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Structure, Bonding, and Asymmetric Induction in (R,R)-2,3-dimethoxy-1,4-bis(dimethylamino)butane Complexes with Organolithium Compounds: A Semiempirical Computational Study

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Abstract: Semiempirical PM3 calculations were performed on several organolithium complexes with (R,R)-2,3-dimethoxy-1,4-bis(dimethylamino)butane. The calculations showed that the ligand binding mode is dependent on the aggregation state of the organolithium, and may bind via the nitrogen atoms, oxygen atoms, or both. The complex with t-butyllithium exists as a monomer, while the complexes with several other organolithium compounds exist primarily as dimers. Complexes between the various chelated forms of butyllithium and propanal were examined in order to better understand the mechanism of asymmetric induction.

Introduction

Complexes between the chiral ligand (R,R)-2,3-dimethoxy-1,4-bis(dimethylamino)butane (DDB) and organolithium compounds have been shown to result in asymmetric induction in the nucleophilic addition of alkyllithium compounds to prochiral aldehydes and ketones. Early work by Seebach and coworkers showed that modest optical yields could be obtained with DDB-alkyllithium ratios of 10:1.[1-4] Although the optical purity varied with the nucleophile and carbonyl compound, an enantiomeric excess of 22.5% was obtained from the addition of butyllithium to cyclohexanecarboxaldehyde in the presence of DDB. Similar results were obtained with Michael additions to unsaturated ketones.[4] More recent work with anionic polymerizations has revived interest in the use of DDB and other chiral ligands in the study of helix-sense selective polymerizations, in which one of two possible polymer helices is formed in excess.[5-10] Of all the chiral ligands used for asymmetric induction, DDB is of particular interest because it can form chelates to the lithium compound through either the nitrogen or oxygen atoms, or both.

In spite of the importance of organolithium complexes with DDB, an extensive literature search failed to reveal any studies of the structure and bonding of these complexes. Although NMR coupling between ^{13}C and ^{7}Li was observed as early as 1968[11, 12], the aggregation behavior of alkyllithium compounds in solution was not fully appreciated until the ^{13}C-^{6}Li double labeling studies of Fraenkel and coworkers in 1980, which showed that simple alkyllithiums exist primarily as a tetramer-hexamer mixture in hydrocarbon solvents, with a minor contribution from other aggregates.[13] Later studies of phenyllithiums[14, 15] and lithium dialkylamides[16] showed similar aggregation behavior, with the cyclic dimer being the most common aggregate in these compounds.

These and other studies have shown that the aggregation behavior is strongly solvent dependent, and that the addition of strongly binding ligands may alter the aggregate equilibrium in sometimes unexpected ways.[17-19] Although NMR coupling information is a valuable tool for solution structure determination in many cases, its usefulness is limited by the availability of isotopically labeled compounds. While many ^{13}C labeled alkyllithiums and ^{15}N labeled lithium amides are relatively easy to synthesize, isotopically labeled solvents and ligands present a much more severe problem due to the difficulty and expense of synthesizing ^{15}N labeled compounds, and the unavailability of a spin 1/2 isotope of oxygen. Furthermore, short-lived reactive intermediates may be difficult or impossible to observe spectroscopically. Over the last few years computational methods have become increasingly important in the study of organolithium chemistry, particularly with the development of reliable semiempirical methods, which are able to calculate the structures and energies of the actual molecules of interest, including solvating ligands. MNDO calculations have been used to accurately predict the structure and bonding in lithium dialkylamides.[20] Unfortunately, the MNDO parameterization significantly overestimates the lithium-carbon strength[21] and gives incorrect geometries and energies for many systems containing lithium-carbon bonds. Recently, reliable parameters have been developed for the semiempirical PM3 Hamiltonian, which have corrected most of the deficiencies in the MNDO parameterization.[22] Although these parameters were developed from monomeric (unaggregated) organolithium compounds, our recent work has shown the reliability of this parameter set for a wide range of aggregated species as well.[23, 24] PM3 is a good compromise between computational accuracy and economy, and thus was chosen for the study of the structure and bonding between organolithium compounds and DDB.

