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Ketone Enolization with Lithium Dialkylamides: The Effects of Structure, Solvation, and Mixed Aggregates with Excess Butyllithium

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The effects of lithium dialkylamide structure, mixed aggregate formation, and solvation on the stereoselectivity of ketone enolization were examined. Of the lithium dialkylamides examined, lithium tetramethylpiperidide (LiTMP) in THF resulted in the best enolization selectivity. The stereoselectivity was further improved in the presence of a LiTMP−butyllithium mixed aggregate. The use of less polar solvents reduced the enolization stereoselectivity. Ab initio calculations predict LDA and LiTMP to form mixed cyclic dimers in ethereal solvents. The calculations also predict LiTMP−alkyllithium mixed aggregates to competitively inhibit the formation of less stereoselective LiTMP−lithium enolate mixed aggregates.

Introduction

Lithium dialkylamides are strong but relatively non-nucleophilic bases that are extensively used for deprotonation of carbonyl compounds. The resulting enolates are among the most important reagents for the formation of carbon−carbon bonds. Although lithium diisopropylamide (LDA) has been used extensively for ketone enolization, it also undergoes several side reactions, leading to the development of several lithium dialkylamide bases for enolization reactions.[1−3] These bases vary in their ability to perform enolization reactions stereoselectively. Stereoselective Aldol-type reactions are limited by the ability to obtain the stereoisomeric (*E*)- and (*Z*)-enolates separately, and enolization stereoselectivity of lithium dialkylamide bases is a topic of current interest. Although many lithium dialkylamides do generate an excess of one stereoisomer, the stereoselectivity is influenced by the lithium amide structure, the solvent system, and the formation of mixed aggregates with other lithium compounds.

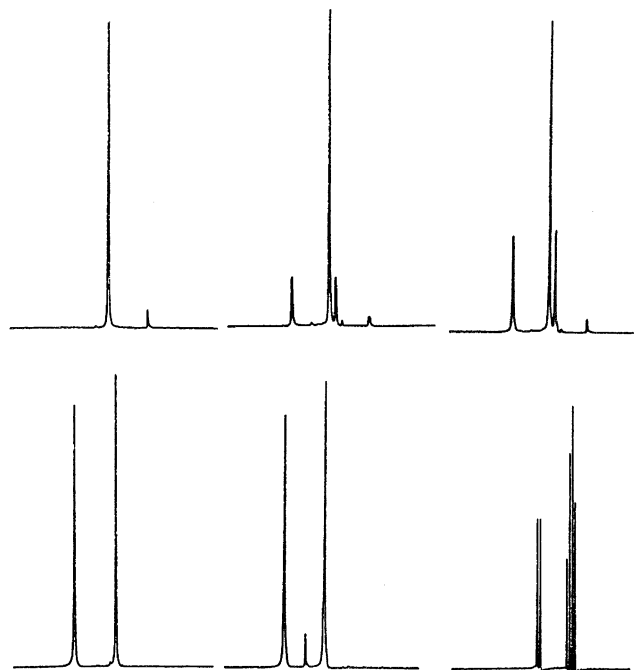Several studies have demonstrated the effects of mixed aggregation on the stereoselectivity of enolate formation.[4−6]

FIGURE 1. [6]Li spectra of LiTMP with added ethyllithium. Top left: 0.05 M LiTMP in 50% THF/50% pentane. Top center: 0.05 M LiTMP, 0.01 M EtLi. Top right: 0.05 M LiTMP, 0.02 M EtLi. Bottom left: 0.05 M LiTMP, 0.05 M EtLi. Bottom center: 0.05 M LiTMP, 0.06 M EtLi. Bottom right: 0.05 M 15N−LiTMP, 0.02 M EtLi.

Collum and co-workers demonstrated the dramatic effects of added lithium halides and lithium enolates on the stereoselectivity of 3-pentanone deprotonation by lithium

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[†] Fisk University.
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[§] Grambling State University.
(1) Majewski, M.; Gleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1.
(2) Cloudsdale, I. S. Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*, 919.
(3) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C.; Thebtaranonth, Y. *Chem. Commun.* **1991**, 1016.
(4) Cory, E. J.; Gross, A. W. *Tetrahedrom Lett.* **1984**, *25*, 495.
(5) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.
(6) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

tetramethylpiperidide (LiTMP). These effects, which included both enhanced and diminished stereoselectivity, were shown to result from mixed aggregate formation, although the mechanism is not yet known.

