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Computational Study of the Enantioselective Deprotonation of a Cyclopropanecarboxamide with an Alkyllithium in the Presence of Sparteine

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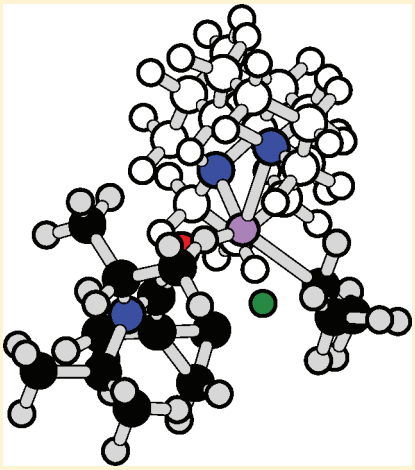
Supporting Information

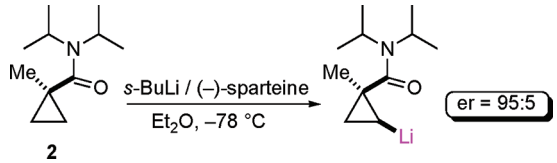
ABSTRACT: The enantioselective deprotonation of *N*,*N*-diisopropy-1-methylcyclopropanecarboxamide (**2**) with *i*-PrLi-(−)-sparteine has been studied at theoretical levels up through B3LYP/6-311+G*. Thirty-six conformationally flexible intermediate complexes involving *i*-PrLi−(−)-sparteine and **2** were located via geometry optimizations The lowest energy complex would lead to abstraction of the *pro-S* hydrogen from **2**, and several higher energy complexes would lead to loss of the *pro-R* hydrogen. The lowest energy complex was found to have the lowest activation energy leading to loss of the *pro-S* hydrogen of **2** as observed experimentally. The results demonstrate that the conformations of the *N*,*N*-diisopropyl groups in the amide moiety of **2** have a large effect on the enantioselectivity of the lithiation



INTRODUCTION

We have been interested for some time in the asymmetric deprotonation of a prochiral carbon by an alkyllithium in the presence of a chiral diamine ligand.[1,2] The prototypical example such a process is the lithiation of *N*-Boc-pyrrolidine (**1**) by *sec*-butyllithium (*s*-BuLi) or isopropyllithium (*i*-PrLi) in the presence of (−)-sparteine pioneered by Beak and co-workers.[3] The reaction, which involves initial formation of a three-component complex of the alkyllithium and (−)-sparteine with **1** followed by rate-determining lithiation, results in highly enantioselective (enantiomer ratio (er) = 97:3) removal of the *pro-S* hydrogen (H_S).[4] A computational investigation at the B3P86/6-31G* level of this asymmetric deprotonation,[2] which gave results entirely consistent with the experimental observations, indicated that the enantioselective lithiation is largely a consequence of sizable differences in steric interactions present in the two lowest energy diastereoisomeric transition states that lead to transfer of the *pro-R* and *pro-S* hydrogens. The most stable complex of alkyllithium/(−)-sparteine/**1**, which leads to transfer of the *pro-S* hydrogen in **1**, was found to have a transition state some 3.2 kcal/mol lower in energy than that of the less stable complex leading to loss of the *pro-R* hydrogen.

Given our interest in asymmetric deprotonation, we were intrigued by a 2008 report describing the enantioselective lithiation of *N*,*N*-diisopropy-1-methylcyclopropanecarboxamide (**2**) using *s*-BuLi−(−)-sparteine in diethyl ether solvent.[5] As illustrated below, the reaction proceeds with a high degree of enantioselectivity (er = 95:5) for removal of the *pro-S* hydrogen of **2** that is cis with respect to the carboxamide.



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In light of the success of ab initio molecular orbital theory to provide detailed insight into the factors responsible for the enantioselectivity of asymmetric deprotonations of amides by alkyllithium−chiral diamine reagents,[1,4] it seemed worthwhile to explore the enantioselective lithiation of **2** using computational methods.

