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# Why Is Alkylation of an Enolate Accompanied by So Much Polyalkylation?

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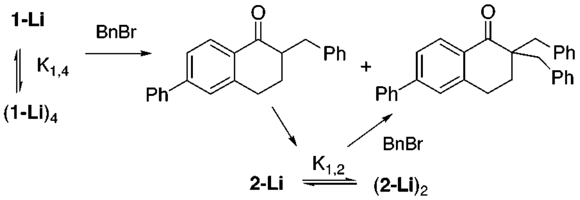
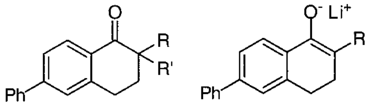
## ABSTRACT



**The lithium enolate 1-Li of 6-phenyl-α-tetralone forms a monomer–tetramer equilibrium in THF at 25 °C with $K_{1,4} = 4.7\mathrm{E}{+}10$ M$^{-3}$. The lithium enolate 2-Li, however, forms a monomer–dimer equilibrium with $K_{1,2} = 3800$ M$^{-1}$. In both cases reaction with benzyl bromide is dominantly with the monomer. The results support an earlier conjecture of House that alkylation of an enolate is frequently accompanied by extensive polyalkylation because the less substituted enolates are more aggregated.**

It has long been known that alkylation of alkali enolates in ethereal solvents is often accompanied by relatively large amounts of di- and polyalkylation.[1] For example, even at only 10% reaction of the lithium enolate of α-tetralone with excess benzyl bromide in THF, dialkylation is one-third of the product (Supporting Information). Various explanations have been offered for this phenomenon; recently, for example, a $\pi-\pi$ interaction between enolate and alkylating agent has been proposed.[2] Three decades ago, however, House[3] conjectured that the explanation could lie in greater aggregation of the less substituted enolate, with the implied assumption that the more highly aggregated enolate is less reactive. To our knowledge no definitive test of this hypothesis has ever been published, but it is consistent with recent quantitative studies of the aggregation and reactivity of lithium and cesium enolates in THF, which show that the monomers are generally more reactive than the dimer or tetramer aggregates in alkylation reactions.[4] In this paper we provide a definitive test with aggregation equilibrium constants and benzylation rates for the lithium enolates (**1-Li** and **2-Li**) of 6-phenyl-α-tetralone, **1**, and 2-benzyl-6-phenyl-α-tetralone, **2**. The experiments required measurements at dilute solutions for which only the UV−vis spectrum is a suitable analytical tool; thus, the 6-phenyl substituent was included to provide a workable chromophore.



R=R'=H: **1**
R=benzyl, R'=H: **2**
R=R'=benzyl: **3**

**1-Li**
**2-Li**

6-Phenyl-α-tetralone came from another study.[4f] The α-benzyl ketone, **2**, was prepared[5] by treatment of the

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[1] (a) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; Chapter 9. (b) Stowell, J. C. *Carbanions in Organic Synthesis*; John Wiley & Sons: New York, 1979; p 128. (c) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1; Chapter 2.

[2] Diez-Barra, E.; Merino, S.; Sanchez-Verdu, P.; Torres, J. *Tetrahedron* **1997**, *53*, 11537−11548.

[3] House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361−2371.

[4] (a) Abbotto, A.; Leung, S. S.-W.; Streitwieser, A.; Kilway, K. V. *J. Am. Chem. Soc.* **1998**, *120*, 10807−10813. (b) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688−4689. (c) Streitwieser, A.; Wang, D. Z. *J. Am. Chem. Soc.* **1999**, *121*, 6213−6219. (d) Streitwieser, A.; Wang, D. Z.; Stratakis, M. *J. Org. Chem.* **1999**, *64*, 4860−4864. (e) Streitwieser, A.; Krom, J. A.; Kilway, K. A.; Abbotto, A. *J. Am. Chem. Soc.* **1998**, *120*, 10801−10806. (f) Wang, D. Z.-R.; Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2000**, *122*, 10754−10760. (g) Wang, D. Z.-R.; Streitwieser, A. *Can. J. Chem.* **1999**, *77*, 654−658.

