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Communications to the Editor

Equilibrium Characterization and Alkylation Kinetics of a Lithium Enolate−Lithium Bromide Mixed Aggregate in THF[1]

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In ether solvents commonly used in organic synthesis, lithium enolates exist in variety of contact ion pair aggregates.[2−5] Additives such as lithium halides can form mixed aggregates with enolates and apparently influence reactivity and selectivity.[6] Participation of higher order aggregates and mixed aggregates in alkylation and aldol addition reactions of enolates has been invoked to rationalize observed product distributions,[7,8] but direct evidence of the kinetically relevant species is largely absent.[9] We report the use of UV−vis spectroscopy and coupled equilibria to characterize the mixed aggregate formed between the lithium enolate (LiSIBP) of *p*-phenylsulfonylisobutyrophenone (SIBP) and lithium bromide in THF and kinetics studies of its role in an alkylation reaction.

We have shown recently that LiSIBP exists in THF primarily as an ion pair dimer, Li_2En_2, that has a characteristic spectrum at $\lambda_{max} = 390$ nm, in equilibrium with small amounts of monomeric LiEn ($K_d(\mathrm{LiEn}) = 5.0 \times 10^4$ M^{-1}).[10] Incremental addition of 1−10 equiv of lithium bromide {LiBr} to THF solutions of {LiEn} (brackets denote "formal concentrations") causes a blue shift in the UV−vis spectra to $\lambda_{max} = 381$ nm, $\epsilon = 4600$ M^{-1} cm^{-1} (Figure S1, supporting information). An isosbestic point at 403 nm indicates formation of a single mixed aggregate species, $(\mathrm{LiEn})_x(\mathrm{LiBr})_y$, eq 1, whose spectrum is known from the absence of further change after addition of about 20 equiv of {LiBr}.

$$x\mathrm{LiEn} + y\mathrm{LiBr} \xrightleftharpoons{K_{agg}} \mathrm{Li}_{x+y}\mathrm{En}_x\mathrm{Br}_y \qquad (1)$$

The ion-pair acidity of SIBP is defined relative to an indicator by the transmetalation equilibrium of eq 2.[11]

$$\mathrm{SIBP} + \mathrm{LiIn} \xrightleftharpoons{K_{eq}} \mathrm{LiEn} + \mathrm{InH} \qquad (2)$$

$$2\mathrm{LiEn} \xrightleftharpoons{K_d} \mathrm{Li_2En_2} \qquad (3)$$

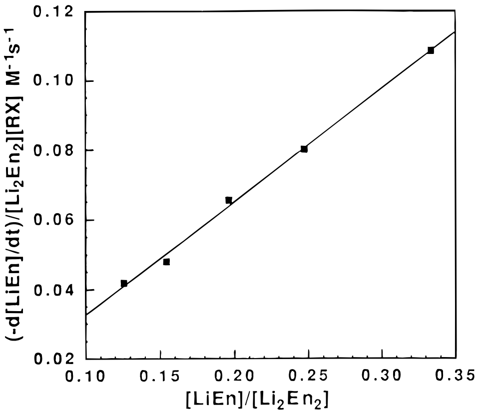
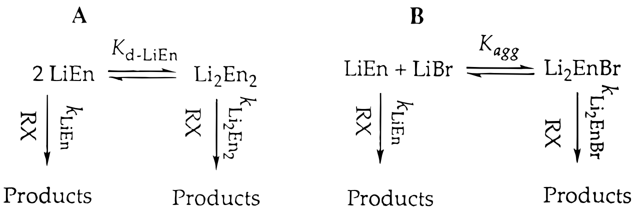


Figure 1. Plot for determining the bimolecular rate constants for the reaction of monomeric and dimeric lithium enolate (Scheme 1A, eq 4). Rates were measured at 25.0 °C and constant [RX] = 4.5×10^{-2} M. The monomer−dimer ratios were determined from the known value of K_d(LiEn) and the initial [{LiEn}]. The slope corresponds to $k_{\mathrm{LiEn}} = 0.32$ M^{-1} s$^{-1,}$ and the intercept is $k_{\mathrm{Li_2En_2}} = 1.2 \times 10^{-4}$ M^{-1} s^{-1}.

