The Role of Monomer in Alkylation Reactions of the Lithium Enolate of *p*-Phenylisobutyrophenone in Tetrahydrofuran[1]

Alessandro Abbotto, Simon Shun-Wang Leung, Andrew Streitwieser,* and Kathleen V. Kilway

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720-1460

Received April 27, 1998

Abstract: The lithium salt of *p*-phenylisobutyrophenone (LiPhIBP) exists in tetrahydrofuran (THF) as a mixture of monomer and tetramer contact ion pairs (CIP). The equilibrium constant, $K_{1,4} = 5.0 \times 10^8$ M^{-3}, indicates that the lithium enolate is primarily tetrameric at higher concentrations, but the monomer is still present in significant amounts even at concentrations typical of synthesis reactions. Alkylation reactions of LiPhIBP with various alkylating agents were investigated in THF at 25 °C at concentrations of 10^{-3} to 10^{-2} M by using UV−vis spectroscopy. The kinetics followed rate laws of 0.50 to 0.30 order in the formal lithium enolate concentration but is first order in the monomer concentration. These rate studies provide direct evidence that the reactive species is the monomer, even when tetramer dominates the equilibrium.

Reactions involving lithium enolates represent a large class of modern organic synthesis reactions and are important methods for C−C bond formation.[2−8] It is now well-known that these species, as well as other organolithium compounds (alkyl- and aryllithiums, lithium amides, etc.), exist generally as aggregates in ethereal solution and in the solid state.[9−19] What has not been clear is the actual role of such enolate aggregates in reactions with electrophiles. A better understanding of this subject is important in view of the possible influence of enolate aggregation and mixed aggregates on reactivity and regio- and stereoselectivity.[20−25]

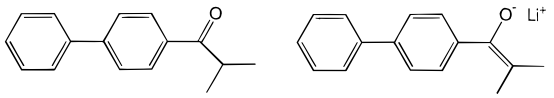
Jackman et al. have studied the lithium salt of isobutyrophenone by NMR and reported that it exists in tetrahydrofuran (THF) solution exclusively as a tetramer.[10,26,27] They concluded that these aggregates are directly involved in the alkylation reaction on the basis of the analysis of the product distribution (C- and O-alkylation)[28] and later hypothesized that dimers could also be involved.[29] This and other indirect evidence, especially the observation that lithium enolates crystallize generally as dimers, tetramers, or hexamers, led Amstutz et al. to propose that a tetrameric cubic structure is a reaction intermediate.[30,31] Although these mechanisms have not been confirmed, they are widely accepted and have been used as working hypotheses in the analysis of the reactivity and selectivity of lithium enolates.[4,16,17,32−34]

We recently showed for the lithium enolate of *p*-phenylsulfonylisobutyrophenone that the dimer and a mixed aggregate with LiBr are much less reactive in an alkylation reaction than the monomer in THF.[35,36] In the accompanying paper we showed that the cesium enolate of 1-(4-biphenylyl)-2-methyl-

(1) Carbon Acidity. 102.
(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982,** *13,* 1−115.
(3) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331.
(4) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983,** *48,* 4330.
(5) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; 1984; Vol. 3, pp 111−212.
(6) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 1, pp 181−238.
(7) Heathcock, C. H. *Mod. Synth. Methods* **1992**, *6*, 1−102.
(8) Braun, M. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; Jai Press Inc.: Greenwich, CT, 1992; Vol. 1, pp 177−247.
(9) *Ion and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley and Sons: New York, 1972.
(10) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737−2769.
(11) Smid, **J.** *Ions and Ion Pairs and Their Role in Chemical Reactions*; Pergamon Press: Oxford, U.K., 1979.
(12) Seebach, D. *Robert A. Welch Foundation Conferences on Chemical Research XXVII*; Houston, TX, 1983; pp 93−145.
(13) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.
(14) Boche, G. *Angew. Chem., Intl. Ed. Engl.* **1989**, *28*, 277.
(15) Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092−6097.
(16) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801−808.
(17) Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354−7360.
(18) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288−7293.
(19) Ciula, J. C.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 431−432; correction p 6686.
(20) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602−8604.
(21) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575−9585.
(22) Bach, R. D.; Andres, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613−618.
(23) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271−1290.
(24) Wei, Y.; Bakthavatchalam, R.; Jin, X. M.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1993**, *34*, 3715−3718.
(25) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343−5346.
(26) Jackman, L. M.; Haddon, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 3687−3692.
(27) Jackman, L. M.; Szeverenyi, N. *M. J. Am. Chem. Soc.* **1977**, *99*, 4954−4962.
(28) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494−4499.
(29) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805−2806.
(30) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617−2621.
(31) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622−2626.
(32) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc* **1987**, *109*, 5539−5541.
(33) Williard, P. G.; MacEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671−7672.
(34) Palmer, C. A.; Ogle, C. A.; Arnett, E. M. *J. Am. Chem. Soc.* **1992**, *114*, 5619−5625.
(35) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−4689.
(36) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136−8137.

10.1021/ja9814366 CCC: $15.00
Published on Web 10/10/1998

1-propanone (*p*-phenylisobutyrophenone, PhIBP, (**1**) consists of monomer, dimer, and tetramer in THF solution but that the monomer dominates alkylation reactions.[37] These results demonstrate the need for more quantitative studies on the role of aggregates in metal enolate reactions. We recently communicated that the lithium enolate of *p*-phenylisobutyrophenone is a mixture of monomer and tetramer.[38] In the present paper we have refined these results and have applied them to several alkylation reactions.