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magnesium salt with benzyl bromide, and the dibenzyl ketone, **3**, was prepared by treatment of **2** with benzyl bromide (Supporting Information). The lithium enolates were prepared by titration with 9-lithium-9,10,10-trimethyldihydroanthracene, a red base that serves as its own indicator.[6] Unlike a number of previous examples, **1-Li** and **2-Li** show only small changes in $\lambda_{max}$ with concentration. **1-Li** has $\lambda_{max}$ of about 338 nm that varied by only a few nm during any given run in which the concentration of enolate was varied. Similarly, $\lambda_{max}$ of **2-Li** varies from 359 to 363 nm over a 10-fold concentration range from $10^{-3}$ to $10^{-4}$ M. Both give linear Lambert−Beer's plots at $\lambda_{max}$ to give extinction coefficients of 10 784 and 12 800, respectively. Because $\lambda_{max}$ changes so little with concentration in both cases, the method of singular value decomposition could not be used to determine the aggregation equilibria;[7] this method had been applicable for several other enolates. The aggregation equilibria were determined, however, by their coupled equilibria with proton transfer to suitable indicators. The proton-transfer equilibrium for the monomer, $R^-M^+$, eq 1, is shifted to the right by the aggregation equilibrium, eq 2. The symbol $\{R^-M^+\}$ is used to denote the formal concentration of $R^-M^+$. The experimental $K_{ob}$ given by eq 3 defines the p$K_{ob}$ relative to the indicator used, eq 4, and based on an assigned p$K$ of fluorene, 22.90.[6]

$$\mathrm{RH} + \mathrm{In}^-\mathrm{M}^+ \xrightleftharpoons{K_0} \mathrm{R}^-\mathrm{M}^+ + \mathrm{InH} \tag{1}$$

$$n\mathrm{R}^-\mathrm{M}^+ \xrightleftharpoons{K_{1,n}} (\mathrm{R}^-\mathrm{M}^+)_n \tag{2}$$

$$K_{ob} = \frac{\{\mathrm{R}^-\mathrm{M}^+\}[\mathrm{InH}]}{[\mathrm{RH}][\mathrm{In}^-\mathrm{M}^+]} \tag{3}$$

$$\mathrm{p}K_{ob}(\mathrm{RH}) = \mathrm{p}K(\mathrm{InH}) - \log K_{ob} \tag{4}$$

Because the aggregation equilibrium makes the ketone effectively more acidic at higher concentrations, p$K_{ob}$ decreases at higher concentrations. This change can be used to deduce the aggregation equilibrium constant.

For a series of aggregates the complete expression is given as eq 5[7]

$$\{\mathrm{R}^-\mathrm{M}^+\} = \sum_n nK_{1,n}K_0^{\,n}\left(\frac{\{\mathrm{R}^-\mathrm{M}^+\}}{K_{ob}}\right)^n \tag{5}$$

This equation can be rearranged into convenient forms for special cases. For example, for a monomer−dimer equilibrium, a plot of $K_{ob}$ vs $\{R^-M^+\}/K_{ob}$ is linear with an intercept $K_o$, the proton-transfer equilibrium constant for the monomer with the indicator, and a slope, $2K_{1,2}K_o^2$, eq 6. For a monomer-tetramer equilibrium, the corresponding linear plot is with $(\{R^-\ M^+\}/K_{ob})^3$, eq 7. If monomer, dimer and tetramer are all involved, neither plot is linear.

$$K_{ob} = K_0 + \frac{2K_{1,2}K_0^{\,2}\{\mathrm{R}^-\mathrm{M}^+\}}{K_{ob}} \tag{6}$$

$$K_{ob} = K_0 + 4K_{1,4}K_0^{\,4}\left(\frac{\{\mathrm{R}^-\mathrm{M}^+\}}{K_{ob}}\right)^3 \tag{7}$$

LiPAT, **1-Li**, was measured against two indicators, 11-phenylbenzo[*c*]fluorene (Ph-3,4-BF, p$K$ = 14.84)[6] and 1,2,3-triphenylindene (TPI, p$K$ = 14.97);[6] the experimental details for four runs are summarized in Table S3 (Supporting Information). The data fit eq 7 (Figure 1) and give average values for **1-Li** of p$K_0$ = 14.22 ± 0.04 and $K_{1,4} = (4.7 \pm 0.5)\mathrm{E}{+}10\ \mathrm{M}^{-3}$ in which p$K_0$ refers to the monomeric enolate and $K_{1,4}$ = [tetramer]/[monomer].[4]