RESULTS AND DISCUSSION

At the outset of this study it was apparent that amide substrates derived from amines bearing enantiotopic hydrogens, such as Boc-pyrrolidine (**1**) and related molecules, and carboxylic acid-derived amides, such as **2**, present rather different computa-

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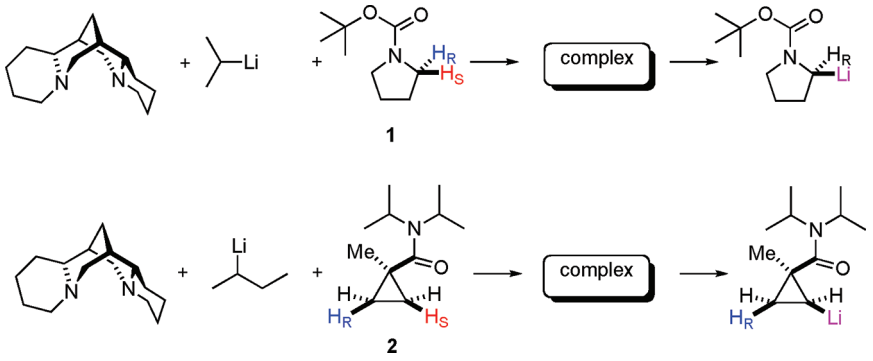
Scheme 1



tional challenges. A comparison of the two substrates, depicted in Scheme 1, exemplifies the major differences. The enantiotopic hydrogens in **1** are related by the mirror plane of the molecule while those in **2** are mirrored in a plane perpendicular to the three-membered ring. A more subtle, computationally intricate difficulty resides in the two isopropyl groups present in **2**. Clearly, many more energetically accessible conformational arrangements are potentially available in a prelithiation complex generated from **2** vis-à-vis **1** and the energy of each complex must be evaluated in any analysis of the reaction course. Consequently, as described below, the enantioselective lithiation of **2** is a much more complex phenomenon than is the seemingly analogous reaction of **1**.

It is also important to note that, in the complex derived from the pyrrolidine substrate (**1**), rotation about the amide C−N bond presents an enantiotopic hydrogen to the *i*-PrLi, and this rotation is hindered by the double bond character of the amide bond. In contrast to this situation, the complex derived from the cyclopropanecarboxamide substrate (**2**) requires rotation about the C(1)-to-carbonyl bond, which has a much lower barrier than rotation about the amide bond in **1** to access the enantiotopic hydrogen.

In view of the potential complexity of the cyclopropanecarboxamide system, we have tried to implement a systematic study of the asymmetric lithiation. Thus, although *s*-BuLi was used in the reported lithiation of **2**, the process was modeled using *i*-PrLi in order to simplify the computational investigation. At the inception of the work, it was necessary to find initial structures for the putative prelithiation complexes that might be further developed.

Initially, three complexes (**A**−**C**) were located that had the reactant (**2**) in "front" of the complexed sparteine as shown in Figure 1. Each complex had a distance between the isopropyl anion and a hydrogen to be extracted of ∼2.6 Å so that it would be appropriate for going to the transition state. In each case the two isopropyl groups attached to the amide nitrogen in **2** were initially given the arrangement R0 (Figure 2) in which the C−N−C−H torsion angles to the unique hydrogens of the isopropyl groups are small.

Geometry optimizations were carried out at the B3LYP/6-31G* level, and the corresponding vibrational frequencies were obtained. The conformations thus obtained are shown in Figure 3. If these were the only conformers to be considered, one would conclude that calculations suggest that H_R would be abstracted. This, of course, is the opposite of the experimental result.[5]

However, as noted above, it is possible to rotate about the C(1)−C(=O) bond of **2** to bring the enantiotopic hydrogen

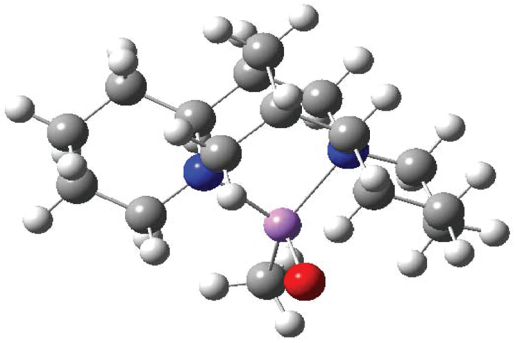


Figure 1. Initial (−)-sparteine complex: methyl represents the alkyl group of the organolithium and the red ball represents the oxygen of the reactant (**2**) that is coordinated with the lithium. This arrangement is defined as having the reactant in "front" of the sparteine.