1 LiPhIBP

Results and Discussion

UV−Vis Spectroscopic Study of LiPhIBP. LiPhIBP was obtained from the deprotonation of PhIBP by the lithium salt of 9,9,10-trimethyldihydroanthracene. All measurements and manipulations were carried out in a glovebox under an argon atmosphere. UV−visible absorption spectra were obtained in THF solution at 25.0 ± 0.1 °C. Since PhIBP absorbs up to 385 nm, which impedes the spectroscopic study of LiPhIBP, the UV spectra of LiPhIBP were studied in the absence of the neutral ketone. This was done by using excess base to ensure complete conversion of the ketone to its enolate. The absorption of the base was then effectively subtracted by fitting a region of the observed spectra in a region where LiPhIBP does not absorb (455 nm to higher wavelength) to the spectra of the base. The lower end of the spectra was limited to 300 nm to avoid interference from 9,9,10-trimethyldihydroanthracene. We had noted previously that the λ_{max} of a number of enolates vary with concentration, indicating that different aggregates have significantly different spectra.[19] In accord with this observation, the spectra of LiPhIBP were found to vary with concentration. The λ_{max} gradually shifted from 333 to 343 nm, as the concentration of LiPhIBP was changed from 4×10^{-3} to 3×10^{-4} M (Figure S1, Supporting Information). An isosbestic point was found at 337 nm, at which the value of the extinction coefficient was found to be concentration-independent, 4350 ± 10 M^{-1} cm^{-1} (14 measurements).

We have shown in other examples how the method of singular value decomposition (SVD) analysis can be applied to such spectra,[39,40] although the example of CsPhIBP shows that the method needs to be used with circumspection.[37] The output of the SVD procedure was a basis set of 14 vectors (basis spectra), each associated with a coefficient (singular value) that corresponds to the weighting factor for the vector in contributing to the observed data. Two principal basis spectra with singular values of 37.0 and 1.30 were found that adequately describe the observed spectra (Figure S2, Supporting Information). The remaining 12 vectors, with singular values falling between 7.4 $\times 10^{-2}$ and 8.4 $\times 10^{-3}$, describe only the noise. This result shows that two distinguishable species are present in solution, a result supported by the presence of an isosbestic point at 337 nm in the observed spectra. To obtain physically meaningful spectra, a linear transformation with an assumption of the stoichiometries of the two species was carried out. The hypothesis of monomer/dimer, equivalent to dimer/tetramer (same stoichiometry), does not lead to meaningful spectra; that is, the assumption of 1:2 stoichiometry does not fit the experimental data. However, the stoichiometry 1:4 leads to meaningful spectra of the two species, and only in this case are the results consistent with the results of the independent ion pair acidity studies described below. This result shows that the two principal species are the monomeric ion pair $(LiPhIBP)_1$ (M) and the tetrameric ion pair $(LiPhIBP)_4$ (T). The concentration of any other aggregate (dimer, etc.), if present, must be less than a few percent throughout the whole range of concentrations studied as estimated by the instrument noise and experimental error. SVD led to the λ_{max} of the monomer and the tetramer as 343 and 329 nm, respectively. Spectra obtained at high dilution, however, gave λ_{max} at a longer wavelength than indicated by SVD for the monomer, even when these spectra were included in the SVD analysis. This surprising result indicates that the linear transformation can incorrectly estimate the spectrum of the monomeric ion pair and suggests that the spectra at low concentration with low absorbance values are not properly weighted in the SVD procedure. Test calculations show that this type of result does not happen with "synthetic" data of accurate precision; the result clearly stems from an improper weighting of experimental error. Nevertheless, at high dilution (in a 1-cm cell), there is no further wavelength shift below a concentration of about 7.5×10^{-5} M. The λ_{max} of the spectrum at this point is 352 nm, 9 nm longer than the calculated SVD "monomer" spectrum, and is taken as the actual spectrum of monomer. The spectra are shown in Figure 3. At the isosbestic point (337 nm), the extinction coefficients for the experimental monomer spectrum and the SVD tetramer spectrum are 4350 and 17 400 M^{-1} cm^{-1}, respectively; that is, the extinction coefficients are the same per LiPhIBP moiety in monomer and aggregate. On fitting the two components to the observed spectra, the tetramerization equilibrium constant $K_{1,4}$ is found to be $(5.0 \pm 0.1) \times 10^8$ M^{-3}.This value is about an order of magnitude higher than the preliminary results obtained from SVD only.[38]

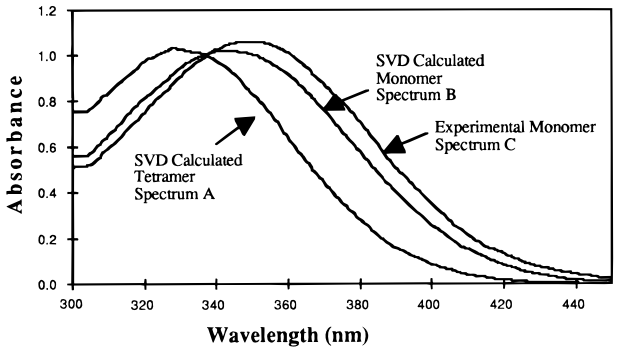


Figure 3. Spectra of the SVD calculated tetramer (A, $\lambda_{max} = 329$ nm), the SVD calculated monomer (B, $\lambda_{max} = 343$ nm), and experimental monomer (C, $\lambda_{max} = 352$ nm) in THF at 25 °C.

