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Mixed Aggregates of Lithium Tetramethylpiperidide with Butyllithium: Stereoselectivity of Ketone Enolization

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Abstract: The enolization stereoselectivity of 3-pentanone by lithium tetramethylpiperidide mixed aggregates with butyllithium was studied and the results were compared to those obtained using lithium tetramethylpiperidide alone. The mixed aggregate resulted in a slightly higher stereoselectivity, and the selectivity increased with decreasing percent conversion of the lithium base. Ab initio and semiempirical PM3 calculations were performed to determine the activation enthalpies for the enolization reactions and the calculations were compared to the experimental results. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

Although it has been known for some time that many organolithium compounds form mixed aggregates with other organolithiums or inorganic lithium salts, it is only in the past decade that the utility of these mixed aggregates in organic synthesis has been appreciated. Several studies have demonstrated the formation of the less stable E enolate under kinetic control rather than the more stable Z enolate. Mixed aggregate formation between alkyllithiums and lithium iodide was reported in 1968 by McKeever and coworkers.[1] Collum and co-workers demonstrated a remarkably high E/Z selectivity of 3-pentanone enolization by lithium tetramethylpiperidide (LiTMP) in the presence of lithium halides in very dilute solutions, although this selectivity decreased with increasing concentration.[2] This high selectivity was attributed to the formation of several different mixed aggregates.[3] The synthetic importance of this mixed aggregate formation was reported by Corey and Gross in a study of enolization reactions in the presence of chlorotrimethylsilane, which generates lithium chloride during the course of the reaction. Although the mixed aggregate formation was not yet known, it was noted that the E/Z enolate selectivity was dependent upon the lithium dialkylamide which was used.[4]

LiTMP was also shown to form a 1:1 mixed aggregate with ethyllithium and phenyllithium,[5] although the exact structure has not yet been determined. The lithium and nitrogen NMR spectra are consistent with either a cyclic mixed dimer **1** or an open mixed dimer **2**. Semiempirical molecular orbital calculations showed that both mixed dimers are minima on the potential energy surface. Regardless of the actual structure of the major species, the reactive aggregate could be either a spectroscopically unobservable minor species, or a small amount of the LiTMP in equilibrium with the mixed dimer.

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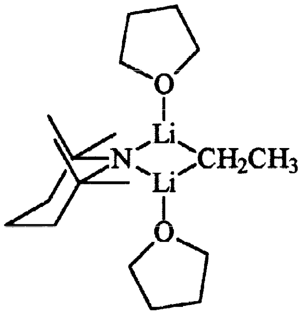
The formation of other lithium mixed aggregates has been extensively documented.[6-8] The anionic polymerization of acrylates results in the formation of an enolate-like species, and mixed aggregates of this enolate has been shown to affect the polymerization kinetics, stereochemistry, and molecular weight distributions.[9-11] Numerous other examples of the synthetic utility of lithium mixed aggregates have also been reported.[12-16]



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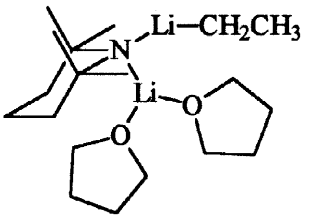

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During the past decade computational methods have become an important tool for the study of organolithium compounds. This is particularly true of the development of reliable semiempirical methods, which are computationally less expensive than ab initio methods, and therefore enable molecular orbital calculations to be performed on the full system of interest, including solvating ligands, which often determine the solution structure of organolithium compounds. The MNDO semiempirical method was a significant improvement over the earlier methods in terms of computational accuracy, and it has correctly predicted the solution structures and aggregation states of lithium dialkylamides.[17] The MNDO parameters were developed with a very limited data base, however, and have been found to severely overestimate the carbon-lithium bond strength in many molecules, thus rendering MNDO unsuitable for this study.[18] The newer PM3 semiempirical program has recently been parameterized for lithium[19] and, for the most part, the computational accuracy of the calculations are improved over those obtained with the MNDO parameterization.[20]