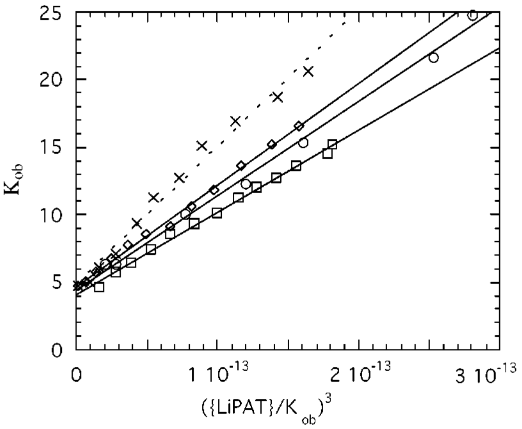

**Figure 1.** Plots of four proton-transfer runs with two indicators (×, TPI; ◇, □, and ○, Ph-3,4-BF). Equations of the regression lines shown and derived $K_{1,4}$ are ×, 4.80 ± 0.38 + (1.02 ± 0.45)E+14$x$ ($R^2$ = 0.983; $K_{1,4}$ = (4.8 ± 1.5)E+10); ◇, 4.68 ± 0.12 + (7.52 ± 0.14)E+13$x$ ($R^2$ = 0.996; $K_{1,4}$ = (3.9 ± 0.5)E+10); ○, 4.44 ± 0.39 + (6.97 ± 0.20)E+13$x$ ($R^2$ = 0.996; $K_{1,4}$ = (4.5 ± 1.6)E+10); □, 4.08 ± 0.15 + (6.13 ± 0.13)E+13$x$ ($R^2$ = 0.995; $K_{1,4}$ = (5.5 ± 0.8)E+10).

Similarly, the p$K$ of **2** was measured relative to the indicator 9-(2′,3′,5′,6′-tetrafluorophenyl)fluorene (TeFPFl, p$K$ = 14.12).[6] The results of two runs are summarized in Supporting Information. A third run gave more scatter and was not included. As shown in Figure 2, $K_{ob}$ is now linear in the first power of $\{\mathrm{LiBnPAT}\}/K_{ob}$, indicating a monomer−dimer equilibrium. The results give $K_0$ = 1.82 and $K_{1,2}$ = 3791 ± 455 $\mathrm{M}^{-1}$, which we round to 3800 $\mathrm{M}^{-1}$. The corresponding p$K$ value is 13.96. LiBnPAT (**2-Li**) is slightly less basic than the unsubstituted LiPAT and is less aggregated. For example, the monomer concentrations of 0.1 M solutions of **1b** and **2b** are 0.001 and 0.005 M, respectively.

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(5) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598.

(6) Streitwieser, A.; Wang, D. Z.; Stratakis, M.; Facchetti, A.; Gareyev, R.; Abbotto, A.; Krom, J. A.; Kilway, K. V. *Can. J. Chem.* **1998**, *76*, 765−769. Note that the value of 14.67 given for the p$K$ of TPI in this reference is incorrect; the statistical factor of −0.30 had inadvertently been applied twice.

(7) Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024−8030.

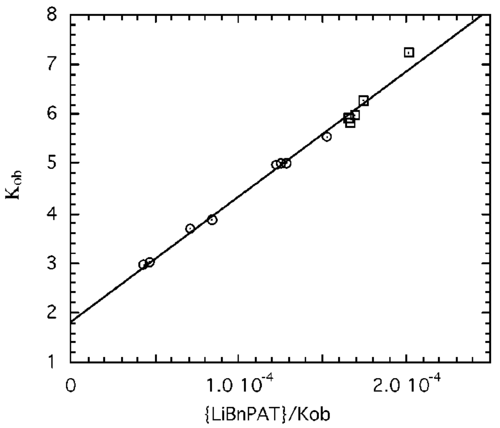

**Figure 2.** Plot of two proton-transfer runs (○ and □) of LiBnPAT vs 9-(tetrafluorophenyl)fluorene. Equation of line shown is (1.815 ± 0.108) + (25262 ± 796)$x$.