$$4[(LiPhIBP)_1] \rightleftharpoons^{K_{1,4}} [(LiPhIBP)_4] \qquad T = K_{1,4}M^4 \quad (1)$$

Analogous spectroscopic studies of LiPhIBP were carried out at 15 and 5 °C. The UV−vis spectrum of LiPhIBP does not shift on going to lower temperature, showing that $K_{1,4}$ is insensitive to temperature change; thus, the enthalpy of tetramerization $\Delta H°$ is negligible. On the basis of $K_{1,4} = 5.0 \times 10^8$ M^{-3}, the entropy of tetramerization, $\Delta S°$, is estimated as

(37) Streitwieser, A.; Krom, J. A.; Kilway, K. V.; Abbotto, A. *J. Am. Chem. Soc.* **1998**, *120*, 10814−10826.
(38) Abbotto, A.; Streitwieser, A. *J. Am. Chem. Soc.* **1995**, *117*, 6358−6359.
(39) Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024−8030.
(40) Abbotto, A.; Streitwieser, A.; Stratakis, M.; Krom, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1718−1723.

40 eu. Thus, this lithium enolate fits Chabanel's generalization of entropy-driven aggregation of 1:1 lithium salts in ethereal solvents.[41] The results can also be compared with a recent theoretical study of the aggregation of lithium vinyloxide solvated by dimethyl ether.[42] Stable species were calculated to be the disolvated monomer and tetrasolvated tetramer with an energy of interconversion of about -17 kcal mol^{-1} per monomer unit. The experimental results then suggest that the more hindered LiPhIBP tetramer is less solvated. The conversion of disolvated lithium vinyloxide monomer to unsolvated tetramer is then calculated to be about -6 kcal mol^{-1} per monomer. In this process eight solvent molecules are released. The experimental entropy change of about 40 eu corresponds, at 5−10 eu per solvent,[42] to four to eight molecules of solvent. Considering the differences between the theoretical model and the experimental system, this agreement is remarkably good.

CsPhIBP has been found to be a mixture of monomer, dimer, and tetramer in THF with $K_{1,2}$ (monomer to dimer) almost equal to $K_{2,4}$ (dimer to tetramer). If the same relationships held for LiPhIBP, the amount of dimer present should have been large enough to be detectable at concentrations in this study. An interesting question then concerns why the cesium salt should have a relatively large amount of dimer and the lithium salt not. The answer probably lies in the differences in electrostatic interaction between charges, which vary as $1/r$, and charge−dipole interactions (as in cation solvation), which vary as $1/r^2$. Thus, coordination with solvent is important for the small lithium cation but much less important than charge−charge interactions for the large cesium cation. As a result, aggregation of the lithium enolate has a relatively small enthalpy but large entropy change, whereas for the cesium enolate the added charge−charge stabilization in the aggregate dominates and is comparably important for dimer and tetramer.

Implicit in the above discussion is the treatment of the lithium enolate as a contact ion pair (CIP). This conclusion also follows from the spectrum: λ_{max} of LiPhIPB monomer of 352 nm is much shorter than that of CsPhIBP (about 420 nm).[39]

Lithium Ion Pair Acidity of PhIBP. Comparison of spectroscopic studies with the coupled equilibria of aggregation and ion pair proton transfer has been shown to be a powerful technique for obtaining quantitative understanding of aggregation.[35−37,39,40] In the present case, the lithium ion pair acidity of PhIBP, eqs 2 and 3, was measured in THF at 25 °C by use of an indicator, In, whose pK_{Li} is known.[43] In eq 3, {LiPhIBP} with curly brackets denotes the formal concentration of the lithium enolate.

$$\text{PhIBP} + \text{LiIn} \overset{K_{ob}}{\rightleftharpoons} \text{LiPhIBP} + \text{In} \qquad (2)$$

$$K_{ob} = \frac{\{\text{LiPhIBP}\}[\text{In}]}{[\text{PhIBP}][\text{LiIn}]} \qquad (3)$$

Since the neutral ketone has a UV−vis absorption that interferes with that of the enolate,[44] the single-indicator technique was applied.[15,45] In this method, the decrease in the absorbance of the lithium indicator on addition of substrate is used to determine how much LiIn is converted to the lithium enolate. 9-Methylfluorenyllithium was used as the base in the acidity study. The lithium ion pair acidity of PhIBP was measured against three indicators: 7-phenyl-3,4-benzofluorene (Ph-3,4-BF, pK_{Li} = 14.88), 9-(*p*-biphenylyl)fluorene (9-BpFl, pK_{Li} = 16.98), and 9-phenylfluorene (9-PhFl, pK_{Li} = 17.60),[43,46] for a total of 26 measurements. These data are summarized in Table S1 (Supporting Information). The values of K_{ob} have been corrected for the dissociation of the solvent-separated ion pair of the lithium salt of the indicators to free ions. For 9-PhFl, K_{diss} is 1.0×10^{-5} M.[46] For the other two indicators the dissociation constants are not known but they are assumed to be the same as other similar carbon acids, 9-phenylfluorene and 3,4-benzofluorene ($K_{diss} = 1.0 \times 10^{-5}$ M). The dissociation of LiPhIBP to free ions is presumably negligible, relative to that of the indicators (vide infra).