Experimental Methods

Tetrahydrofuran (THF) was distilled from blue or purple solutions containing sodium benzophenone ketyl under nitrogen. 2,2,6,6,-Tetramethylpiperidine was obtained from Aldrich and purified by distillation from lithium aluminum hydride. 3-Pentanone was obtained from Pfaltz & Bauer and purified by distillation from phosphorous pentoxide. Triethylamine was obtained from Fisher Scientific Company and purified by distillation from lithium aluminum hydride. Chlorotrimethylsilane (TMSCl) solutions in triethylamine were prepared by stirring the TMSCl with freshly distilled amine, followed by centrifugation of the mixture in a sealed vial. Butyllithium (1.6 M in hexane) was obtained from Aldrich.

Enolization Selectivities. To a rapidly stirred solution of 2,2,6,6,-Tetramethylpiperidine (TMP) in 2 mL of THF at –40°C under N_2 atmosphere was added a 1.6 M solution of n-BuLi/Hexanes. After stirring for 5 minutes the solution was cooled to –78°C and 3-Pentanone was added. After being stirred for 15 minutes the enolates were trapped using a clear 4:1(v/v) mixture of chlorotrimethylsilane (TMSCl)/NEt_3 and the E/Z ratios determined by gas chromatography with a Hewlett Packard model 5890 gas chromatograph equipped with a thermal conductivity detector and a HP-1 crosslinked methyl silicone gum capillary column. Each selectivity experiment was repeated at least three times and the mean E/Z ratios are reported. The data were subjected to a statistical analysis and suspect data were evaluated by the T test at the 95% confidence level.

Because lithium amides are known to form mixed aggregates with lithium halides, it is possible that the lithium chloride generated by the trapping of the enolate could affect the observed regioselectivity by facilitating the isomerization of the enolate. The trapping reaction was repeated as described above, except that the TMSCl was added over a period of five minutes to allow any isomerization to take place as the first bit of LiCl was formed. The observed stereoselectivity was identical (within experimental error) to that obtained by adding the TMSC in a single portion. We therefore concluded that the enolate trapping by TMSCl is rapid on the timescale of any LiCl mediated isomerization.

Computational Methods

Semiempirical PM3 calculations were performed with the Spartan 4.0 set of programs[21] on a Silicon Graphics Indy workstation. All geometry optimizations were performed without symmetry constraints. Frequency calculations were used to verify that each suspected transition state had exactly one imaginary vibrational mode. Ab initio calculations were performed using the 3-21G basis set with geometry optimization, followed by single point energy calculations using the 6-31G* basis set. The ab initio calculations were performed with the Gaussian 94 program[22] on a Silicon Graphics Power Challenge Array and HP Convex Exemplar at the National Center for Supercomputing Applications (NCSA) at the University of Illinois at Urbana-Champaign.

Results and Discussion

Butyllithium-LiTMP mixed aggregates. The enolization of 3-Pentanone was performed in solutions containing varying butyllithium-LiTMP ratios, starting from 0.8 mmol of BuLi and adding varying amounts of tetramethylpiperidine from 0 to 0.8mmol, for a total lithium concentration of 0.32 M. Table 1 refers to the following five solutions: Butyllithium (0.8 mmol, **1**); butyllithium-mixed aggregate (0.4 mmol each, **2**); mixed aggregate (0.8 mmol, **3**); mixed aggregate-LiTMP (0.4 mmol each, **4**); and LiTMP (0.8 mmol, **5**). Tables 2 and 3 refer to the same butyllithium-mixed aggregate ratios, with lower total lithium concentrations. In each case an excess of base was present, with sufficient 3-pentanone added to take the reaction to 80%, 40%, 20%, and 10% conversion with respect to the lithium base. At the lower TMP concentrations the addition of butyllithium to the ketone was the predominant reaction, although sufficient deprotonation occurred to determine the E/Z selectivity in these solutions. From the table it is seen that the E/Z ratio increases when the amount of TMP was varied from 0 to .4 mmol , and above 0.4 mmol there was little change in the E/Z ratio at 80% conversion. At lower percent conversions the E/Z selectivity was slightly higher, and the selectivity appeared to reach a maximum in solutions 3 or 4, before dropping again in the solution containing only LiTMP. Although this difference in selectivity was small, it does suggest that the reactive species is the mixed aggregate rather than LiTMP.