Reaction kinetics were measured for **1-Li** and **2-Li** and benzyl bromide (BnBr). The total reaction is dissected into contributions by monomer and aggregate, eq 8. Rearrangement to eq 9 provides a linear expression in the [M]/[agg] ratio, which is known from the aggregation equilibrium constants.

$$\frac{\text{rate}}{[\text{BnBr}]} = k_{\text{M}}[\text{M}] + k_{\text{agg}}[\text{agg}] \qquad (8)$$

$$\frac{\text{rate}}{[\text{BnBr}][\text{agg}]} = \frac{k_{\text{M}}[\text{M}]}{[\text{agg}]} + k_{\text{agg}} \qquad (9)$$

Initial rates were determined by the decrease in absorbance of varying amounts of enolate with a fixed large excess of BnBr for the first 10−20% reaction. The results are summarized in Tables S5 and S6 (Supporting Information) and plotted in Figure 3. For both enolates the reaction is dominantly with the monomer; the reactivities of the aggregates of **1-Li** and **2-Li** are too small to measure.

Since only monomer contributes to the rate, $k_{\text{M}}$ can be determined directly from a plot of rate/[BnBr] vs [M]. Figure S3 (Supporting Information) gives the second-order rate constants: **1-Li**, 0.0945 ± 0.0010 $\text{M}^{-1}\ \text{s}^{-1}$, **2-Li**, 0.174 ± 0.003 $\text{M}^{-1}\ \text{s}^{-1}$, essentially the same values as from Figure 3. It is interesting to note that although the monomer of **2-Li** is less basic than that of **1-Li**, it is 1.8 times as reactive in alkylation with benzyl bromide. This difference contributes to the tendency to give dialkylation, but the principal determinant is the larger amount of reactive monomer present with the substituted enolate. For example, even at only 10% reaction at synthesis concentrations dialkylation proceeds at 24 times the rate of monoalkylation, at least under equilibrium conditions for the two enolates. In practice, the actual ratio is smaller because deprotonation of the monosubstituted enolate is not rapid[4c,8]and becomes part of a complex rate-determining step.

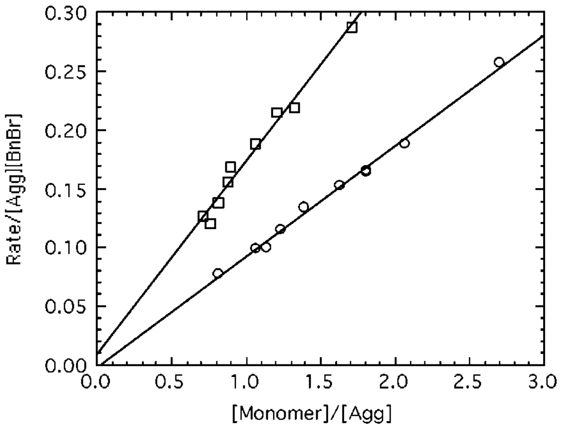

**Figure 3.** Reactivities at 25 °C of **1-Li** (○) and **2-Li** (□) toward BnBr according to eq 8. The regression lines are **1-Li**, (−0.0014 ± 0.0036) + (0.094 ± 0.002)$x$, $R^2 = 0.9956$; **2-Li**, (0.0090 ± 0.0099) + (0.168 ± 0.009)$x$, $R^2 = 0.979$. Values for [monomer]/[agg] > 3 not used.

In conclusion, the House conjecture[3] that dialkylation occurs competitively with monoalkylation because the more substituted enolate is less aggregated has been shown to be correct for a specific case by measurement of aggregation equilibrium constants and kinetic study.

**Acknowledgment.** This work was supported in part by grants from the National Science Foundation. We also thank Kai-Cha Feng for some preparations and preliminary experiments.

**Supporting Information Available:** Experimental methods, tables of spectral data, ion pair acidities and alkylation kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341−1348.