Computational methods

Semiempirical PM3[25] calculations were performed with the MOPAC[26] program and the Insight II graphical interface, produced by Biosym[27] on a Silicon Graphics Indigo 2 workstation. All PM3 geometry optimizations were performed in Cartesian coordinates without symmetry constraints, using the PRECISE keyword, which improves the convergence criteria by a factor of one hundred. The PM3 lithium parameters of Anders[22] were used as an external parameter set. Transition states were located by eigenfollowing via the TS keyword and verified by force calculations. When necessary, spurious imaginary frequencies were eliminated by eigenfollowing along the spurious mode until the transition state was located.

Results and Discussion

Six organolithium compounds were chosen for this study. Methyllithium, n-butyllithium, and t-butyllithium are representative examples of simple alkyllithiums. Phenyllithium was also chosen due to its importance in synthetic organic chemistry, as well as the variety of its known aggregated forms. Lithium dimethylamide was chosen as an example of relatively non-nucleophilic lithium nitrogen bases. N-lithio-N, N'-diphenyl-ethylenediamine (LiDPEDA) was also chosen for study due to its use as an anionic polymerization initiator. Calculations were performed on the three isomeric unaggregated DDB chelating forms of these compounds, as shown in Figure 1. The relative energies of the N-N, O-O, and N-O chelates are summarized in Table 1. In each case the

predominant isomer is chelated via the two nitrogens, with a minor contribution from the mixed chelating form. For example, at -78 °C, the N-O chelating form would make up 0.1 % of the n-butyllithium monomer composition, while the oxygen chelating form would be only 2.7 X 10^{-6} %.

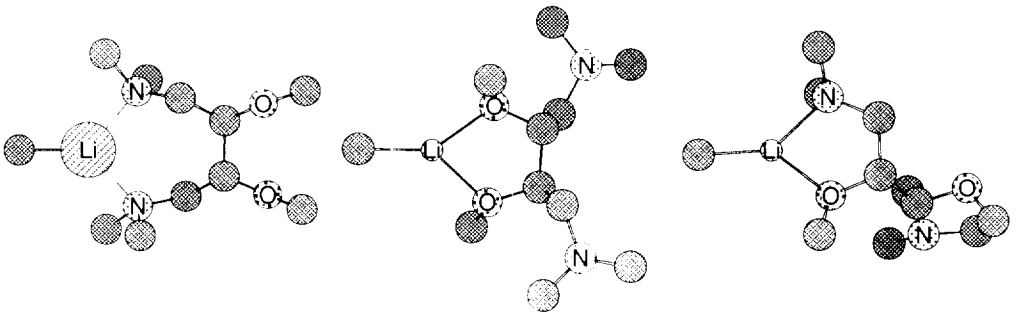


Figure 1. Methyllithium monomer chelates with DDB. (a) Nitrogen chelate (b) Oxygen chelate (c) Mixed N-O chelate. Hydrogens are omitted for clarity.

Table 1. Relative energies of DDB chelating organolithium isomers.

R-Li	N-N	O-O	N-O
MeLi	0.0	6.0	2.0
n-BuLi	0.0	6.8	2.7
t-BuLi	0.0	7.6	3.6
PhLi	0.0	6.4	2.6
Me_2NLi	0.0	5.9	3.2
LiDPEDA	0.0	7.3	1.9

Calculations were performed on the cyclic dimers of each organolithium molecule. Although most alkyllithiums exist primarily as tetramers in simple ethereal solvents, the additional steric hindrance of the chelating ligand precludes aggregation to the tetrameric form, as was seen while attempting to build the DDB solvated tetramer model. As in the case of the monomer, the ligand could bind to the alkyllithium dimer via the nitrogens, oxygens, or both. Two different diastereomeric forms are possible for the N-O chelated cyclic dimer. The four isomers are shown in Figure 2 for methyllithium, and the relative energies of each compound are given in Table 2. Although t-butyllithium is known to aggregate in hydrocarbon solvents and simple ethers, each of the chelated dimeric starting geometries optimized to a pair of loosely bound monomers. The other alkyllithiums and phenyllithium adopted the mixed N-O chelating Z isomer as the most stable form. In contrast, the lowest energy of lithium dimethylamide was the nitrogen chelate, while the more sterically hindered LiDPEDA was most stable as the E mixed chelate. No stable minima could be located for a geometry in which the ligands bridged the two lithiums.