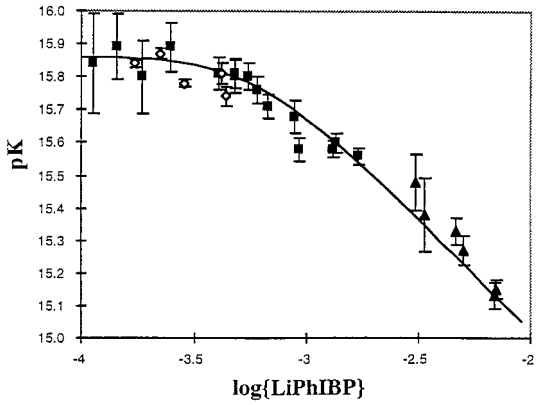


Figure 4. Ion pair acidity plot for LiPhIBP in THF at 25 °C. The curve shown is the theoretical curve for pK(monomer) = 15.86 and $K_{1,4} = 5.0 \times 10^8$ M^{-3}. Three indicators were used: Ph-3,4-BF, 9-phenyl-3,4-benzofluorene (squares); 9-BpFl, 9-*p*-biphenylylfluorene (diamonds); 9-PhF1, 9-phenylfluorene (triangles) (26 measurements).

A major concern in this acidity study is the amount of water in THF. 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. To minimize this interference quartz cuvettes were used, and the solution of (9-methylfluorenyl)-lithium was allowed to stand in the cuvettes for about 1 day to neutralize any acidic components. After this treatment, the absorption shape of the indicator anion was stable for at least several hours. However, the best check for accuracy is the reproducibility of the experiments and, more importantly, the use of more than one indicator with a total range of three pK_a units. For each acidity measurement a different cuvette, differing amounts of the substrates, and a different stock solution of (9-methylfluorenyl)lithium in THF were used. The internal consistency of the pK values obtained in this way is strong evidence that indicator anion decomposition is not an important source of error in this work.

Figure 4 shows the plot of pK vs log{LiPhIBP}. In the presence of aggregation the observed acidity is concentration-dependent.[15] When monomer and tetramer are simultaneously present, K_{ob} depends on the formal concentration of the enolate {LiPhIBP} according to the following equation:

(41) Chabanel, M. *Pure Appl. Chem.* **1990**, *62*, 35−46.
(42) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255−11268.
(43) Streitwieser, A.; Wang, D. Z.; Stratakis, M.; Facchetti, A.; Gareyev, R.; Abbotto, A.; Krom, J. A.; Kilway, K. V. *Can. J. Chem.*, in press.
(44) PhIBP absorbs up to 385 nm. The region of the spectrum of LiPhIBP which can be analyzed in the "double-indicator technique" (385−470 nm) is too far from the maximum absorption to assure accuracy and, in particular, a precise deconvolution into different components.
(45) Xie, L.; Bors, D. A.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 4986−4990.
(46) Kaufman, M. J.; Gronert, S.; Streitwieser, A., Jr. *J. Am. Chem. Soc* **1988**, *110*, 2829−2835.

$$K_{ob} = K_a + 4K_{1,4}K_a^4(\{\text{LiPhIBP}\}/K_{ob})^3 \quad (4)$$

where K_a is the monomer lithium ion pair acidity constant of PhIBP relative to the indicator. The variation of the acidity was studied over a range of {LiPhIBP} corresponding to 2 orders of magnitude (from 10^{-4} to 10^{-2} M). At low concentration, the variation of the observed acidity with concentration is small, indicative of the monomeric ion pair as the dominant species. Indeed, averaging the four lowest concentration measurements (which contain over 96% monomeric ion pair) leads to a lithium ion pair pK of PhIBP of 15.86. On the other hand, the large slope obtained at higher concentrations is evidence for the increasingly important role of the tetrameric species. Using the value of $K_{1,4}$ (5.0×10^8 M^{-3}) from the spectroscopic investigation, the theoretical curve is readily calculated. Although there are substantial errors associated with the single indicator technique, Figure 4 shows excellent agreement between the experimental data and the calculated curve.

The average aggregation number n of a metalated species is defined from eq 5.[37] By applying the newly found $K_{1,4}$, the percentage of monomer and tetramer and the average aggregation number $\bar{n}_{agg}$ can be calculated as a function of the formal concentration of the enolate, which are shown in Figure S5 (Supporting Information).

$$\bar{n}_{agg} = \{\sum n^2[(\text{LiPhIBP})_n]\}/\{\sum n[(\text{LiPhIBP})_n]\} \quad (5)$$

Kinetic Study of Alkylation Reactions of LiPhIBP. Kinetics of the alkylation of LiPhIBP with several alkylating reagents were studied at 25 °C in THF. Initial rates (ca. 10% reaction) were measured by following the decrease in the absorption at 385 nm of the lithium enolate after the addition of the alkylating agent. Alkylations were followed only in the early stage of the reaction to avoid complications and interference from any mixed aggregates between the lithium enolate and lithium bromide.[36] Alkylation reactions of LiPhIBP and *p-tert*-butylbenzyl bromide (BBB) were studied with 10 runs carried out with initial formal concentrations of LiPhIBP from 6.2×10^{-4} to 1.1×10^{-2} M. The kinetic results are summarized in Tables S2 and S3 (Supporting Information). Experimental data fit the rate law

$$\log(\text{rate}/[\text{BBB}]) = \log k + \alpha \log\{\text{LiPhIBP}\} \quad (6)$$