LiTMP forms a 1:1 mixed aggregate with ethyllithium by lithium NMR. The spectra are shown in Figure 1. Addition of ethyllithium to a solution of LiTMP resulted in two new lithium peaks corresponding to a mixed LiTMP−ethyllithium mixed aggregate. This mixed aggregate was in equilibrium with excess LiTMP (top center, top right) and with excess ethyllithium (bottom center). The doubly labeled ^{6}Li−^{15}N spectrum (bottom right) shows two nonequivalent lithium nuclei of the mixed aggregate coupled to one nitrogen, superimposed on the triplet from the LiTMP dimer. These spectra are consistent with either a mixed cyclic dimer (**1**), in which lithium exchange is slow on the NMR time scale, or a mixed open dimer (**2**). Other examples of similar mixed aggregates have been reported.[7,8]

mixed cyclic dimer (**1**)   mixed open dimer (**2**)
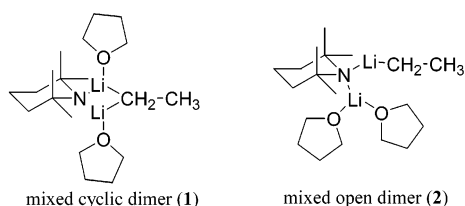
The LiTMP−butyllithium mixed aggregate has been examined for the stereoselective formation of the lithium enolates of 3-pentanone (**3**), and the highest stereoselectivity was obtained from an equimolar mixture of the mixed aggregate and uncomplexed LiTMP in THF.[9] Although several synthetic methods have been shown to generate the (*E*)-enolate with high stereoselectivity, the effects of alkyllithium−lithium amide mixed aggregates are synthetically important because they are easily prepared and because it is difficult to prepare the lithium salts of some very hindered secondary amines with the complete consumption of the alkyllithium.[8] Thus, alkyllithium mixed aggregates may inadvertently appear in the reaction mixture.

E (**3a**)   Z (**3b**)

The goals of this study are threefold. First, we examined the effects of the lithium amide structure, solvent effects, and the effects of excess butyllithium on the stereoselectivity of enolate formation. Next, we determined that the mixed aggregates are, in fact, reactive species in THF, as opposed to an equimolar mixture of free lithium dialkylamide and free butyllithium. Finally, ab initio calculations were performed to estimate the energy of mixed aggregate formation for three different lithium dialkylamides with butyllithium. This was done to better understand the steric effects of the lithium dialkylamide on mixed aggregate formation.

(7) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693.

(8) Sakuma, K.; Gilchrist, J. H.; Romesberg, F. E.; Cajthami, C. E.; Collum, D. B. *Tetrahedron Lett.* **1993**, *34*, 5213.

(9) Balamraju, Y.; Sharp, C. D.; Gammill, W.; Manuel, N.; Pratt, L. M. *Tetrahedron* **1998**, *54*, 7357.

Experimental Methods

Butyllithium (1.6 M in hexanes) and chlorotrimethylsilane were used as received. The amines (diisopropylamine, 2,2,6,6-tetramethylpiperdine, 1,1,1,3,3,3-hexylmethyldisilizane, and TMEDA) were distilled from calcium hydride, and 3-pentanone and acetophenone were distilled from diphosphorus pentoxide prior to use. All reactions were performed under a dry nitrogen atmosphere.

Lithium-6 NMR spectra were acquired on a 400 MHz spectrometer operating at 58.84 MHz. Solutions of LiTMP and ethyllithium were prepared under inert atmosphere in 50% THF and 50% pentane by volume. Spectra were acquired at −115 °C. The preparation of the isotopically labeled ethyllithium and LiTMP has been described previously.[10]