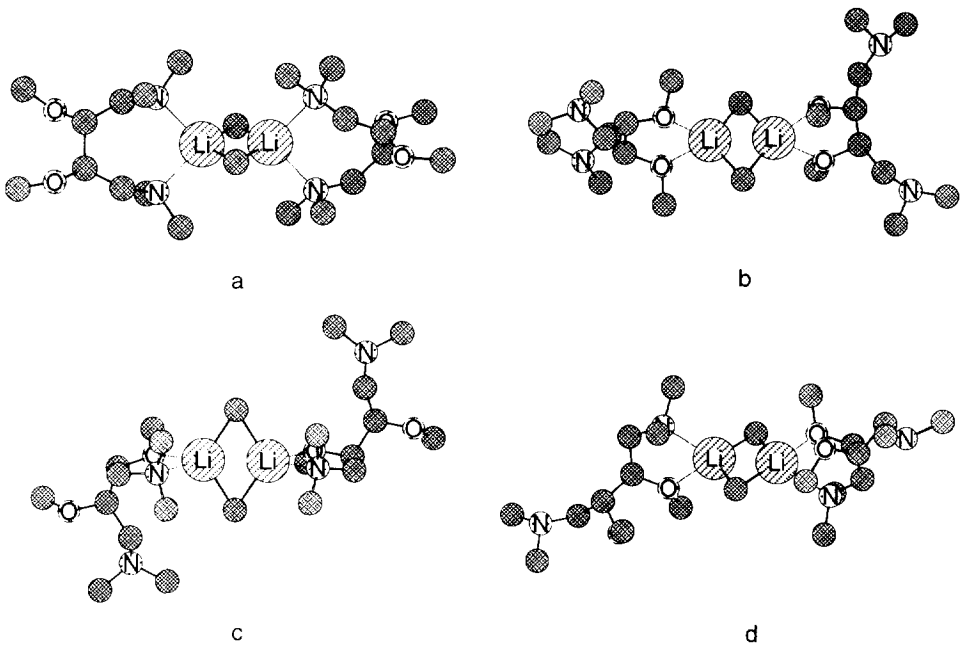


Figure 2. Methyllithium dimer chelates with DDB. (a) Nitrogen chelate (b) Oxygen chelate (c) Mixed N-O chelate Z isomer (d) Mixed N-O chelate E isomer

Table 2. Relative energies (Kcal/mole) of the chelated organolithium cyclic dimers. Dimerization energies of the most stable dimer relative to the most stable monomer are shown.

R-Li	N-N	O-O	N-O (Z)	N-O (E)	E Dimerization
MeLi	13.9	1.4	0.0	7.2	-17.8
n-BuLi	13.4	4.2	0.0	3.6	-9.3
PhLi	11.9	4.5	0.0	7.4	-16.1
Me_2NLi	-3.3	3.0	0.0	-2.6	-30.4
LiDPEDA	2.7	-4.7	0.0	-8.1	-6.8

Open dimers of lithium dialkylamides, in which one lithium is solvated by strongly coordinating ligands, have recently been proposed as reactive intermediates in ketone deprotonation reactions.[18,20] Open dimers have also been proposed as reactive intermediates in the alkylation of aldehydes in THF[28, 29], and the analogous structures were examined by PM3 for each of the three possible chelating forms, as shown in Figure 3 for methyllithium. The open dimers were found to represent local minima on the potential energy surface, except for t-butyllithium, which dissociated to a chelated monomer loosely bound to an unsolvated monomer. The most stable isomer was the mixed chelating form (Figure 3c), except for LiDPEDA, which was most stable in the nitrogen chelating form. These results are summarized in Table 3. It should be noted that the alkyllithium

and aryllithium open dimers are stable only in conformations in which the non-bridging methyl group is prevented from bonding to the chelated lithium atom by steric hindrance from the ligand, as shown in the figure. Otherwise, the structure optimized back to the cyclic dimer. Thus, the open dimer represents a high energy local minimum which may or may not be an important intermediate in alkyllithium reactions.