where {LiPhIBP} is the initial formal concentration of the lithium enolate and α is its order. Rate orders of the alkylating reagents were found to be close to unity in all cases; thus, the alkylating reagents are treated as first order. A similar finding was observed in the reaction of CsPhIBP with MeOTs.[37] It has been shown that α is equal to $\bar{n}_k/\bar{n}$, where $\bar{n}$ is the average equilibrium aggregation number and $\bar{n}_k$ is the average kinetic aggregation number.[37,47] A plot of log(rate/[BBB]) vs log{LiPhIBP} is depicted in Figure S6 (Supporting Information). In this range of concentrations the equilibrium aggregation number changes with the concentration of LiPhIBP and ranges from 1.6 to 3.6. To account for this change, a second-order polynomial equation was fitted to the experimental data (Figure S6). The derivative of the polynomial ($y' = -0.0123 - 0.159x$) provides the slope which increases from 0.30 (higher concentrations) to 0.50 (low concentrations). The computed data are reported in Table S2 (Supporting Information). The average kinetic aggregation number is 1.05 ± 0.12, which clearly indicates that the monomeric ion pair is the reactive species in the alkylation reaction. In a more straightforward approach, log(rate/[BBB]) can be compared directly to log[monomer] (Figure S7, Supporting Information), which can be calculated from the formal concentration {LiPhIBP} and $K_{1,4}$. The result is a linear relationship with slope = 1.08 ± 0.05, which is consistent with the conclusion that the monomeric ion pair is the true reactant.

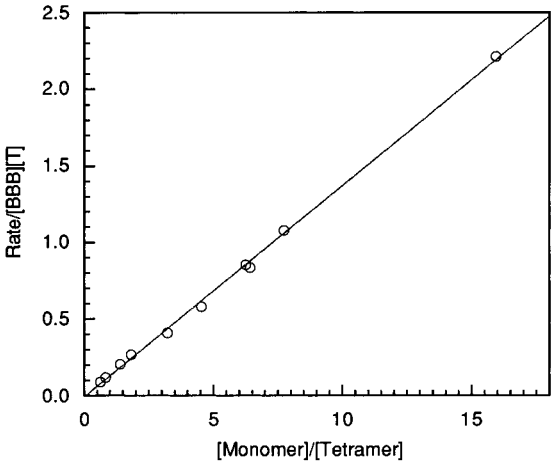


Figure 8. Plot for determining the bimolecular rate constants for the reaction of monomeric and tetrameric lithium enolate with *p-tert*-butylbenzyl bromide (BBB). The equation of the line shown is $y = (-0.009 \pm 0.013) + (0.138 \pm 0.002)x$; $R^2 = 0.998$.

Alternatively, the total rate of the alkylation reaction can be written as eq 7 and can be rearranged to eq 8.[36]

$$\text{rate} = k_M[\text{RX}][\text{monomer}] + k_T[\text{RX}][\text{tetramer}] \quad (7)$$

$$\text{rate}/[\text{RX}][\text{tetramer}] = k_M([\text{monomer}]/[\text{tetramer}]) + k_T \quad (8)$$

Applying eq 8 to the kinetic data for the reaction with BBB provides the results in Figure 8. The slope and the intercept of the straight line give k_M and k_T, respectively. The intercept is zero within 1 standard deviation; thus, $k_M \gg k_T$, in agreement with the results above, and only k_M, 0.138 ± 0.002 M^{-1} s^{-1}, is physically meaningful. Finally, the observed rates can be compared directly with the concentration of monomer alone, as in Figure S9 (Supporting Information). The resulting linear correlation gives a second-order rate constant of 0.141 ± 0.002 M^{-1} s^{-1} and, most importantly, shows no upward tendency at higher concentrations that would imply a significant contribution from higher aggregates.

Alkylation rates were also measured for benzyl bromide (BB), *m*-chlorobenzyl bromide (mCBB), *o*-chlorobenzyl bromide (oCBB), and *o*-methylbenzyl bromide (oMBB) in THF at 25 °C. The kinetic experiments are summarized in Table S4 (Supporting Information). The kinetic results are summarized in Table 5. Plots of log(rate/[RX]) vs log[monomer] are all linear with slopes between 0.895 and 1.08. Plots of rate/[tetramer][RX] vs [monomer]/[tetramer], which are shown in Figure 10, also give linear relationships with k_M between 0.109 and 0.255 M^{-1} s^{-1}. Among the bromide family, the effect on the reaction rate of changing the substituent is rather small. The most reactive electrophile, *o*-chlorobenzyl bromide, is 1.9 times faster than *p-tert*-butylbenzyl bromide and the slowest alkylating reagent, benzyl bromide, is only 21% slower than *p-tert*-butylbenzyl bromide. The ortho substituents have little effect, showing the absence of major steric effects in the reaction. The three substituents to which a Hammett plot could be applied, H, *p*-t-Bu, *m*-Cl, do not give a linear Hammett relation; both

(47) Krom, J. A.; Streitwieser, A. *J. Am. Chem. Soc.* **1992**, *114*, 8747−8748.