Table 1. E/Z ratios of 3-pentanone enolization in 0.32 M (total lithium concentration) solutions of butyllithium-LiTMP

		% E enolate as a function of percent conversion of Li base			
Solution	BuLi / LiTMP (mmol)	80%	40%	20%	10%
1	0.8 / 0.0	35.6 ± 0.8	42.3 ± 0.9	38.3 ± 3.0	35.7 ± 1.8
2	0.6 / 0.2	53.8 ± 3.0	57.3 ± 2.0	49.7 ± 0.3	49.5 ± 4.0
3	0.4 / 0.4	72.0 ± 3.5	85.7 ± 3.2	81.8 ± 5.1	87.4 ± 4.5
4	0.2 / 0.6	74.8 ± 4.8	92.7 ± 0.5	96.7 ± 1.7	90.8 ± 4.9
5	0.0 / 0.8	76.7 ± 0.4	86.3 ± 1.2	93.0 ± 3.8	91.8 ± 1.9

The experiment was repeated with a total lithium concentration of 0.16 M, as shown in Table 2. Although the E/Z selectivity ratios were a bit lower than at the higher lithium concentration, there was a maximum E/Z selectivity with equimolar butyllithium-LiTMP concentrations when using a large excess of base.

Table 2. E/Z ratios of 3-pentanone enolization in 0.16 M (total lithium concentration) solutions of butyllithium-LiTMP

		% E enolate as a function of percent conversion of Li base			
Solution	BuLi / LiTMP (mmol)	80%	40%	20%	10%
1	0.4 / 0.0	35.5 ± 3.7	37.0 ± 1.7	36.3 ± 2.1	50.2 ± 1.0
2	0.3 / 0.1	63.2 ± 4.3	68.2 ± 3.0	66.0 ± 4.5	74.3 ± 2.0
3	0.2 / 0.2	69.5 ± 1.7	81.8 ± 0.2	90.0 ± 0.2	89.8 ± 4.9
4	0.1 / 0.3	70.2 ± 4.3	75.6 ± 5.8	74.0 ± 4.2	85.0 ± 2.8
5	0.0 / 0.4	65.4 ± 1.3	72.6 ± 1.6	67.9 ± 1.7	81.0 ± 1.5

In order to observe the effects of increased dilution, the experiment was repeated a third time with a total lithium concentration of 0.08 M. Overall the results were similar to the experiment using a total lithium concentration of 0.16 M, although the dilution made it difficult to accurately integrate the peak areas. In most cases, the enolate peaks from the deprotonation by butyllithium alone (Solution 1) were too small to integrate. As in the previous two experiments, a higher percent conversion caused a slight reduction in E/Z selectivity, suggesting the possible formation of a second mixed aggregate with lithium chloride. The results are summarized in Table 3.

Table 3. E/Z ratios of 3-pentanone enolization in 0.08 M (total lithium concentration) solutions of butyllithium-LiTMP

