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Communications to the Editor

Aggregation of the Lithium Enolate of *p*-Phenylisobutyrophenone in THF: The Unexpected Importance of Monomer[1]

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Several studies have shown that many metal enolates exist as aggregated species (dimers, tetramers, and higher units) in nonpolar or weakly polar solvents.[2] However, the role of such aggregates in the reaction with electrophiles is still not clear. Understanding this role has synthetic significance because of mechanistic implications in reactivity and stereoselectivity.[3] Jackman has reported that the methylation of the lithium salt of isobutyrophenone proceeds through aggregates, the only species he observed in 0.5 M solutions using NMR spectroscopy.[4] Recently, we reported that the reactive intermediate in the methylation of the cesium enolate of 1-(4-biphenylyl)-2-methyl-1-propanone[5] (*p*-phenylisobutyrophenone, PhIBP) in tetrahydrofuran (THF) is the free enolate ion.[6] After that report was published, we discovered that the spectrum of the cesium enolate varies with concentration and deviates slightly from Beer's law. These changes indicate that different aggregates have slightly different spectra. Analyzing the data by singular value decomposition (SVD)[7] changes the results sufficiently to show that the reactive species in alkylation is not the free ion but the monomeric ion pair.[8] In this paper we present our preliminary results of the application of this approach to the lithium salt of PhIBP (LiPhIBP) in THF.[9]

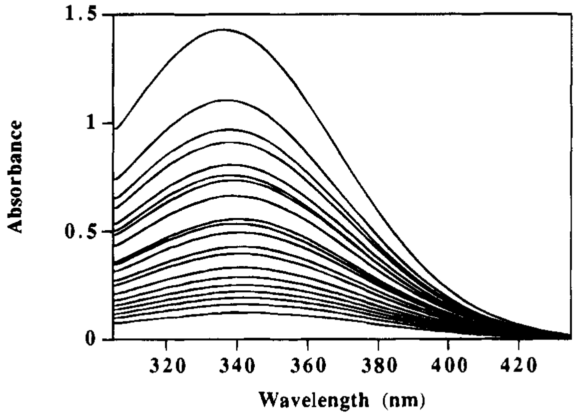

Figure 1. Concentration dependence of the UV−vis spectrum of LiPhIBP in THF at 25 °C. Formal concentrations range from 3.34×10^{-3} (top spectrum, $\lambda_{max} = 336$ nm) to 2.71×10^{-4} M (bottom spectrum, $\lambda_{max} = 342$ nm) (1 mm cell).

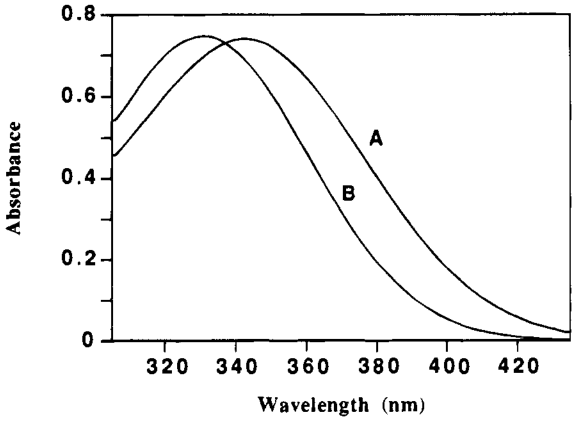

Figure 2. Spectra of the monomer $(LiPhIBP)_1$ (A, $\lambda_{max} = 343$ nm) and the tetramer $(LiPhIBP)_4$ (B, $\lambda_{max} = 331$ nm) in THF at 25 °C ([monomer] = 4[tetramer] = 1.708×10^{-3} M in a 1 mm cell). At 337 nm, the extinction coefficients for the monomer and the tetramer are 4280 and 17 000 M^{-1} cm^{-1}, respectively.