Scheme 1



Aggregation of LiEn (eq 3) increases the apparent acidity of SIBP and causes the observed Δp*K* to be dependent on the formal enolate concentration (Figure S2, supporting information).[10] From this dependence the average aggregation number of the enolate ion pair can be deduced.[11]

Similarly, when LiBr is present in amounts sufficient to convert LiEn essentially completely to the mixed aggregate, the dependence of the observed acidity of SIBP at a given LiBr concentration on the formal concentration of the mixed aggregate provides the average stoichiometric number (x) of LiEn in $(\mathrm{LiEn})_x(\mathrm{LiBr})_y$.

Ion-pair acidity measurements of SIBP were made at different concentrations of $\{\mathrm{Li}_{x+y}\mathrm{En}_x\mathrm{Br}_y\}$ and 6.0×10^{-2} M {LiBr}[12] using the indicator 7-phenyl-7*H*-benzo[*c*]fluorene ($\mathrm{p}K_{\mathrm{InH}} = 14.88$). In the concentration range 6×10^{-5} to 5×10^{-3} M $\{\mathrm{Li}_{x+y}\mathrm{En}_x\mathrm{Br}_y\}$, the observed p*K* is essentially constant at 13.12 ± 0.08 (Figure S2), indicating that only one LiEn molecule is present in the complex ($x = 1$).

For the correct stoichiometry of LiBr in the mixed aggregate, a plot of the ratio of $[\mathrm{LiEn(LiBr)}_y]$ to monomeric [LiEn] against monomeric [LiBr] raised to the appropriate order required by eq 1 should be linear.

Spectra of the enolate in the presence of 1−10 equiv of {LiBr} were deconvoluted into the spectra of pure LiEn and $\mathrm{LiEn(LiBr)}_y$, and the corresponding concentrations were determined. Using the dimerization constants $K_d(\mathrm{LiEn}) = 5.0 \times$

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[1] Carbon Acidity. 95.

[2] Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

[3] Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York; p 93.

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[6] (a) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. (b) Hasegawa, Y.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 1963. (c) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202.

[7] (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654. (b) Juristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopahyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271−1290.

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[9] Palmer, C. A.; Ogle, C. A.; Arnett, E. M. *J. Am. Chem. Soc.* **1992**, *114*, 5619−5625.

[10] Abu Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−4689.

[11] For a description of the equilibrium ion-pair acidity method, see: Kaufman, M. J.; Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092−7.

[12] Under these conditions, the absorption spectrum of the enolate is insensitive to its concentration, indicating that equilibrium concentrations of enolate-containing species other than $\mathrm{LiEn(LiBr)}_y$ are negligible.

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10^4 M^{-1} [10] and K_d(LiBr) = 20 M^{-1} [13] only $y = 1$ (Li_2EnBr, 1:1 mixed aggregate), gives a linear equilibrium plot for eq 1 (Figure S3, supporting information) and yields $K_{agg} = 3.6 \times 10^3$ M^{-1} for the equilibrium between monomeric LiEn and monomeric LiBr.

We showed previously that the reaction of LiSIBP with *p-tert*-butylbenzyl bromide (RX) involves dominantly the monomer and yields primarily C-alkylated products.[10] The complete rate law corresponding to reaction of monomer and dimer (Scheme 1A) is given by eq 4

$$\frac{-\mathrm{d}[\{\mathrm{LiEn}\}]}{\mathrm{d}t} = k_{\mathrm{Li_2En_2}}[\mathrm{Li_2En_2}][\mathrm{RX}] + k_{\mathrm{LiEn}}[\mathrm{LiEn}][\mathrm{RX}] \quad (4)$$

