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Aggregation and Alkylation Kinetics of the Lithium Enolate of *p*-(Phenylsulfonyl)isobutyrophenone[1]

Faraj Abu-Hasanayn, Manolis Stratakis, and Andrew Streitwieser*

Department of Chemistry, University of California, Berkeley, California 94720-1460

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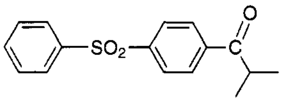
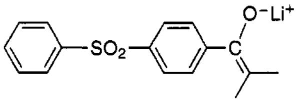
Lithium enolates are among the important reagents in modern organic synthesis. In ether solvents important in synthesis lithium enolates are known to exist in a variety of ion-pair aggregates. The role of these different aggregates in reactions of enolates is still almost unknown. In this paper we report on the aggregation state of the lithium enolate (LiSIBP) derived from *p*-(phenylsulfonyl)isobutyrophenone (SIBP) and the kinetics of an alkylation reaction.[2]



SIBP



LiSIBP

The λ_{max} of the lithium salt of *p*-phenylisobutyrophenone is close to that of the ketone, and determination of the ion pair acidity (defined in terms of the transmetalation equilibrium 1 with the p*K*'s per hydrogen relative to fluorene = 22.9)[3] required the single indicator technique in which the equilibrium constant is determined by the change in absorbance of the indicator on adding a known amount of substrate. Nevertheless, the lithium enolate was found recently to be primarily monomer and tetramer in THF.[4]

$$RH + R'^{-}M^{+} = R^{-}M^{+} + R'H \qquad (1)$$

LiSIBP has λ_{max} at much longer wavelength and could be studied readily by the double indicator technique in which the equilibrium constant is determined by absorbance measurements of the carbanion salt of both substrate and indicator. The equilibrium ion-pair acidity measured against the lithium salt of 7-phenyl-7*H*-benzo[*c*]fluorene (InH; $pK_{InH} = 14.88$) in THF gives an almost linear plot of pK_{ob} vs the formal concentration of LiSIBP; the slope over the concentration range 3×10^{-5}–3×10^{-3} M corresponds to an average aggregation number of 1.8,[5] indicating that at these concentrations LiSIBP is mostly dimeric with only a small amount of monomer.

In previous studies we have shown that different aggregation states of organoalkali compounds often have significantly different absorption spectra.[4,6] Dilution of LiSIBP from 3×10^{-3} to 5×10^{-5} M caused λ_{max} to shift gradually from 390 to 394 nm. Singular value decomposition (SVD) analysis[6] revealed the presence of two spectroscopically distinct species (singular values $S_1 = 16.66$ and $S_2 = 0.24$). Transformation gave the spectra of the monomer ($\lambda_{max} = 409$ nm) and dimer ($\lambda_{max} = 390$ nm).[7] All measured spectra could be properly reconstructed using the spectra of these components and gave a dimerization constant $K_d = (5.0 \pm 0.1) \times 10^4$ M^{-1}. By use of this value and the acidity equilibria, the p*K* of monomeric SIBP, pK_{SIBP}, derived for Scheme 1 is 14.69.[8,9]

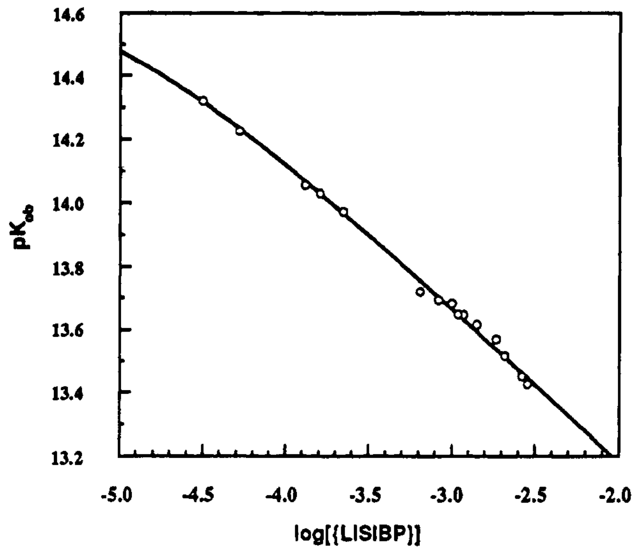


Figure 1. Experimental p*K* compared to the formal concentration of LiSIBP, [{LiSIBP}]. Circles are experimental data. The solid curve is the theoretical pK_{ob} plot derived for Scheme 1 ($K_{ob} = K_{eq}(0.5 + 0.5(1 + 8K_d[\{LiSIBP\}])^{1/2})$[9] using $pK_{SIBP} = 14.69$, $pK_{InH} = 14.88$, and $K_d = 5.0 \times 10^4$ M^{-1}.

Scheme 1

$$SIBP + LiIn \overset{K_{eq}}{\rightleftharpoons} (LiSIBP)_1 + InH$$

$$2\,(LiSIBP)_1 \overset{K_d}{\rightleftharpoons} (LiSIBP)_2$$

The theoretical aggregation plot of LiSIBP calculated using these values provides an excellent fit to the experimental data (Figure 1).