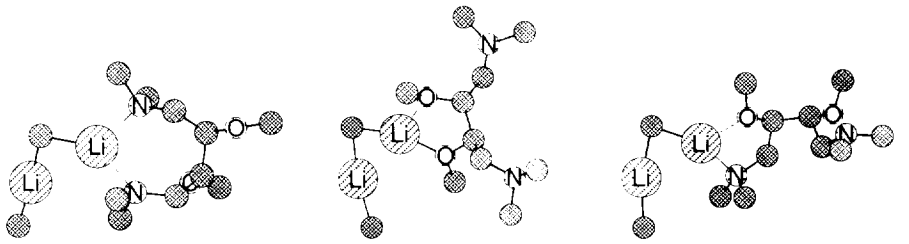


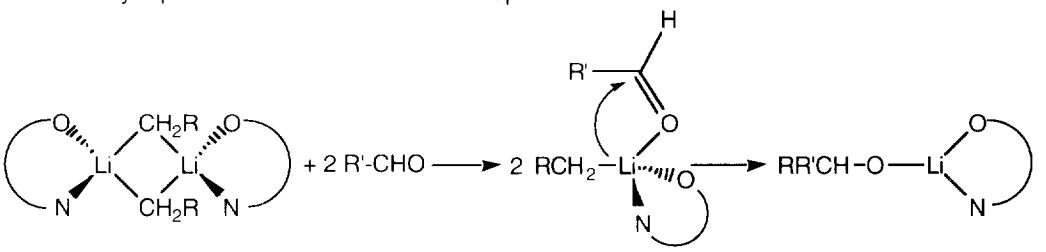
Figure 3. Methyllithium open dimer chelates with DDB. (a) Nitrogen chelate (b) Oxygen chelate (c) Mixed N-O chelate

Table 3. Relative energies (Kcal/mole) of the chelated organolithium open dimers.

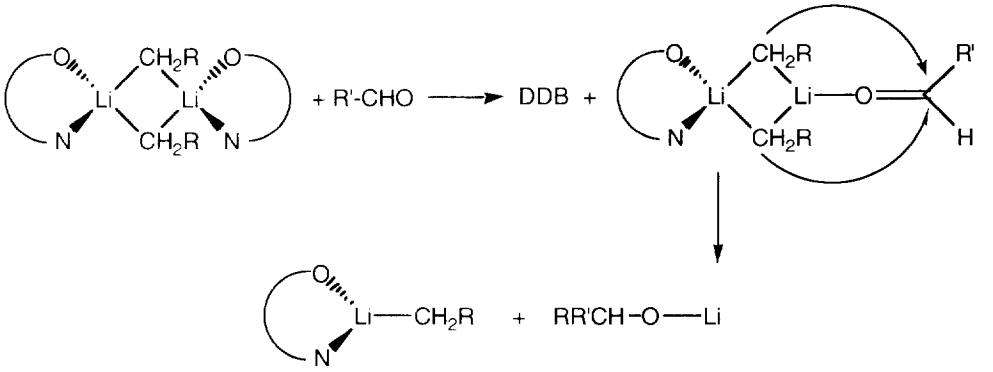
R-Li	N-N	O-O	N-O
MeLi	5.8	2.9	0.0
n-BuLi	7.5	5.4	0.0
t-BuLi	N/A	N/A	N/A
PhLi	2.7	3.3	0.0
Me_2NLi	2.6	2.6	0.0
LiDPEDA	-2.4	-0.5	0.0