The enolization of 3-pentanone was performed in solutions containing varying butyllithium−lithium dialkylamide ratios. In each reaction flask, 0.8 mmol of butyllithium was added to 2.0 mL of solvent at −78 °C, and then varying amounts (from 0.4 to 0.8 mmol) of the amine (tetramethylpiperidine, diisopropylamine, or hexamethyldisilazane) were added, for a total lithium concentration of 0.32 M. The tables refer to the following four solutions: lithium dialkylamide alone (0.8 mmol, **1**); lithium dialkylamide and mixed aggregate mixture (0.4 mmol each, **2**); the mixed aggregate alone (0.8 mmol, **3**), and mixed aggregate and alkyllithium mixture (0.4 mmol each, **4**). Sufficient 3-pentanone was then added to each flask to consume 80% of the base (80% conversion), and the reaction was quenched after 5 min with chlorotrimethylsilane. To ensure that the *E/Z* ratios were not skewed by equilibration, the experiment was repeated with a 15 min quench time, and no significant change was noted in the *E/Z* ratios. The experiments were repeated at 40 and 20% conversion of the lithium base. The *E/Z* ratios of the enolate TMS ethers were determined by gas chromatography with a thermal conductivity detector and a HP-1 cross-linked methyl silicone gum capillary column according to a previously published procedure.[9] The data were subjected to a statistical analysis, and suspect data were evaluated by the T test at the 95% confidence level.

Computational Methods

All single-point energy calculations, geometry optimizations, and frequency calculations were performed using the Gaussian 98 package on Pentium workstations or on the University of Minnesota and University of Kentucky supercomputers. All calculations were performed at the B3LYP/6-31+G(d) level of theory, and reported energies include zero-point corrections. Frequency calculations were performed to verify that the optimized geometries represent minima on the potential energy surface. Geometry optimizations were performed on all gas-phase structures, as well as microsolvated structures formed by placing dimethyl ether ligands on each lithium atom. To determine whether conformational effects have a significant effect on the calculated energies, a few different conformations of the LiTMP−ethyllithium micro-

(10) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.

SCHEME 1. Ketone Enolization by Lithium Dialkylamides and Their Mixed Aggregates with Alkyllithiums
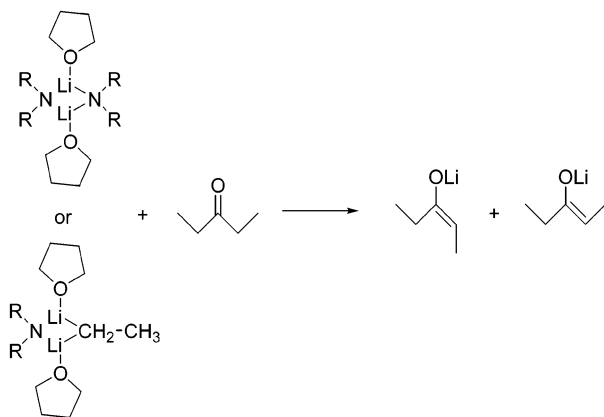
solvated mixed cyclic and open dimers were optimized at the HF/3-21G level. The energy differences of the different conformations were typically a few tenths of 1 kcal/mol or less.

Although the microsolvation model is widely used for lithium compounds, it has not been established that microsolvation alone reproduces most of the solvent effects. Therefore, single-point bulk solvated calculations were performed on each of the microsolvated structures using the polarizable conductor (CPCM) method with the UAHF model of Barone[11] and co-workers. In this model, the dielectric polarization effects are approximated by a cavity model in a continuous dielectric. The mirror charges, induced in the dielectric by partial atomic charges, reside on the surface of the dielectric. Thus, the conductorlike terminology is used for the CPCM model. In all continuum solvent calculations, the default UAHF force field atomic radii were used, which are identical to those of the UFF force field for the atoms used in this study. The radii are 1.950 Å for methyl and methylene groups, 1.500 Å for oxygen, and 1.370 Å for lithium. The dielectric constant parameters for THF were 7.58 (default) at 298 K. The solution energies reported were the "total free energy in solution", which is actually a hybrid of electronic internal energy and free energy of solvation. The solvation free energy terms were obtained directly from the CPCM calculations and included terms for solute−solvent interaction, solute polarization, cavitation energy, dispersion energy, and repulsion energy.

Results and Discussion

Scheme 1 shows the enolization of 3-pentanone by lithium dialkylamides and their alkyllithium mixed aggregates. The effects of the lithium dialkylamide structure are shown in Table 1. Of the three lithium amides studied, LiTMP generated the highest E/Z ratios with and without an excess of butyllithium. At 80% conversion of LiTMP, little difference was observed between the solutions with and without an excess of butyllithium. The highest stereoselectivity was observed with a 1:1 mixture of the LiTMP−butyllithium mixed aggregate and free LiTMP at 20% conversion of the base.