Initial rates (up to 10% completion) of the reaction of LiSIBP with excess *p*-*t*-butylbenzyl bromide (RX) were

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* To whom correspondence should be addressed. E-mail: ASTREIT@garnet.berkeley.edu.

(1) Carbon Acidity. 90.

(2) *p*-(Phenylsulfonyl)isobutyrophenone is a new compound prepared from the reaction of *p*-(phenylsulfonyl)benzaldehyde and isopropylmagnesium bromide followed by oxidation of the alcohol product with sodium dichromate. *p*-(Phenylsulfonyl)benzaldehyde was prepared by oxidation of phenyl *p*-tolyl sulfone with chromium trioxide and acetic anhydride following the procedure of Burton and Hu: Burton, H.; Hu, P. F. *J. Chem. Soc.* **1948**, 601.

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(4) Abbotto, A.; Streitwieser, A. *J. Am. Chem. Soc.* **1995**, *117*, 6358−9.

(5) Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092−7.

(6) Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024−30.

(7) Since an isosbestic point could not be observed when the concentration of LiSIBP was varied, we make the approximation that at λ_{max} of the monomer and dimer $\epsilon_d = 2\epsilon_m$ (= 7720 M^{-1}cm^{-1}).

(8) K_{ob} is defined as K_{ob} = [{LiSIBP}][InH]/[LiIn][SIBP]; [{LiSIBP}] and [LiIn] are measured spectroscopically (double indicator method). The equilibrium ion-pair p*K* of SIBP is defined as: $pK_{SIBP} = pK_{InH} - \log K_{eq}$; where K_{eq} = [LiSIBP][InH]/[LiIn][SIBP]. [LiIn] was corrected for dissociation into free ions using $K_{diss} = 1.0 \times 10^{-5}$ M^{-1}, a typical value for free ion dissociation of benzofluorenyllithium ion pairs (ref 3).

(9) Ciula, J. C.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 431−2. Correction: *Ibid.* 6686.

(10) Krom, J. A.; Streitwieser, A. *J. Am. Chem. Soc.* **1992**, *114*, 8747−8. Note that after this paper was published we discovered that λ_{max} of the cesium enolate changes significantly with concentration. Correction for this change makes the monomeric ion pairs rather than the free ions the reactive species.

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

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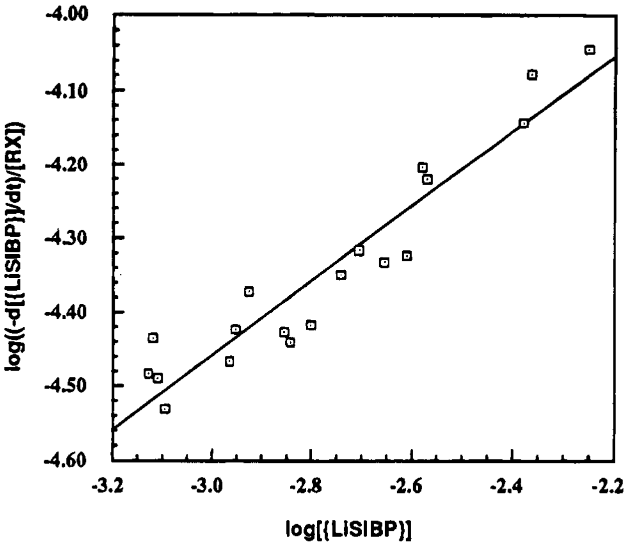

Figure 2. Each square is a separate kinetic run showing the initial rate of reaction with *p-tert*-butylbenzyl bromide as a function of the formal concentration of LiSIBP. The slope of the line shown corresponds to (n_k/n_a) and has the value 0.50 ± 0.04.

measured in THF at 25.0 °C by following the decrease in the absorbance of LiSIBP at 390 nm. Initial formal concentrations of LiSIBP were varied from 7×10^{-4} to 5×10^{-3} M; in this region monomer ranges from 11 to 4.5% of the total enolate. The observed data summarized in Figure 2 fit a straight line of slope 0.50 ± 0.04. For a reaction unimolecular in the alkylating agent, the slope at any point in such a figure corresponds to (n_k/n_a) where n_k is the average kinetic aggregation number.[10] In this concentration region $n_a = 1.87$; hence, $n_k = 0.94 \pm 0.07$. That is, reaction occurs via the monomeric ion pair even in the presence of a large excess of dimer. Note that the measured value of K_d means that at concentrations used in synthesis of several tenths molar the lithium enolate is still almost 1% monomer and the monomer undoubtedly is still primarily involved in the alkylation reaction. This result compares with the alkylation in THF of the cesium enolate of *p*-phenylisobutyrophenone and methyl tosylate which also involves the monomeric enolate ion pairs in an equilibrium dominated by aggregates.[10] These results show that a proposed mechanism of reaction of metal enolate aggregates[11] does not occur generally and may, in fact, have limited applicability.

To identify the reaction products, some kinetic runs were allowed to go to completion; THF was evaporated and the residue was taken into a deuterated solvent. ^{1}H and ^{13}C NMR spectra of corresponding solutions are in agreement with formation of primarily the C-alkylated product. Similar results were observed when reactions were quenched with benzoic acid after 10% completion.

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Supporting Information Available: Experimental procedures and characterization data (1 page).

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