From the structures of the monomeric and dimeric species alone, it is not possible to accurately predict or rationalize the amount of asymmetric induction found in alkylation reactions of alkyllithium reagent complexes with DDB. A systematic search for all possible transition states is a formidable problem, even for semiempirical methods. As a first approximation, this can be reduced to a much more computationally tractable problem due to the tendency of organolithiums to form precomplexes with polar molecules prior to reaction. These precomplexes have been implicated in a wide range of organolithium reactions[30-34], and have even been observed spectroscopically.[35] Since the alkylation reaction is highly exothermic, the early transition state will resemble the precomplex. Thus, for the carbonyl alkylation reaction of prochiral aldehydes, the problem is reduced to a study of the pro-R and pro-S precomplexes, as illustrated in the three proposed alkylation mechanisms shown in Scheme 1. The first mechanism involves the deaggregation of the chelated organolithium dimer to a pair of monomers, which are coordinated by both the DDB ligand

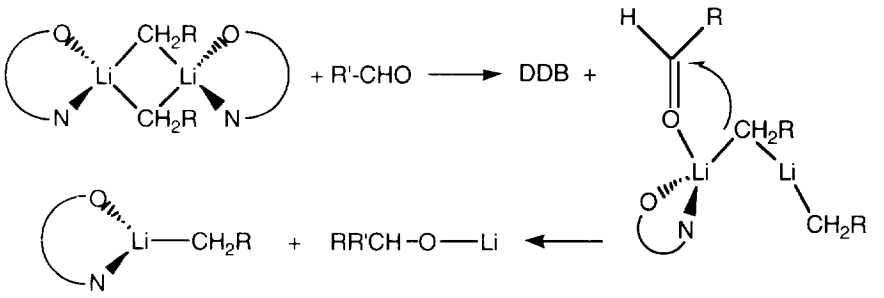
and the carbonyl group of the aldehyde. In the second mechanism one DDB ligand is displaced from the dimer by the aldehyde, followed by addition to the carbonyl group. The chiral ligand may tend to favor addition to either the pro-R or pro-S face of the aldehyde, although due to the distance from the chiral center, this effect is likely to be small. The third mechanism is via the open dimer, analogous to the recently reported mechanism for ketone deprotonation.[18,20]