(11) Barone, V.; Cossi, M.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

TABLE 1. Enolization Stereoselectivity of Butyllithium−Lithium Dialkylamide Mixed Aggregates in THF

solution	*n*-Bu-Li/LiNR$_2$ (mmol)	% E as a function of percent conversion of Li Base		
		80%	40%	20%
1(LiTMP)	0.0/0.8	76.7 ± 0.4	86.3 ± 1.2	93.0 ± 3.8
2(LiTMP)	0.2/0.6	74.8 ± 4.8	92.7 ± 0.5	96.7 ± 1.7
3(LiTMP)	0.4/0.4	72.0 ± 3.5	85.7 ± 3.2	81.8 ± 5.1
4(LiTMP)	0.6/0.2	53.8 ± 3.0	57.3 ± 2.0	49.7 ± 4.0
LDA				
1(LDA)	0.0/0.8	65.8 ± 0.84	69.7 ± 1.5	74.1 ± 3.9
2(LDA)	0.2/0.6	63.2 ± 2.3	66.0 ± 3.1	59.7 ± 0.70
3(LDA)	0.4/0.4	62.0 ± 2.3	58.9 ± 1.3	55.3 ± 2.6
4(LDA)	0.6/0.2	50.7 ± 1.1	62.1 ± 4.0	55.3 ± 2.6
LiHMDS				
1(LiHMDS)	0.0/0.8	42.7 ± 2.3	36.5 ± 1.5	33.4 ± 5.5
2(LiHMDS)	0.2/0.6	44.3 ± 4.1	39.2 ± 4.4	31.1 ± 7.7
3(LiHMDS)	0.4/0.4	46.4 ± 1.3	42.6 ± 6.7	35.0 ± 2.4
4(LiHMDS)	0.6/0.2	45.3 ± 2.6	43.2 ± 7.3	32.5 ± 8.6

TABLE 2. Solvent Effects on the Enolization Stereoselectivity on LiTMP and LiTMP−Butyllithium Mixed Aggregates

solution	n-BuLi−LiTMP THF−pentane 1:1 *n*-Bu-Li/LiTMP (mmol)	% E as a function of percent conversion of Li base		
		80%	40%	20%
1	0.0/0.8	76.7 ± 0.4	86.3 ± 1.2	93.0 ± 3.8
2	0.2/0.6	74.8 ± 4.8	92.7 ± 0.5	96.7 ± 1.7
3	0.4/0.4	72.0 ± 3.5	85.7 ± 3.2	81.8 ± 5.1
4	0.6/0.2	53.8 ± 3.0	57.3 ± 2.0	49.7 ± 4.0
n-BuLi−LiTMP ether				
1	0.0/0.8	61.0 ± 1.3	66.4 ± 1.3	79.5 ± 7.5
2	0.2/0.6	62.2 ± 1.2	67.0 ± 2.2	71.0 ± 2.3
3	0.4/0.4	61.9 ± 2.5	65.5 ± 3.9	83.4 ± 4.8
4	0.6/0.2	61.2 ± 2.9	61.9 ± 2.3	62.3 ± 3.5
n-BuLi−LiTMP THF−TMEDA 3:1				
1	0.0/0.8	74.6 ± 6.4	74.0 ± 2.0	81.4 ± 3.1
2	0.2/0.6	70.8 ± 5.8	82.8 ± 4.5	84.5 ± 3.7
3	0.4/0.4	62.9 ± 5.8	82.9 ± 3.5	91.9 ± 1.6
4	0.6/0.2	65.7 ± 2.5	80.5 ± 3.5	93.2 ± 1.8

The formation of LiTMP mixed aggregates with lithium enolates has been observed by NMR, and these mixed aggregates can reduce the E/Z selectivity, as shown by the reduced E/Z ratios with increasing percent conversion in the LiTMP solutions.[2,3]

In contrast to LiTMP, the use of lithium diisopropylamide (LDA) resulted in a lower stereoselectivity, and the use of an excess of butyllithium caused a slight decrease in the E/Z ratios. This decrease in stereoselectivity was most pronounced at 20% conversion, with an E/Z ratio of 55:45 with the mixed aggregate and 74:26 with uncomplexed LDA.