UV−vis spectra of the lithium enolate LiPhIBP[10] in THF[11] are shown as a function of concentration in Figure 1. The results clearly show a shift of λ_{max} to longer wavelength at higher dilution.[12] The dependence of the UV spectrum of LiPhIBP on the concentration is evidence of the simultaneous presence of more than one species (aggregates $(LiPhIBP)_n$), each with a different absorption, and shows that their relative concentrations $[(LiPhIBP)_n]$ change with the total formal concentration of the anion {LiPhIBP}. These spectra were digitized at 0.5 nm intervals, and the resulting large matrix was subjected to the

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(1) Carbon Acidity. 89. For part 88, see: Xie, L.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 1339.

(2) For reviews, see: (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (c) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277. See also: (d) Kaufman, M. J.; Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092. (e) Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354. (f) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801. (g) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288−7293. (h) Ciula, J. C.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 431.

(3) See, for example: (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622−2626. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810−1815. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602−8604. (d) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575−9585. (e) Galiano-Roth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053−5055. (f) Bach, R. D.; Andres, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613−618. (g) Wei, Y.; Bakthavatchalam, R.; Jin, X. M.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1993**, *34*, 3715−3718. (h) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343−5346.

(4) (a) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. (b) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494. (c) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805−2806.

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(9) The lithium enolate of isobutyrophenone is not suitable since it absorbs in a UV region where strong aromatic bands arise from indicators and bases. The introduction of a phenyl ring in the para position shifts the absorption sufficiently toward the visible region, without significantly perturbing the steric and electronic nature of the ion-pair species.

(10) LiPhIBP was obtained in THF solution using the lithium salt of 9-methylfluorene or 9,9,10-trimethyldihydroanthracene as a base, obtained from the corresponding neutrals and twice sublimed LDA. All of the measurements and the manipulations were carried out in a glovebox under an argon atmosphere.The UV−vis experiments were performed in THF solution at 25.0 ± 0.1 °C.

(11) The THF was refluxed for several hours over calcium hydride under nitrogen, distilled, degassed, stirred over sodium−potassium alloy until the characteristic blue color appeared, and vacuum transferred into a dried receiver. The solvent was then stored in the glovebox over activated 3 Å molecular sieves. In this way, the typical amount of water in the solvent is about 5×10^{-5} M, as determined by the quenching of a THF solution of (diphenylmethyl)cesium.

(12) At 337 nm the value of the extinction coefficient is insignificantly dependent on the concentration of the anion and equal to 4240 ± 20 M^{-1} cm^{-1} (22 measurements).

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SVD procedure.[7] The first vector resulting from this analysis is the mean spectrum, the second is the first-order deviation from the mean, and the remaining vectors describe noise. This indicates that only two species are necessary to describe all of the spectra. The two vectors were subjected to a linear transformation[7] in which different stoichiometries were assumed between the two species. The observed concentration effects can be fit only if the two species are in the ratio monomer and tetramer. The two aggregates have the derived spectra shown in Figure 2. Of special interest is the finding that the amount of dimer present is too small to detect.

The ion-pair acidity study of LiPhIBP provided us with an independent approach to confirm and validate the spectroscopic evidence. The p*K* of LiPhIBP was determined as a function of concentration. The observed acidity with an aggregated ion-pair species is dependent on concentration, the sensitivity of the change being directly related to the degree of aggregation of the metalated species in solution.[2d] These determinations required the "single indicator method" [13] because the spectrum of the large amount of neutral ketone present interfered with the direct measurement of enolate.[14] The plot in Figure 3 shows the relatively large error bars of about ±0.1 p*K* units. The curve shown is that derived from the spectroscopic measurements, $K_{\text{tetramer}} = [\text{tetramer}]/[\text{monomer}]^4 = 5.2 \times 10^7\ \text{M}^{-3}$. The high slope at 10^{-2} M (corresponding to an average aggregation number of 3.3)[2d] shows that at this concentration the enolate is primarily tetrameric, in agreement with Jackman's findings for lithium isobutyrophenone at typical NMR concentrations. In contrast, the leveling off of the p*K* values at about 10^{-4} M is evidence of the exclusive presence of the monomer at low concentrations. More importantly, even at concentrations typical of synthesis experiments, 0.1−1 M, the monomeric ion pair is calculated to be 1−5% of the total enolate, an amount that may well be kinetically significant, especially considering our findings for the reactivity of CsPhIBP[6] and the lithium salt of *p*-phenylsulfonylisobutyrophenone.[15] Kinetic studies of alkylation are currently in progress.