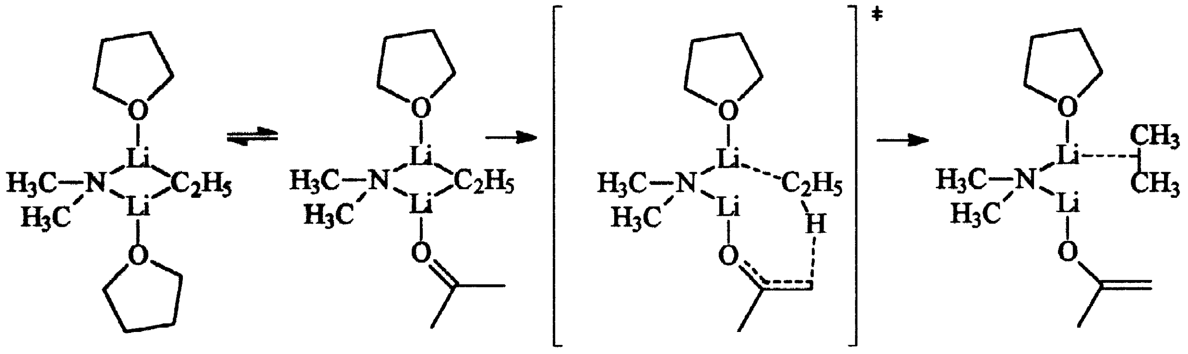
		% E enolate as a function of percent conversion of Li base			
Solution	BuLi / LiTMP (mmol)	80%	40%	20%	10%
1	0.2 / 0.0	N/A	33.8 ± 7.2	N/A	44.5 ± 0.5
2	0.15 / 0.05	63.2 ± 2.7	75.3 ± 7.9	81.0 ± 10.8	86.4 ± 6.2
3	0.1/ 0.1	71.4 ± 4.7	78.3 ± 7.2	85.3 ± 6.9	76.1 ± 4.9
4	0.05 / 0.15	70.5 ± 2.0	75.5 ± 11.1	86.7 ± 8.8	79.5 ± 4.7
5	0.0 / 0.2	73.7 ± 7.6	90.5 ± 4.8	71.3 ± 10.9	86.7 ± 2.9

Although the scatter in the data points at high dilution makes it difficult to precisely correlate stereoselectivity with the aggregation state, some general trends were clearly observed. The lowest E/Z ratios were obtained at 80% conversion of the butyllithium and the best selectivity was observed at 10% and 20% conversion for each of the three data sets. This suggests that at high percent conversions, a new mixed aggregate of LiTMP with the newly formed enolate may compete with the LiTMP-butyllithium mixed aggregate, as was suggested by Collum and coworkers with other mixed aggregate systems.[2] At low percent conversion, little of the enolate will be formed, and even though some of the LiTMP-enolate mixed aggregate may be present, the major species will still be the LiTMP-butyllithium mixed aggregate. The lower E/Z selectivity at high percent conversion is consistent with the formation of the new LiTMP-enolate mixed aggregate, which was reported to result in a lower E/Z selectivity than pure LiTMP.[3] We therefore conclude that the butyllithium-LiTMP mixed aggregate is more stereoselective than either the LiTMP-enolate mixed aggregate or LiTMP alone.

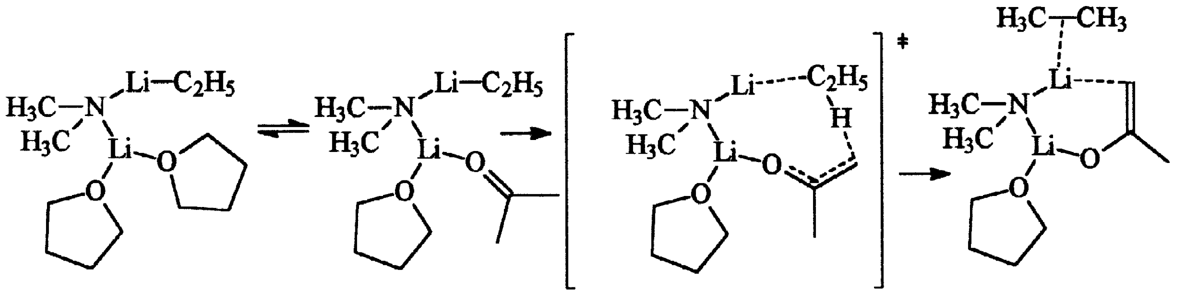
Semiempirical PM3 calculations were used in an attempt to determine the mechanism of ketone deprotonation by the mixed aggregate. Mechanisms involving both the mixed cyclic dimers and mixed open dimers were considered. Activation enthalpies were calculated for the acetone enolate formation from the ethyllithium-lithium dimethylamide (LiDMA) cyclic and open dimers, as shown in Scheme 1. For comparison, the PM3 geometries were reoptimized using the Gaussian 94 program with the 3-21G basis set, and single point energies calculated with the 6-31G* basis set at the 3-21G geometry. The results are shown in Table 4. While these calculations were performed at relatively low levels of theory due to the size of the molecules, the large difference in calculated energy values indicates that the mixed open dimer pathway is favored over the mixed cyclic dimer mechanism. The calculated transition states are shown in Figure 1.