The effects of solvent polarity on the enolization selectivity by LiTMP are shown in Table 2. The best E/Z stereoselectivity was obtained in THF. Use of the less polar diethyl ether as a solvent resulted in a loss of stereoselectivity with both the LiTMP and its mixed aggregate with butyllithium. The use of diethyl ether also greatly reduced the difference in stereoselctivity between the uncomplexed LiTMP and the LiTMP−butyllithuim mixed aggregate. Similar but less dramatic effects were observed with the THF−TMEDA solvent system.

The large effects of lithium dialkylamide structure and solvent polarity on the enolization stereoselectivity are suggestive of several possible deprotonation mechanisms

TABLE 3. Calculated Gas-Phase Energies of Mixed Dimer Formation

1/2(LiNR₂) + 1/2(EtLi)₂ → mixed cyclic dimer

LiNR₂	energy of mixed dimer formation (kcal/mol)
LiDMA	−0.01
LDA	−0.07
LiTMP	−3.2

via different aggregated forms. These aggregates include lithium dialkylamide monomers and dimers, mixed aggregates with excess butyllithium, and mixed aggregates with the newly formed enolate. The very sterically hindered LiTMP forms mixed aggregates with alkyllithiums. It is not yet known if similar mixed aggregates are formed with LDA or LiHMDS. Addition of excess butyllithium to the latter two bases had very little effect on the enolization stereoselectivity.

To determine whether lithium dialkylamide−butyllithium mixed aggregates were the reactive species in the enolization reaction, as opposed to the lithium dialkylamide and butyllithium reacting separately, the following experiment was performed. A 1:1 mixture of the lithium dialkylamide (LiTMP, LDA, or LiHMDS, 0.5 mmol) and butyllithium (0.5 mmol) in 5.0 mL THF was prepared, and acetophenone (0.25 mmol) was added at −78 °C. The mixture was stirred for 5 min before adding 1.0 mmol TMSCl, and the mixture was analyzed by GC−mass spectrometry. Control experiments were performed with 1.0 mmol of each lithium dialkylamide without mixed aggregate formation. An additional control used butyllithium alone to determine the amount of enolization, carbonyl addition, and other products that are formed with acetophenone. Acetophenone was chosen for this experiment because it generates a single enolate and because it is well separated from the solvent signals in the gas chromatogram.

If the lithium dialkylamides quantitatively formed reactive mixed aggregates with butyllithium, the GC−MS would show the enolate as the only reaction product of acetophenone. The reaction with butyllithium alone indicated the enolate as the major product, with significant amounts of the carbonyl addition product and other unidentified byproducts. Enolization of acetophenone by LDA, LiHMDS, and their mixed aggregates showed little or no addition product from free butyllithium. A small amount of addition product was observed with both LiTMP and its butyllithium mixed aggregate, which is consistent with the known difficulty of quantitative deprotonation of hindered amines by butyllithium at low temperatures.[8] The absence of or small quantities of butyllithium reaction products with acetophenone indicates that the mixed aggregates are, in fact, major reactive species in the enolizations.

The energies of mixed aggregate formation were calculated from the lithium dialkylamide dimers (lithium dimethylamide, LiDMA; lithium diisopropylamide, LDA;

and lithium tetramethylpiperidide, LiTMP; and the ethyllithium dimer. Although the aggregation state of ethyllithium depends on the solvent, the dimer was used throughout to enable a direct comparison of the calculated energies. Calculations were performed in the gas phase for the mixed cyclic dimer only, as all attempts to optimize the mixed open dimer in the gas-phase reverted to the mixed cyclic dimer geometry. The gas-phase results are shown in Table 3.

The gas-phase calculations predict the mixed aggregates to be in equilibrium with the homodimers in nearly a 1:1 ratio. From prior NMR studies in hydrocarbon solutions, alkyllithiums and LiTMP exist as higher aggregates in noncoordinating solvents, which would favor the homoaggregates over the mixed aggregates.[12−14] In contrast, solvation with dimethyl ether ligands favored mixed cyclic dimer formation, both with and without the inclusion of bulk solvation. In each case, formation of the mixed open dimer was found to be endothermic. These results are shown in Table 4.

