Communications

Effect of Addends on Aggregation and Reactivity of the Lithium Enolate of *p*-Phenylisobutyrophenone[1]

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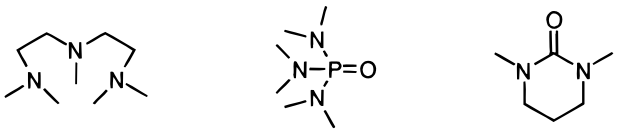
We recently reported[2] that the UV−vis spectrum of the lithium enolate (LiPhIBP) of *p*-phenylisobutyrophenone in THF varies with concentration. Analysis of the spectra led to a mixture of monomer and tetramer with λ_{max} 352 and 329 nm, respectively, and the aggregation equilibrium constant, $K_{1,4} = 5.0 \times 10^8$ M^{-3}. We now report the effect of the addends PMDTA, HMPA, and DMPU on this spectrum and on the reactivity of LiPhIBP. Such addends have been used to accelerate the reactivity and alter the selectivity of metal enolates.[3,4]



Small amounts of HMPA cause a dramatic shift in the spectrum of LiPhIBP to longer wavelengths. After 68 equiv of HMPA, further changes are small as shown in Figure 1. The λ_{max} at this point, 353 nm, is essentially the same as that of the THF-solvated monomer. In pure HMPA, λ_{max} is at longer wavelength, 390 nm, and is probably that of a looser but not completely solvent-separated ion pair (SSIP); we note that the SSIP would be expected to have a wavelength somewhat longer than that of the cesium enolate monomer whose λ_{max} has been found to be about 420 nm.[5]

With the assumption that HMPA produces a solvated monomer having the same spectrum as the monomer in THF without HMPA, the additional monomer produced with HMPA can be computed from the spectra and treated according to the equilibrium (1) and the equilibrium constant (2).

Spectra were taken of a series of mixtures of LiPhIBP containing HMPA such that comparable amounts of the three components, tetramer, monomer (M), and HMPA-solvated monomer (M(HMPA)), were present. From the experimental data in Table S1 (Supporting Information), a plot of log([M(HMPA)]/[M]) vs log[HMPA] gives a straight line with a slope of 1.23 (Figure 2); that is, *n* in equilibrium (1) is 1.23. Thus, dissociation of the tetramer to monomer is accompanied by solvation of each monomer by 1−2 molecules of HMPA. One possibility is that the tetramer is initially solvated by three molecules of HMPA, which then provides each monomer with two molecules of HMPA.[6] This is an entirely reasonable possibility but cannot be proved by these data alone. In the present case, the amount of normal monomer present was calculated from the spectrum of the tetramer present using the $K_{1,4}$ value (5.0×10^8 M^{-3}) applicable in THF; tetramer solvated by HMPA probably has a somewhat different value and would give a different plot from Figure 2. The difference, however, is probably small and the conclusion that monomer in the presence of $\sim 10^{-2}$ M HMPA is solvated by 1−2 mol of HMPA appears to be reasonably secure.

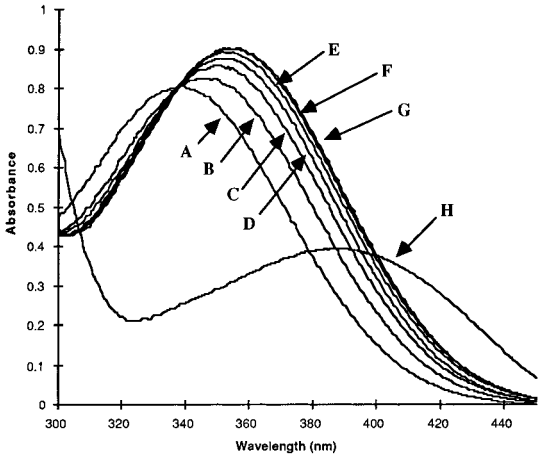


Figure 1. Effect of HMPA on the spectrum of LiPhIBP in THF at 25 °C. For each lettered spectrum the λ_{max} (nm), concentration of HMPA (M), and equivalents relative to LiPhIBP are given as A, 338.0, 0, 0; B, 345.5, 0.026, 13; C, 350.5, 0.057, 30; D, 352.0, 0.091, 47; E, 352.5, 0.013, 68; F, 353.0, 0.19, 98; G, 353.5, 0.23, 120; H (HMPA solvent), 390.0, 5.8, 4600.

$$\text{monomer} + n\text{HMPA} \overset{K_{\text{HMPA}}}{\rightleftharpoons} \text{monomer(HMPA)}_n \quad (1)$$

$$\frac{[\text{M(HMPA)}]}{[\text{M}][\text{HMPA}]^n} = K_{\text{HMPA}} \quad (2)$$

HMPA has an equally dramatic effect on reactivity. LiPhIBP was found to alkylate dominantly as the monomer, and reactivities had been determined for methyl tosylate (MeOTs) and for several benzylic bromides.[2] Even small amounts of HMPA increase these reactivities substantially; for example, 0.01 M HMPA doubles the rate of reaction of LiPhIBP with *p-tert*-butylbenzyl bromide (BBB). This reactivity is so high that the kinetics was done with 2×10^{-4} M enolate. At this concentration, LiPhIBP is 99% monomer; thus, HMPA is doing more than just converting aggregate to monomer. A plot of the initial rate constant (initial rate divided by [BBB] and [LiPhIBP]) vs HMPA concentration is shown in Figure 3. The reaction is actually first order in [HMPA] with a large slope. NMR study of the reaction products showed only C-alkylation in the presence or absence of HMPA.