1. Disassociation of dimer to monomer, followed by addition to carbonyl group

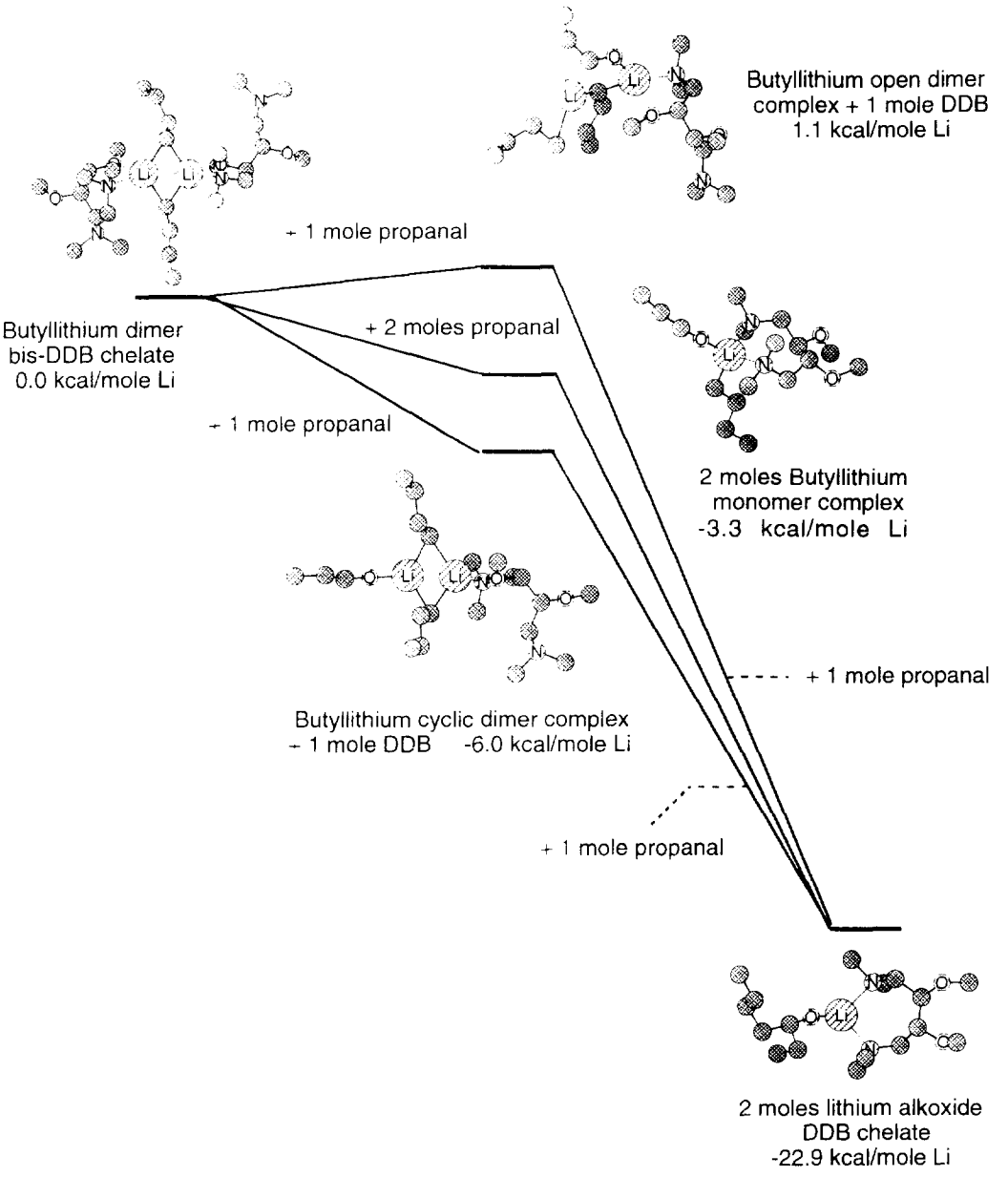


2. Displacement of DDB ligand by aldehyde, followed by addition from pro-R or pro-S face



3. Disassociation to open dimer, followed by addition to carbonyl group

Scheme 1. Possible aldehyde alkylation mechanisms of alkyllithium-DDB complexes.



Scheme 2. Energy diagram of precomplexes for the three possible alkylation mechanisms. For each species, lowest energy conformer or chelating form is shown.

The relative energies of the precomplexes between propanal and the different butyllithium aggregates are shown in Scheme 2. The formation of discrete open dimer complexes is

energetically unfavorable, compared to the other pathways. The lowest energy precomplex is the cyclic dimer, in which one DDB ligand has been displaced by an aldehyde molecule. A similar precomplex has been proposed as an intermediate in the reactions of formaldehyde with a mixed dimer of lithium amide and lithium hydride.[36] Calculations on several conformations of this complex showed little preference for an attack by the butyl group on the carbonyl group from either the pro-R or pro-S face, in contrast to the experimental results of Seebach and coworkers.[1] Although this complex has the lowest energy of the three, it is less favored under the actual reaction conditions, where a large excess of DDB is used, which tends to drive the reaction back toward the bis-DDB chelated dimer. Furthermore, the steric hindrance of the bis-DDB chelated form, shown in the space filling model in Figure 4, leaves little room for coordination of an aldehyde molecule to the lithium, thus requiring the disassociation of one DDB ligand prior to complexation with the aldehyde. This process, although endothermic by only 0.5 kcal/mole, is highly unfavorable in the presence of a large excess of DDB.

A calculated transition state for the propanal alkylation via the butyllithium dimer complex is shown in Figure 5. The calculated activation enthalpy for the dimer reaction is 49.0 kcal/mole, compared to 10-11 kcal/mole for the monomer reaction, which is described below. Due to the large size of the molecules, imperfect transition state parameterization and the lack of correlation effects in the calculations, the activation enthalpy values should not be taken too literally, but rather as a qualitative comparison of the two mechanisms. In contrast to the monomer, the dimer transition state involves the breaking of both carbon-lithium bonds at the same time, while the new carbon-carbon bond is still largely unformed. In addition, the coordination of the aldehyde molecule to the lithium atom requires the negatively charged butyllithium carbon to pass over the partially charged carbonyl oxygen. Thus, even though the activation energy is probably overestimated by the calculation, the dimer mechanism appears to be energetically unfavorable relative to the monomer mechanism.