The energies of mixed aggregate formation depend both on the steric bulk of the lithium dialkylamide and on solvation by ethereal solvents. Both LDA and LiTMP are predicted to form mixed cyclic dimers. The sum of the gas-phase energy of reaction and the change in solvation free energy is positive for mixed open dimer formation in all cases, and the cyclic dimers appear to be the dominant species in solution. This does not preclude the possibility of mixed open dimers acting as transient intermediates in ketone enolization reactions, as was suggested by prior semiempirical and ab initio calculations.[9]

The best enolization stereoselectivity occurred with LiTMP at 20% conversion, and the relatively large difference in *E/Z* ratios between 80 and 20% conversion suggests that a LiTMP−enolate mixed aggregate is detrimental to high stereoselectivity. Much smaller differences between the *E/Z* ratios at 80 and 20% conversion were found with LDA and LiHMDS. With LiTMP, the highest *E/Z* ratio was found with a 1:1 mixture of LiTMP and its mixed aggregate (solution 2). No LiTMP−ethyllithium mixed trimers have been observed by NMR, although it is possible that a reactive but spectroscopically unobservable higher mixed aggregate could be formed. An alternate explanation is that the formation of the LiTMP−alkyllithium mixed dimer competitively inhibits the formation of the LiTMP−enolate mixed dimer. Calculations were performed to test this hypothesis, as shown in Scheme 2, and used a combined solvation model consisting of microsolvation by dimethyl ether as well as the CPCM continuum solvation model. With the lithium enolate of acetaldehyde (LiOV), the equilibrium was calculated to favor the LiTMP−LiOV mixed aggregate and free ethyllithium. When the lithium enolate of 3-pentanone was used, the LiTMP−enolate mixed aggregate was favored by only 0.5 kcal/mol. It is

TABLE 4. Calculated Energies of Solvated Mixed Cyclic Dimer and Mixed Open Dimer Formation (kcal/mol)

1/2(LiNR₂)·2ether + 1/2(EtLi)₂·2ether → mixed cyclic dimer·2ether → mixed open dimer·2ether

LiNR₂	*E* cyclic dimer microsolvated	*E* cyclic dimer micro + bulk	*E* open dimer microsolvated	*E* open dimer micro + bulk
LiDMA	+0.89	+0.60	+10.7	+9.0
LDA	−5.5	−5.4	+11.1	+9.1
LiTMP	−5.2	−5.6	+10.0	+8.1

SCHEME 2. Equilibrium between LDA and LiTMP Mixed Aggregates with Ethyllithium and Lithium Acetaldehyde Enolate
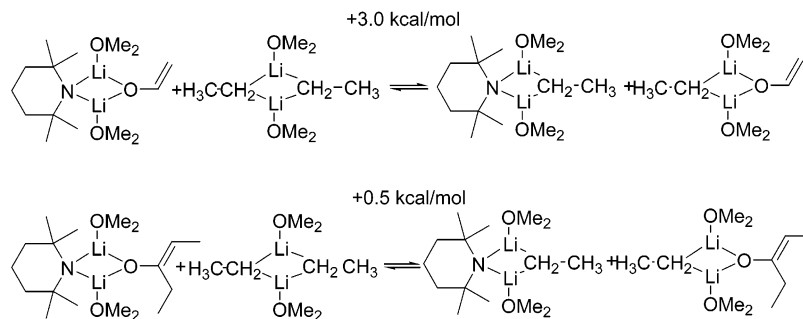
likely that with the more strongly binding THF ligand, steric effects would drive the equilibrium further to the right. Thus, it appears that the inhibition of the less stereoselective LiTMP−lithium enolate mixed aggregate is a factor that contributes to the high stereoselectivity of 3-pentanone enolization in the presence of excess butyllithium.

Conclusions

The *E*/*Z* stereoselectivity of ketone enolization is dependent on the structure of the lithium dialkylamide base, the formation of mixed aggregates with excess butylithium, and solvation. The highest *E*/*Z* ratios were obtained with LiTMP−butyllithium mixed aggregates in THF. The use of LiHMDS resulted in a reversal of the *E*/*Z* selectivity.

The formation of lithium dialkylamide mixed dimers with ethyllithium is favored by increasing the steric bulk of the lithium amide and by ethereal solvents. The use

of microsolvation appears to be sufficient to represent the solvent effects, as little change in the energies of mixed aggregate formation was found when bulk solvation effects were included. The computational results are consistent with the $^6Li-^{15}N$ spin coupling patterns.

Supporting Information Available: Tables S1−S21 of optimized geometries of lithium dialkylamides, ethyllithium, and their mixed aggregates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 3345.

(13) Kim, Y. J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

(14) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 7949.