(1) Carbon Acidity. 107.

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(6) Suggested by Prof. David Collum.

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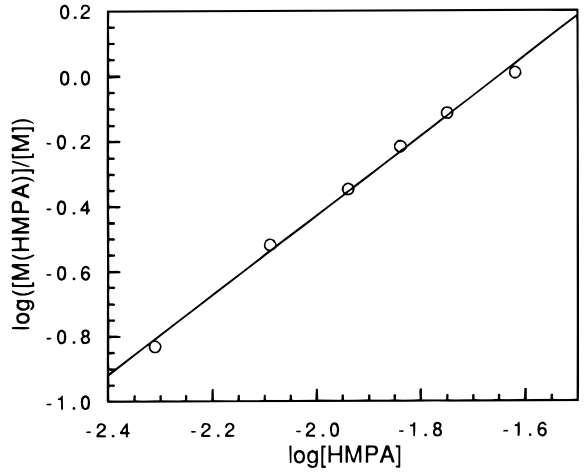

Figure 2. Plot of [monomer·*n*HMPA]/[M] vs log[HMPA]. The equation of the line shown is $2.024 + 1.225x$; $R^2 = 0.995$.

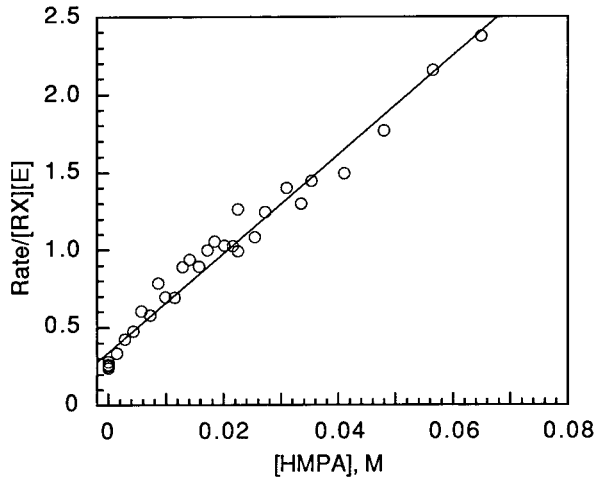

Figure 3. Initial second-order rate constant for reaction of LiPhIBP (about 10^{-4} M) with *p-tert*-butylbenzyl bromide and HMPA. The line shown is $0.342 + 31.8$[HMPA]; $R^2 = 0.972$.

Similar results were found for other alkylating agents. Methyl tosylate is almost 2 orders of magnitude less reactive than BBB toward LiPhIBP. Kinetics experiments carried out with 10^{-3} M enolate (65% monomer) again showed first-order behavior in HMPA (Figure S1, Supporting Information); the second-order rate constant is linear in HMPA: k_2 (M^{-1} s^{-1}) = $0.0034 + 0.93$[HMPA]. *p-tert*-Butylbenzyl chloride (BBC) is about 3 orders of magnitude less reactive toward LiPhIBP than BBB. Kinetics experiments with 10^{-3} M LiPhIBP also showed first-order behavior in HMPA; the second-order rate constant $k_2 = 1.33 \times 10^{-4} + 0.0228$[HMPA] (Figure S2, Supporting Information).

These results indicate that additional HMPA is used at the transition structure in addition to that used for solvating the lithium enolate. We suggest that its function is to provide additional solvation of the Li^+ to provide a solvent-separated leaving group. Reich[7−9] has shown that many lithium salts are converted to SSIPs with HMPA in THF.

PMDTA,[10] in contrast to HMPA, produced no significant spectral change with LiPhIBP; addition of 20 equiv gave the same λ_{max} (Figure S3, Supporting Information). PMDTA clearly does not compete with THF in solvating the lithium in the enolate. This result agrees with Collum's conclusion that its diamine analogue TMEDA also does not compete with THF in solvating lithium cation.[4] PMDTA also has only a small effect on the alkylation rate. The use of 54 equiv of PMDTA (0.05 M) with 8.6×10^{-4} M LiPhIBP increased the rate of reaction with BBB only 1.7-fold.

DMPU[11] has more of an effect on the spectrum than does PMDTA, but the effect is still relatively small; 34 equiv shifts λ_{max} by 4 nm (Table S4 and Figure S4, Supporting Information). A solution of the enolate ({LiPhIBP}=1.7×10^{-3} M) containing 34 (0.06 M) equiv of DMPU gave a 2-fold increase in rate with BBB.

Conclusion. HMPA has a pronounced effect in converting LiPhIBP tetramer to 4 mol of monomer that depends on the fifth power of [HMPA]. The approximate equilibrium constant measured corresponds to a conversion with 0.6 M HMPA of a formal concentration of LiPhIBP of 0.1 M, in which almost 98% of the enolate is present as the tetramer, to one in which 98% is now the monomer solvated by HMPA. HMPA also increases the rate of alkylation; 0.1 M HMPA gives rate increases of 10-, 18-, and 27-fold with *p-tert*-butylbenzyl bromide and chloride and with methyl tosylate, respectively. PMDTA and DMPU have much smaller effects on the aggregation equilibrium and alkylation rate.

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Supporting Information Available: Figures S1−S4, Tables S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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