Table 4. Calculated activation energies (kcal/mole) for ketone deprotonation by the mixed cyclic dimer and mixed open dimer mechanisms.

Method	PM3	3-21G	6-31G*//3-21G
Mixed cyclic dimer	15.2	18.4	25.2
Mixed open dimer	3.0	10.6	16.7



Cyclic dimer pathway



Open dimer pathway

Scheme 1

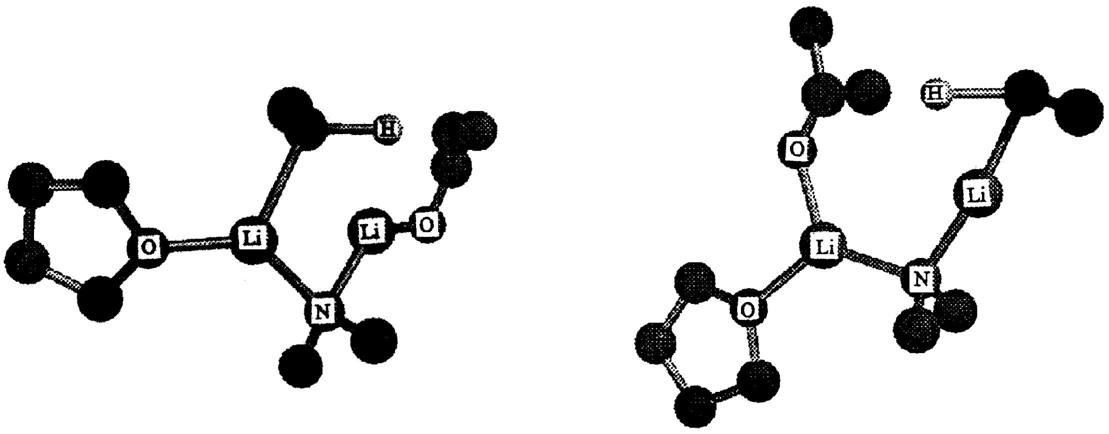


Figure 1. PM3 calculated transition states for the deprotonation of acetone by the ethyllithium-LiDMA mixed aggregate. Mixed cyclic dimer mechanism (left) and mixed open dimer mechanism (right)

Calculations were performed on the deprotonation of 3-pentanone by the mixed open dimers of ethyllithium with both LiDMA and LiTMP. In both cases, the transition state leading to the E enolate was favored over the Z enolate transition state. For comparison, calculations were also performed on the ground and transition states for the deprotonation of 3-pentanone by the open dimer of LiTMP.[2, 17] In the case of the LiDMA mixed aggregate, the calculated activation enthalpies for the formation of the E and Z enolates were 2.95 and 3.89 kcal/mole, respectively, for a theoretical E/Z ratio of 11.7 at −78 °C. With the LiTMP mixed aggregate the calculated activation enthalpies were 3.09 and 4.40 kcal/mole for the E and Z enolates, respectively, for a theoretical E/Z ratio of 27.9. For the LiTMP open dimer (without mixed aggregation), the calculated activation enthalpy for the E enolate formation was only 1.11 kcal/mole, compared to 5.16 for the Z enolate. This calculation predicts an E/Z ratio of $3.29\text{x}10^4$, which is much greater than the highest E/Z ratio reported for LiTMP in very dilute solutions.[3]

Although the calculated activation enthalpies are in qualitative agreement with the experimental results, several factors may be responsible for the large differences between the calculated and experimental selectivities. First, the semiempirical methods remain imperfect. Because the parameters were generated from a relatively small data base of compounds, bond strengths in the various aggregates are not always accurately represented, although the results are for the most part consistent with known structures. Steric strain is often overestimated by the semiempirical methods, and differences in the amount of steric strain in the transition state is the reason for the observed stereoselectivity. Thus, the calculated E/Z ratios are probably overestimated. Furthermore, these calculations include a few solvating ligands but do not account for bulk solvation effects, which may affect the reaction stereochemistry. Previous computational work with lithium dialkylamides using explicit solvent ligands rather than bulk solvation models generated good qualitative results which were consistent with experimental data.[17] In spite of the imperfections described above, the semiempirical and ab initio calculations do correctly predict the formation of the E enolate as the major product, and the difference in calculated activation energies is sufficiently large so that the conclusions would not be changed by relatively small errors in the calculated energies.