Dividing through by $[Li_2En_2]$ gives a linear equation in the monomer−dimer ratio. Initial rates were measured for the first 10% of reaction by following the absorbance at $\lambda = 390$ nm at constant [RX] (4.5×10^{-2} M) and varying [{LiEn}] (4×10^{-4} to 3×10^{-3} M); the slope of the plot given in Figure 1 gives $k_{LiEn} = 0.32$ M^{-1} s^{-1}, and the intercept gives $k_{Li_2En_2} = 1.2 \times 10^{-4}$ M^{-1} s^{-1}. Thus, in this concentration region the ratio of reaction taking place *via* LiEn compared to Li_2En_2 is between 470 and 170.

The rate of this alkylation reaction is inhibited by LiBr. A complete kinetic treatment corresponding to Scheme 1B is given by eq 5

$$\frac{-\mathrm{d}[\mathrm{Li_2EnBr}]}{\mathrm{d}t} = k_{\mathrm{Li_2EnBr}}[\mathrm{Li_2EnBr}][\mathrm{RX}] + \frac{k_{\mathrm{LiEn}}[\mathrm{Li_2EnBr}][\mathrm{RX}]}{K_{\mathrm{agg}}[\mathrm{LiBr}]} \quad (5)$$

Initial rates, determined by following the absorbance of Li_2EnBr at 381 nm for 10% reaction, give the linear plot in Figure 2. Using $K_{agg} = 3.6 \times 10^3$ M^{-1}, the slope in Figure 2 yields $k_{LiEn} = 0.33$ M^{-1} s^{-1}, in good agreement with the result obtained in absence of LiBr. The intercept gives $k_{Li_2EnBr} = 7.8 \times 10^{-4}$ M^{-1} s^{-1}, a value similar to but somewhat larger than that of $k_{Li_2En_2}$.

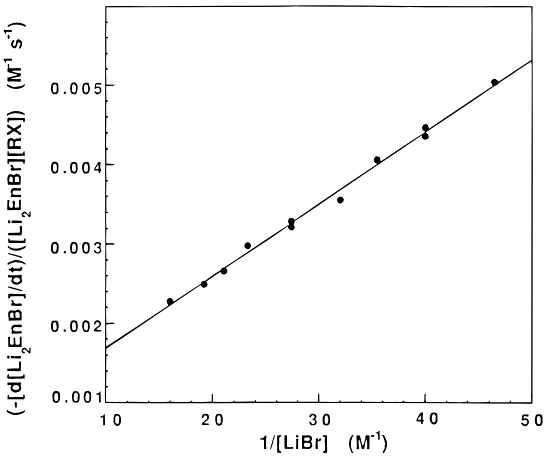

Figure 2. Plot for determining the bimolecular rate constants for reaction of monomeric LiEn and Li_2EnBr (Scheme 1B, eq 5). Monomeric [LiBr] was obtained using K_d(LiBr) = 20 M^{-1}. Rates were measured at 25.0 °C with $[Li_2EnBr]$ of ca. 2×10^{-3} M and [RX] of ca. 4.5×10^{-2} M.

According to these results, in the range 0.04−0.22 M [{LiBr}] and ca. 2×10^{-3} M [{LiEn}], the ratio of [LiEn] to $[Li_2EnBr]$ is between 6×10^{-3} and 2×10^{-3}, and the ratio of reaction proceeding *via* LiEn to that *via* Li_2EnBr is between 5.5 and 1.9. Thus, although LiBr suppresses the concentration of monomeric LiEn, the monomer continues to be the dominant reactant in the overall reaction, although at higher LiBr concentrations the contribution from reaction of Li_2EnBr becomes substantial.

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Supporting Information Available: Figures, tables, and experimental data (5 pages). See any current masthead page for ordering and Internet access instructions.

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[13] Determined from the apparent molecular weights of LiBr in THF (Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem.* **1972**, *34*, 3615) assuming a monomer−dimer equilibrium.