Table 5. Kinetics for the Reaction of LiPhIBP with Various Benzyl Bromides in THF at 25 °C

electrophile (RX) and no. of measurements	kinetic rate order of [monomer][a]	k_M[b]	k_T[b]	relative reactivity of [monomer][c]
p-*tert*-butylbenzyl bromide (BBB), 10	1.08 ± 0.05	0.138 ± 0.002	−0.009 ± 0.013	(1.00)
benzyl bromide (BB), 11	1.05 ± 0.11	0.109 ± 0.003	−0.012 ± 0.015	0.79
m-chlorobenzyl bromide (mCBB), 15	0.944 ± 0.119	0.255 ± 0.011	−0.006 ± 0.059	1.9
o-chlorobenzyl bromide (oCBB), 9	0.918 ± 0.100	0.143 ± 0.006	−0.003 ± 0.015	1.0
o-methylbenzyl bromide (oMBB), 10	0.895 ± 0.094	0.210 ± 0.006	−0.047 ± 0.019	1.5

[a] Determined by plots of log(rate/[RX]) vs log(monomer). [b] Values are slopes and *y*-intercepts of the fitting lines in Figures 8 and 10. [c] Relative to BBB.

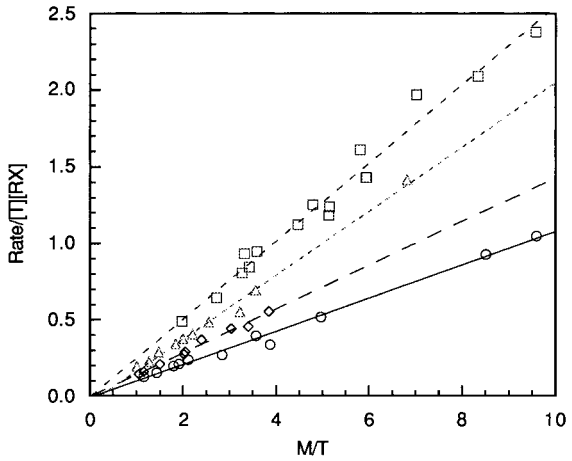
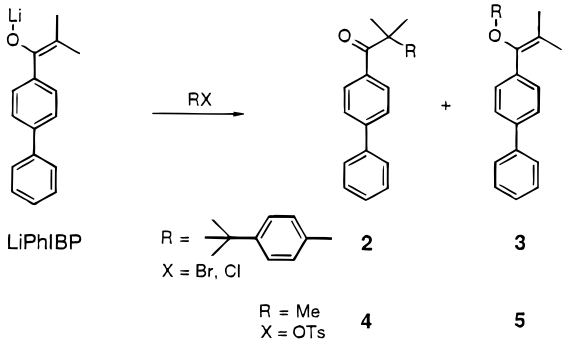


Figure 10. Plots for determining the bimolecular rate constants for the reactions of monomeric and tetrameric lithium enolate with the following (top to bottom): *m*-chlorobenzyl bromide (mCBB), squares; *o*-methylbenzyl bromide (oMBB), triangles; *o*-chlorobenzyl bromide (oCBB), diamonds; benzyl bromide (BB), circles. The equations of the lines shown are, respectively, $y = (-0.006 \pm 0.059) + (0.255 \pm 0.011)x$; $y = (-0.047 \pm 0.019) + (0.210 \pm 0.006)x$, $R^2 = 0.993$; $y = (-0.003 \pm 0.015) + (0.143 \pm 0.006)x$, $R^2 = 0.988$; and $y = (-0.012 \pm 0.015) + (0.109 \pm 0.003)x$, $R^2 = 0.992$.

Scheme 1



the electron donating *tert*-butyl and electron accepting *m*-chloro substituents give small rate enhancements compared to the unsubstituted bromide.

The possibility that free ions are the true reactant in the alkylation reactions cannot be easily precluded by the above kinetic data. However, addition of lithium tetraphenylborate to the alkylation of LiPhIBP with mCBB gave no change in rate. Since this salt would have given large rate suppression from the common ion effect if free ions were involved, this result clearly shows that free ions play no significant role.

Analysis of the products of the alkylation reaction (C- vs O-alkylation) with BBB, *p*-*tert*-butylbenzyl chloride (BBC), and methyl tosylate (MeOTs) were made by proton NMR at 10% and completion of the reaction (Scheme 1). The order of reactivity is as follows: BBB ≫ MeOTs ≫ BBC. In the first two cases (benzylation reaction), only the products deriving from C-alkylation (**2**) were detected. In contrast, for the reaction with MeOTs, both C- and O-addition products (**4** and **5**, respectively) were observed, and furthermore, the product distribution (ratio C/O) was found to depend on the extent of reaction. These results are summarized in Table 6.

Table 6. Product Distribution (C- and O-Alkylation) for the Reaction of LiPhIBP with Alkylating Agents (RX) in THF at 25 °C

run	RX[a]	[RX] (×10² M)	{LiPhIBP} (×10³ M)	% reacn	C/O[b]
1	BBB	2.1	9.9	10	only C
2	BBB	2.6	11	>99	only C
3	BBB	2.5	12	>99	only C
4	BBC	60	6.3	10	only C
5	BBC	14	6.3	20	only C
6	BBC	81	7.2	>99	only C
7	MeOTs	7.0	5.4	10	0.95 ± 0.09
8	MeOTs	7.3	6.0	10	0.80 ± 0.08
9	MeOTs	11	8.6	10	0.95 ± 0.10
10	MeOTs	84	5.6	>99	0.49 ± 0.02
11	MeOTs	7.5	6.4	>99	0.44 ± 0.01
12	MeOTs	11	9.3	>99	0.44 ± 0.01
13	MeOTs	11	9.8	>99	0.43 ± 0.03

[a] BBC = *tert*-butylbenzyl chloride and MeOTs = methyl *p*-toluenesulfonate. [b] C/O ratio determined by proton NMR spectroscopy. Values are the averages of different signals.