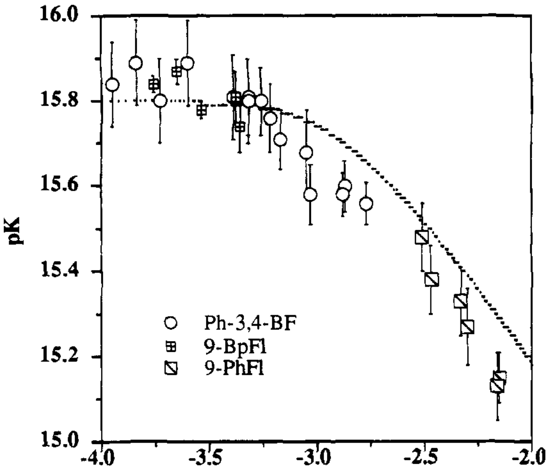

Figure 3. Aggregation plot for LiPhIBP in THF at 25 °C. The curve shown is the theoretical curve for p*K*(monomer) = 15.80 and $K_{\text{tetramer}} = 5.2 \times 10^7\ \text{M}^{-3}$. Three indicators were used: Ph-3,4-BF, 9-phenyl-3,4-benzofluorene; 9-BpFl, 9-*p*-biphenylylfluorene; 9-PhFl, 9-phenylfluorene (26 measurements).

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Note Added in Proof: Kinetics of the alkylation reaction of LiPhIBP by *p-tert*-butylbenzyl bromide were studied in THF at 25 °C. Twelve experiments were carried out with initial values of the formal concentration of LiPhIBP between 1.1×10^{-3} and 1.3×10^{-2} M. In this range, the average aggregation number of the ion pair is 1.4−3.4. The kinetics followed rate laws of 0.5−0.25 in the lithium enolate, in accord with the change in monomer concentration. The derived average aggregation number of the kinetically active species[6] is 0.9 ± 0.1; that is, the monomer ion pair is found to be the reactive species even at concentrations where the tetramer dominates.

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(14) In a typical experiment, an aliquot of a solution of 9-methylfluorenyllithium in THF was added to a known amount (0.5−1 g) of THF in a UV cell. A known amount (0.5−5 mg) of the indicator was added to this solution, and the resulting spectrum of its lithium salt was obtained. The ketone (0.5−5 mg) was then added, and the decrease in the absorbance of the lithium salt of the indicator was followed until the equilibrium was reached. The proton transfer from the ketone to the lithium indicator was much slower than that for the cesium salt[6] and resulted in only a gradual decrease in absorbance readings with time. A stable equilibrium endpoint was considered to be reached only when the absorbance shape of the lithium indicator did not show any significant change in a period of several hours. A particular point of concern is the amount of water in THF,[11] for the decrease of the absorbance of the indicator anion caused by quenching with moisture (or any other acidic impurity) is not distinguishable from that corresponding to the reaction with PhIBP. In order to minimize this interference, quartz cuvettes were used and the solution of the base was allowed to stay in the cuvettes for 24 h, so as to neutralize most of the acidic components. It was found that after this treatment of the cell, the reading of the absorbance of the indicator anion is stable for several hours. However, the best accuracy was the reproducibility of the experiments and the use of more than one indicator. The internal consistency of the p*K* values obtained in this way is compelling evidence that the indicator anion or LiPhIBP decomposition is not an important source of error in our work.

(15) A kinetic study of the alkylation of the lithium salt of *p*-phenylsulfonylisobutyrophenone with *p-tert*-butylbenzyl bromide and with methyl tosylate has shown that the monomeric species is the reactive intermediate, even though this salt is present in solution almost entirely as dimer at 10^{-3} M (Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A., *J. Org. Chem.*, submitted).