monomer, k_{M} , and mixed aggregate, k_{Mixed} , were determined from plots of $1/[\text{LiHMDS}]$ vs $\text{rate}/([\text{Mixed}][\text{BnBr}])$ (Figure 3).

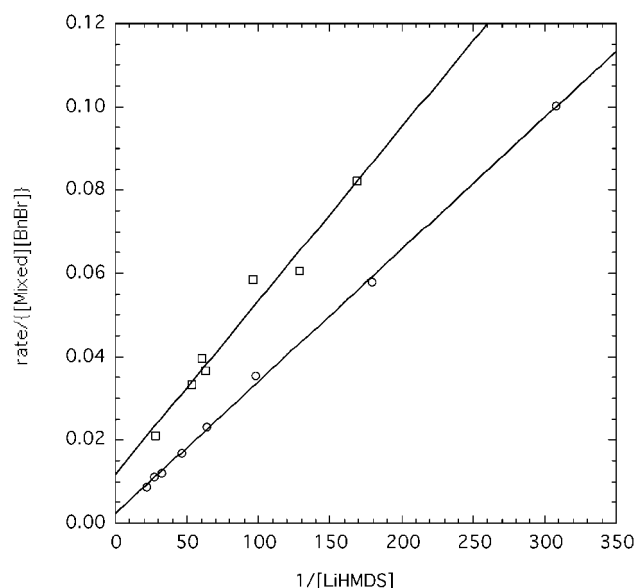


Figure 3. Plot for determining the rate constants for the reaction of monomeric LiEn and Li_2EnHMDS . The regression lines are: LiSIBP (circles), $(0.0024 \pm 0.0005) + (0.00032 \pm 4 \times 10^{-6})x$, ($R^2 = 0.999$; $K_{\text{agg}} = 760$); LiBnPAT (squares), $(0.012 \pm 0.003) + (4.16 \pm 0.33) \times 10^{-4}x$ ($R^2 = 0.969$; $K_{\text{agg}} = 560$).

The initial rates give the linear plots in Figure 3. Using $K_{\text{agg}} = 760$ and 560 M^{-1} , the slopes in Figure 3 yield $k_{\text{M}} = 0.241 \pm 0.003$ and $0.233 \pm 0.019 \text{ M}^{-1} \text{ s}^{-1}$ for LiSIBP and LiBnPAT, respectively. The accuracy is probably not as good as the precision but the results are in good agreement with those obtained in the absence of LiHMDS, 0.32 (for *p*-*tert*-butylBnBr which is expected to be somewhat more reactive than BnBr) and $0.174 \text{ M}^{-1} \text{ s}^{-1}$, respectively.^{8,10} The intercepts give $k_{\text{Mixed}} = 0.0024 \pm 0.0005$ and $0.012 \pm 0.003 \text{ M}^{-1} \text{ s}^{-1}$ for LiSIBP and LiBnPAT, respectively, which are much smaller values, by factors of 100 and 20, respectively, than k_{M} .

The significance of these results can be demonstrated by a hypothetical synthesis example of an alkylation reaction

run with 0.25 M LiSIBP and 0.5 M LiHMDS. Sixty percent of the starting enolate is present as the mixed aggregate and 40% is present as the dimer. The amount of monomer is less than 1% and would be invisible to NMR, yet 40% of an initial alkylation reaction will involve the monomer and only 60% is with the mixed aggregate. For a chiral lithium amide with comparable numbers, much of the product would derive from the achiral enolate monomer, and the product ee, at least in THF, would necessarily be disappointing.

An extension of this work was attempted with LDA, but the above lithium enolates were found to be unsuitable. LiSIBP reacts in some manner with LDA and was not studied further. LiBnPAT is deprotonated by LDA to form a dianion. The lithium enolates LiPhAT (from 2-phenyl- α -tetralone) and LiPhPAT (from 2,6-diphenyl- α -tetralone) were explored. Incremental addition of LDA generated a blue shift as in LiHMDS addition (Figure 4). Since LDA itself absorbs up

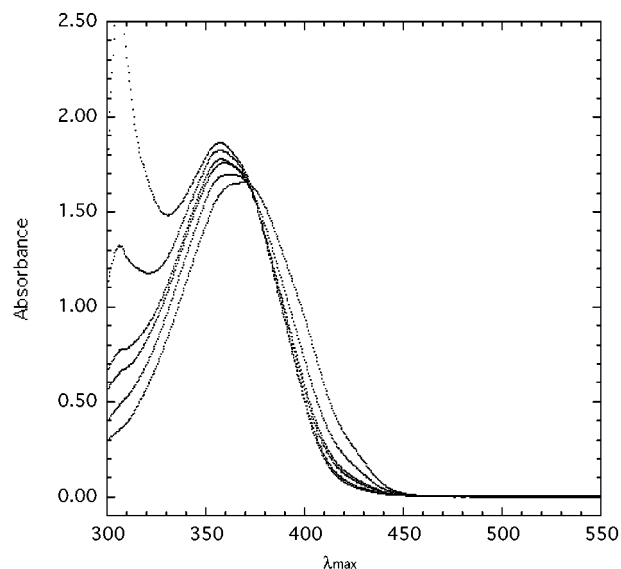


Figure 4. Effect of incremental addition of LDA to a solution of LiPhAT in THF at 25 °C.

to 350 nm, it was not possible to assign the λ_{max} for the mixed aggregates. It was also not possible to derive K_{agg} because the $K_{1,2}$ for LDA is not known, although it is known that LDA exists primarily as a dimer in THF solution at 25 °C. Tables S3 and S4 (Supporting Information) summarize the experimental data. Approximate evaluation, however, indicates that K_{agg} is much higher for LDA than for LiHMDS.

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Supporting Information Available: Tables of spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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