Discussion and Conclusions

The combination of UV−vis spectroscopy with the study of the coupled equilibrium ion pair acidity provided the stoichiometry of the principal aggregates of LiPhIBP in THF. LiPhIBP exists as a mixture of monomeric and tetrameric ion pairs in THF at 25 °C, each with a distinctive absorption spectrum. The tetramerization constant $K_{1,4} = (5.0 \pm 0.1) \times 10^8\ M^{-3}$ is larger than that reported earlier.[38] The incorrect monomer spectrum in the earlier work led to the underestimation of $K_{1,4}$ in the previous report and shows that SVD analysis must be used with circumspection. In particular, it is important to collect spectral data at such high dilution that the monomer dominates.

The average aggregation number at {LiPhIBP} = 0.1 M is calculated to be 3.9, in accord with the NMR studies of the Jackman group with the lithium enolate of isobutyrophenone in which only tetramer was observed at this concentration.[26,27] At this concentration, LiPhIBP is 5% monomer, 95% tetramer, but since the tetramer contains four molecules of enolate, only 1.3% of the lithium enolate moieties are present as monomer. This number is too small to see conventionally by NMR but still clearly has kinetic significance. Even under synthesis conditions of several tenths molar, alkylation occurs dominantly via the monomer. Thus, the characterization of this system in dilute solution has relevance to the much higher concentrations in organic synthesis reactions.

The generalization that alkylation reactions of lithium enolates occur primarily via monomers even in the presence of dominating amounts of higher aggregates is suggested now by two

examples, the present case of LiPhIBP and the lithium enolate of *p*-phenylsulfonylisobutyrophenone (LiSIBP).[35] The generalization extends to other systems now under study in our laboratory. On comparing LiPhIBP with LiSIBP, some significant differences are of interest.

LiSIBP (pK = 14.69) is less basic than LiPhIBP (pK = 15.86), undoubtedly because of the electron-attracting effect of the sulfonyl group, and is less aggregated—it forms a monomer−dimer mixture. Nevertheless, monomeric LiSIBP (k_M = 0.32 M^{-1} s^{-1}) is *more* reactive toward *p-tert*-butylbenzyl bromide than is monomeric LiPhIBP (k_M = 0.14 M^{-1} s^{-1}). These results indicate that the reactivity of lithium enolates in alkylation reactions does not necessarily parallel their basicity.

CsPhIBP was also found to give almost entirely C-alkylation with benzyl halides but comparable amounts of C- and O-alkylation with methyl tosylate.[37] This difference was explained on the basis of six-membered ion pair transition structures; an alkyl halide can give a six-membered transition structure only with C-alkylation, whereas a sulfonate can give such structures with either C- or O-alkylation. The difference in the C/O ratio in the initial reaction and for the total reaction is not so readily explained. Jackman et al. also observed a variation in the C/O ratio for MeOTs as a function of the extent of reaction with lithioisobutyrophenone in dioxolane at 30 °C.[29] Since the addition of lithium perchlorate was also found to lead to a decrease in the C/O ratio, they concluded that mixed aggregates are involved.[27,48] Thus, the LiOTs produced during the reaction with no salt added might affect the C/O ratio similarly. However, some other observations appear to contradict this interpretation. A similar strong decrease in the C/O ratio by the addition of the bulky lithium tetraphenylborate, which might not form comparable mixed aggregates as readily, is difficult to explain by this rationale. Moreover, the absence of an effect with lithium chloride in the reaction of lithioisobutyrophenone with dimethyl sulfate in dioxolane and dimethoxyethane at various temperatures also leads to some inconsistency with this conclusion. These questions cannot be resolved at present but are under current study in our laboratory.

Experimental Section

General. Spectroscopic, ion pair acidity, and kinetic studies were carried out in a Vacuum Atmospheres glovebox under an argon atmosphere. The UV−vis spectra were recorded on a computer-driven Shimadzu UV-2101PC spectrometer. Details of the apparatus have been previously described.[38,39] Parameters for UV−vis measurements were as follows: scan speed, 200 nm min^{-1}; slit width, 2.0 nm; sampling interval, 0.5 nm. Experiments were usually carried out in 1-mm quartz cells, but 1-cm cells were used for the high-dilution experiments. The product distribution of the alkylation reactions was determined by ^{1}H NMR spectroscopy.

Materials. Anhydrous THF[39] and lithium diisopropylamide[40] (LDA) were prepared as described previously. 1-(4-Biphenylyl)-2-methyl-l-propanone (*p*-phenylisobutyrophenone, PhIBP, (**1**) was prepared according to the procedure of Long and Henze;[49] the isolated material was purified by recrystallization from ethanol followed by double sublimation under vacuum. The hydrocarbon indicator acids used in this work either were available from our previous studies or were synthesized by published procedures. All of the indicators were carefully purified prior to use by repeated recrystallization followed by vacuum sublimation. *p-tert*-Butylbenzyl bromide (Aldrich) was dried with $MgSO_4$ followed by fractional distillation under vacuum. *p-tert*-Butylbenzyl chloride (Aldrich) was stirred several hours over calcium hydride at 70 °C under an argon atmosphere followed by fractional distillation under vacuum. Methyl *p*-toluenesulfonate (Aldrich) was distilled under vacuum prior to use. Benzyl bromide, *m*-chlorobenzyl bromide, *o*-chlorobenzyl bromide, and *o*-methylbenzyl bromide were obtained from Aldrich and stirred over CaH_2 followed by fractional distillation.