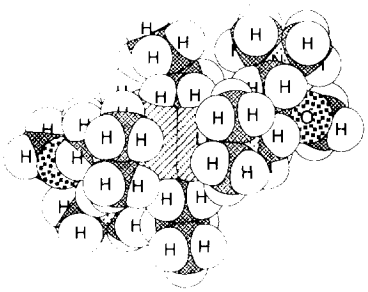


Figure 4. Space filling model of the bis-DDB chelated butyllithium dimer.

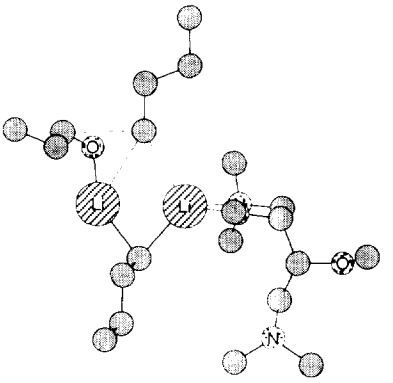


Figure 5. Calculated transition state structure for the propanal alkylation via the butyllithium dimer.

The other plausible mechanism of aldehyde alkylation is via disassociation of the bis-DDB chelated dimer into the monomer, followed by complexation by the aldehyde. This complex may exist in N-N, O-O, and N-O chelated forms, with the N-N chelate being the most stable. Calculations were performed on each of the monomeric complexes in which the pro-R and pro-S faces of the aldehyde faced the butyl group, prior to nucleophilic attack. Each calculation was performed three times, after making small perturbations in the starting geometry, in order to obtain the most stable conformation. The calculated geometries and relative energies are shown in Figure 6. The most stable monomeric precomplex is the nitrogen chelating form, in which the pro-S conformation is favored over the pro-R by about one kcal/mole, which is consistent with the published experimental data for the alkylation of propanal by butyllithium in the presence of DDB.[1] In the oxygen chelating monomer, the pro-R conformer is favored, while the two are of nearly equal energy in the mixed N-O chelate. These forms are higher in energy than the N-N chelate, and would make only a minor contribution to the alkylation in a thermodynamically controlled reaction step. It should be noted that while the N-N chelate has the butyl group positioned in a favorable orientation for addition to the carbonyl group, the orientation is much less favorable in the other two chelates, as shown in Figure 6.

Transition states were calculated for the alkylation of propanal via the most stable pro-R and pro-S monomeric precomplexes of Figure 6. The calculated transition state geometries are shown in Figure 7. The pro-S activation enthalpy was calculated to be higher than the pro-R by 0.6 kcal/mole. This value is within the uncertainty of the calculated energies, and so the activation energies can be considered to be nearly equal. The calculated activation energies of 10-11 kcal/mole are substantially lower than that calculated for the alkylation via the dimer precomplex. Thus, the experimentally determined enantiomeric excess of 11.5% appears to result from a balance between the thermodynamic stability of the precomplexes and the kinetic activation barriers of alkylation. Although a large portion of the reaction will take place via the most stable monomeric precomplex, a substantial portion of the butyllithium will react via the less stable precomplexes, resulting in the

relatively low stereoselectivity observed. It is interesting to note that neither the cyclic nor open dimers are stable minima in the case of t-butyllithium, and the monomeric chelate mechanism takes place almost exclusively in this case.