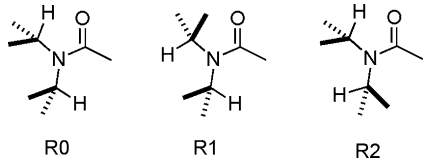


Figure 2. Conformations of the *N*-isopropyl groups.

close to the isopropyl anion. This was done for each of the **A**, **B**, and **C** conformations, and the conformers thus obtained were first optimized at the HF/3-21G level with the distance between the H and the isopropyl anion fixed at the distance originally found. Subsequent relaxed optimizations (HF/3-21G followed by B3LYP/6-31G*) led to new conformers, and their names correspond to that of the original conformation followed by an m (for modified).

Yet another way in which to change conformations **A**−**C** is to reverse the positions of the amide and the isopropyl group of *i*-PrLi placing the former in "back" of the sparteine ligand (Figure 1) and the latter in front. These new geometries were then optimized. Their names are related to their origins by adding a Z prefix. Thus, the original three complexes were doubled by rotating about the C(1)−C=O bond and doubled again by switching the reactant from the "front" of sparteine to the "back". In total, 12 potential prelithiation complexes are thus generated. Their geometries were optimized as described above.

There is one additional way to change the conformations discussed above: the *N*-isopropyl groups of **2** may be rotated about the C−N−C−H bond to give the arrangements termed R1 and R2 in Figure 2. These terms are appended to the

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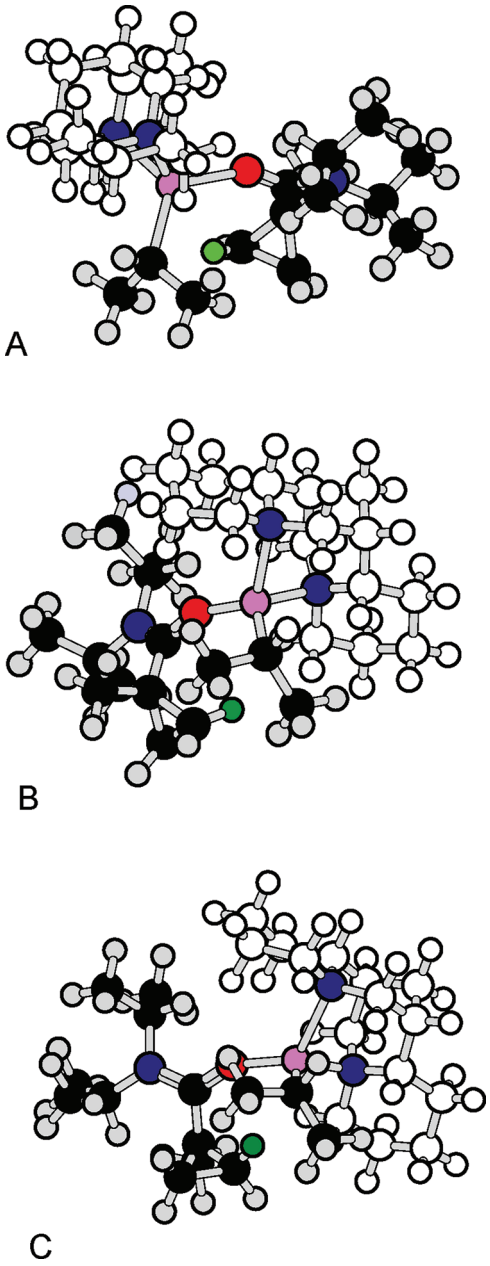

Figure 3. Conformations **A**–**C** for the *i*-PrLi/(−)-sparteine/**2** complexes. The hydrogen that is closest to the isopropyl anion is shown in green and is H_R for **A** and **B**, and H_S for **C**. The sparteine component is shown as open circles.

original names: thus, the conformation termed "ZAR2m" is based on conformer **A**; it has **2** in "back" (Z), has the R2 arrangement of the *N*-isopropyl groups, and has been rotated about the C(1)–C(=O) bond to present the opposite hydrogen from ZAR2 (i.e., m). It should be noted that rotation of both *N*-isopropyl groups in **2** led to complexes with higher energies.