(9-Methylfluorenyl)lithium and (9,9,10-Trimethyldihydroanthracenyl)lithium. In the glovebox, freshly sublimed LDA (0.20−0.30 mmol) was added to a solution of twice recrystallized (EtOH) and twice sublimed 9-methylfluorene (20−30% excess) in THF (2 mL). The resulting reddish orange mixture was allowed to stand overnight. The solvent and the formed diisopropylamine were removed under vacuum, and the residue was taken into the glovebox. THF (2−3 mL) was added to the yellow solid, giving rise to a reddish orange solution (ca. 0.1 M solution of (9-methylfluorenyl)lithium in THF). The solution, which was kept in the glovebox at −10 °C, was stable for at least 1 month. A solution of the (9,9,10-trimethyldihydroanthracenyl)lithium in THF was prepared in a similar manner, except that the reaction mixture of LDA and the neutral precursor was allowed to stand at room temperature for 4 days.

Absorption Spectra and Extinction Coefficient of LiPhIBP. The spectra were obtained over the wavelength range of 280−650 nm. The neutral 9,9,10-trimethyldihydroanthracene does not absorb in this region. A solution of PhIBP (0.742 mg, 3.308 × 10^{-3} mmol) in THF (0.694 g, 0.781 mL) was prepared in a 1-mm quartz UV cell. Aliquots of a stock solution of (9,9,10-trimethyldihydroanthracenyl)lithium in THF were added (2−3 μL each time) via microsyringe until the absorption of (9,9,10-trimethyldihydroanthracenyl)lithium persisted. At this point the initial PhIBP had been converted completely to LiPhIBP. Known amounts of THF (0.1−0.6 g each time) were added and the absorption spectrum recorded after each addition. LiPhIBP does not absorb in the region 455−650 nm. This region of the spectrum was used to evaluate the component due to the absorption of (9,9,10-trimethyldihydroanthracenyl)lithium in the original spectra. After subtraction of the absorbance band of (9,9,10-trimethyldihydroanthracenyl)lithium, 14 spectra of LiPhIBP at different concentrations (from 4.18 × 10^{-3} to 3.16 × 10^{-4} M) were obtained and processed by SVD. The same set of spectra was used to calculate the extinction coefficient at 337 nm according to Beer's law (at this wavelength the extinction coefficient was found to be concentration-independent). Low-temperature experiments were carried out in a similar fashion. The solutions were allowed to stand in the thermostated cell at least 20 min before the spectrum was recorded.

Lithium Ion Pair Acidity Study of PhIBP (Single Indicator Method). In a typical experiment, an aliquot of a stock solution of (9-methylfluorenyl)lithium 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[37] 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.

Kinetic Studies. Kinetic experiments were performed in the glovebox using the same apparatus as that for spectroscopic and acidity studies. In a typical run, a known amount of PhIBP was dissolved in a known quantity of THF. Aliquots of a stock solution of (9,9,10-trimethyldihydroanthracenyl)lithium in THF were added (2−3 μL each time) via microsyringe until a little excess of (9,9,10-trimethyldihydroanthracenyl)lithium was observed. Then a small amount of PhIBP was added via microbeaker to make sure that there was no excess (9,9,10-trimethyldihydroanthracenyl)lithium in the reaction mixture, and the solution was allowed to stand for about 30 min. The spectrum was monitored at 25.0 °C to verify the stability of the enolate solution. A known amount of alkylating reagent was then added to the enolate solution; the reactor was shaken vigorously and placed in the thermostated cell holder of the spectrophotometer. The decrease in the absorbance was monitored at 385 nm at a 0.5−1.0-s interval until the reaction was at least 20% completed. For the first 10% reaction, a

(48) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202−1210.

(49) Long, L. M.; Henze, H. R. *J. Am. Chem. Soc.* **1941**, *63*, 1939.

first-order equation gave a satisfactory fit to the curve. The initial rates and the initial formal concentration of the enolate were then obtained from the slope and the *y*-intercept of the fitted straight lines, respectively. Note that the reaction products do not absorb at 385 nm.

Product Distribution in the Alkylation Reactions of LiPhIBP. These experiments were carried out in a manner similar to those of the kinetic studies. For the analysis at completion (>99%), the reaction was allowed to stand until the absorbance of LiPhIBP at 385 nm was equal to the instrument noise (≤0.005 absorbance units). None of the products absorbs at this wavelength. For the analysis at 10 and 20% completion, an excess of benzoic acid was added to the UV cell, and the spectrum was recorded to verify the actual quenching of all the residual enolate. *p-tert*-Butylbenzyl bromide and methyl *p*-toluenesulfonate were added via microsyringe, but the benzyl chloride was added via glass pipette. The cell was then taken out of the glovebox, and the solvent was evaporated. The residue was dissolved in deuterated chloroform, and a proton NMR spectrum was recorded. In benzylation reactions, a new product was observed, which was identified as the C-alkylated product **2**.[37,47] In reactions with MeOTs, both C- and O-alkylated products were formed (**4** and **5**, respectively). The C/O ratio was determined by analyzing the signals of the methyl groups in the α position of **4** and the olefinic as well as the O-methyl groups of **5**.

Acknowledgment. This research was supported in part by grants from the National Science Foundation.

Supporting Information Available: Figures S1, S2, S5−S7, S9 and Tables S1−S4 (9 pages, print/PDF). See any current masthead page for ordering and Internet access instructions.

JA9814366