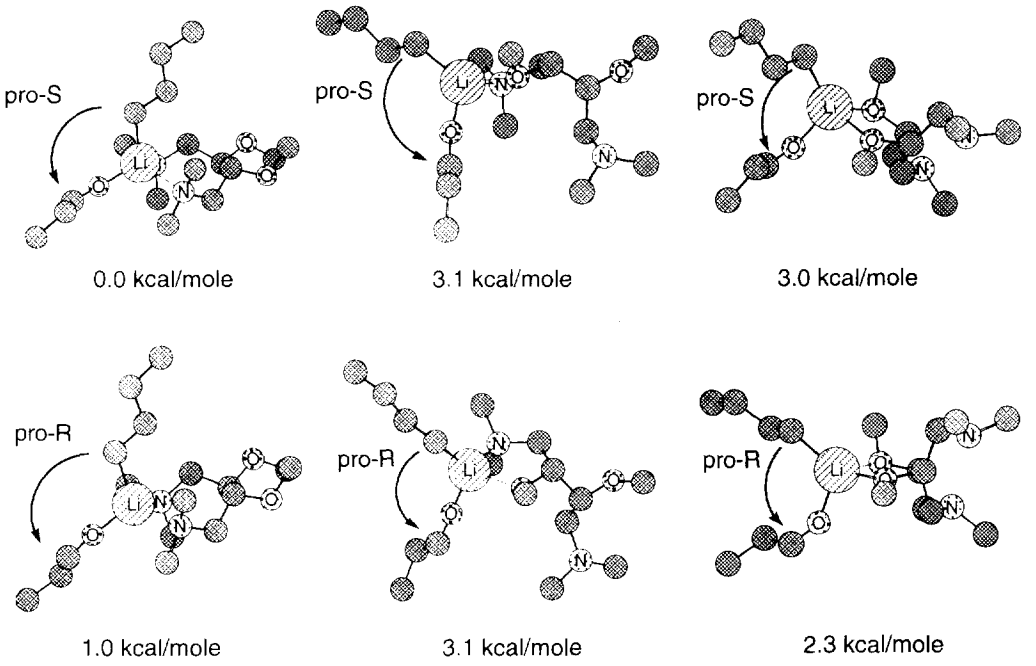


Figure 6. Relative energies of butyllithium-DDB monomer complexes with propanal.

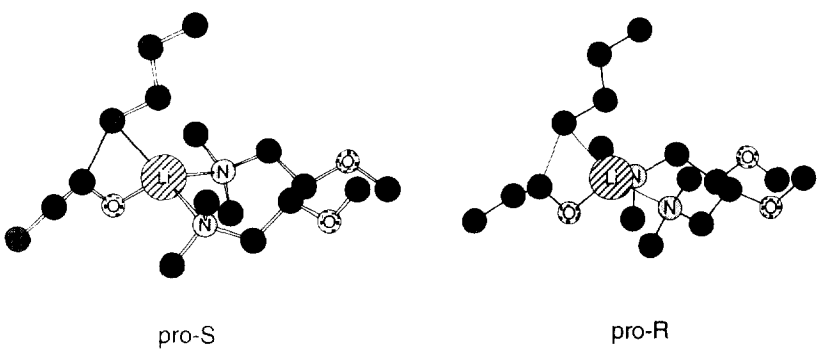


Figure 7. Calculated pro-S and pro-R transition state geometries for butyllithium alkylation of propanal via the monomeric precomplex.

Conclusions

DDB forms chiral chelating complexes with many simple organolithium compounds. Both the monomeric and cyclic dimeric forms are stable local minima on the potential energy surface for sterically unhindered alkyllithiums, while the open dimer is a higher energy minimum which is stable only in a few conformations, and probably does not contribute significantly to aldehyde alkylation reactions. DDB chelates of very sterically hindered alkyllithiums, such as t-butyllithium, exist only in the monomeric form. Each of the monomers, cyclic dimers, and open dimers may exist as either the N-N, N-O, or O-O chelated form, and the cyclic dimer may exist as two different diastereomers of the N-O chelate. Three possible mechanisms of aldehyde alkylation by butyllithium were examined. The formation of discrete open dimer complexes was calculated to be an energetically unfavorable process. The precomplex between the cyclic dimer and the aldehyde is disfavored when a large excess of DDB is used, as the complex formation generates a mole of disassociated DDB. This mechanism was calculated to have a large activation barrier, compared to the monomer mechanism. It is unlikely that the dimeric mechanism would generate much enantiomeric excess, as the chiral centers are far removed from the reaction center. Alkylation via the monomeric precomplex shows a substantially lower activation barrier than from the dimeric precomplex. We therefore conclude that primary aldehyde alkylation mechanism is via the monomer, with a minor contribution from the cyclic dimer.

Acknowledgments

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