Figure 2 shows the calculated transition states for the ketone deprotonation by the LiTMP-ethyllithium mixed aggregates. The transition state leading to the Z enolate is more sterically hindered, thus favoring the formation of the E enolate. Although the exact E/Z ratios are not accurately predicted by the semiempirical calculations for reasons described above, the experimental results indicate that the mixed aggregate results in a slight improvement in stereoselectivity over that of LiTMP alone. Thus, the use of alkyllithium-lithium dialkylamide mixed aggregates shows potential for improved stereoselectivity in deprotonation reactions, and other mixed aggregate systems are currently being examined.

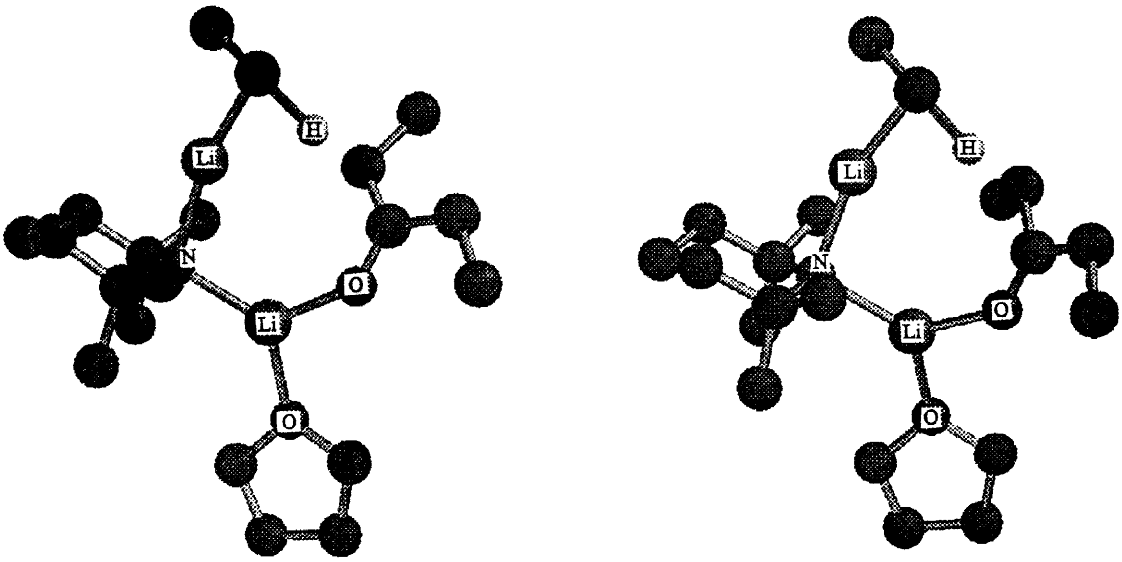


Figure 2. PM3 calculated transition states for the deprotonation of 3-pentanone by the ethyllithium-LiTMP mixed open dimer mechanism. E-enolate (left) Z-enolate (right)

Conclusions

Butyllithium mixed aggregates with LiTMP results in a slightly higher E/Z stereoselectivity than LiTMP alone in the deprotonation of 3-pentanone. Ab initio and semiempirical molecular orbital calculations show that the most likely mechanism involves a mixed open dimer as either the ground state or a reactive intermediate, and that the reaction proceeds through an open dimer-like transition state. Calculations on the transition states are consistent with the observed stereoselectivity, and indicate that this selectivity results from greater steric hindrance in the transition state leading to the Z enolate. The use of other related mixed aggregates to improve stereoselectivity is currently under investigation.

Acknowledgments

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