As a result of this extended analysis, each of the 12 complexes derived from the original **A**, **B**, and **C** conformations led to two more derived by rotation of one or the other of the two *N*-isopropyl groups giving a total of 36 starting conformations. Geometry optimization at the HF/3-21G level found that all 36 geometries gave stationary points having no imaginary frequencies. In a few cases, the final structures starting from a pair of the 36 conformers were found to result in the same final structure. Each of the unique complexes were then reoptimized at the B3LYP/6-31G* level, and in many cases, single-point calculations were carried out at the B3LYP/6-311+G* level using the B3LYP/6-31G* geometries. All of the results resulting from this analysis are summarized in the Supporting Information; a subset of the results for complexes having relative energies less than 8 kcal/mol are presented in Table 1.

Table 1 summarizes the following data: the torsion angle (τ1) between the O=C and C–H which is transferred in to the *i*-PrLi, the C–N–C–H torsion angles (τ2 and τ3) for the *N*-isopropyl groups of **2**, the distance between the hydrogen closest to the isopropyl anion, and that the hydrogen is H_S or H_R. The relative enthalpy values (ΔH, 298K) are given for both B3LYP calculations (6-31G* and 6-311+G*); they are essentially the same. The effect of zero-point energies and corrections for the difference in energy between 0 and 298 K had negligible effect on the relative energies. The ΔG values were generally about the same as ΔH, but are less reliable because of the large number of very low calculated vibrational frequencies (*viz.*, 20–50 cm^{-1}) in the complexes. The column marked $\Delta H(1)$ gives the B3LYP/6-31G* enthalpy change at 298K with respect to the lowest energy complex and $\Delta H(2)$ gives the corresponding larger basis set (6-311+G*) relative energies. In the latter case, the B3LYP/6-31G* zero-point and thermal corrections were used. Full data are available in the Supporting Information.

Cursory examination of the results summarized in Table 1 reveals that there are a number of relatively low energy complexes that involve rotation of the *N*-isopropyl groups in **2**. The lowest energy complexes, termed ZBR1m and ZCR2 in Table 1, became identical after geometry optimization. This complex has the H_S hydrogen (the one observed to be removed in the reaction)[5] closest to the isopropyl anion. Clearly however, there is no requirement that the lowest energy ground-state complex would lead to the lowest energy transition state for the lithiation.

Therefore, it is necessary to determine which complex would lead to a transition state having the lowest activation energy. For each of the complexes having a relative energy less than 8 kcal/mol with respect to the lowest energy form, an approximate transition state was developed in which the hydrogen closest to the isopropyl anion was moved toward the latter by ∼0.5 Å, and in each case, these structures led to an appropriate imaginary frequency. Geometry optimizations to a transition state were carried out for these structures, first using HF/3-21G followed by B3LYP/6-31G*, and in each case only one imaginary frequency was found. Finally, single point B3LYP/6-311+G* calculations made use of the B3LYP/6-31G* geometries. The results of these calculations are summarized in Table 2 for transition states having a relative energy less than 6 kcal/mol; full results may be found in the Supporting Information.

The lowest energy transition state (Table 2) is derived from complex ZCR2, the lowest energy ground-state complex that was found (cf. Table 1), and this geometry leads to removal of the H_S hydrogen in **2** which is in accord with the experimental results. There are four transition states with an energy ∼1.5 kcal/mol higher in energy than that computed for ZCR2 and, in these cases, H_R would be abstracted. The lowest energy transition states identified for the removal of the H_R and H_S hydrogens in **2** are shown in Figure 4. Given the complexity of the structures involved in this analysis, the 1.5 kcal/mol difference in activation energy favoring removal of the *pro-S*

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Table 1. Calculated Relative Energies of the Ground-State Complexes (kcal/mol)

complex	t1	τ2	t3	hydrogen[a]	r(C···H)	ΔH(1)[b]	ΔH(2)[c]
A	−31.8	−25.1	−5.8	H_R	2.63	2.8	2.4
ZA	−35.3	−28.4	−4.2	H_R	2.75	2.7	2.4
AR2	−33.0	−176.0	0.6	H_R	2.65	0.9	0.8
ZAR2	−39.7	179.1	0.5	H_R	2.73	0.7	0.8
AR2m	13.5	178.7	−9.3	H_S	2.70	4.2	4.1
ZAR2m	44.8	−175.8	3.6	H_S	5.62	1.8	1.9
Bm	34.5	6.5	7.9	H_S	2.65	3.1	2.9
ZBm	34.4	25.5	5.4	H_S	2.65	1.8	1.7
BR1	−37.0	−79.2	1.0	H_R	3.63	2.8	1.9
ZBR1	−26.5	−177.0	3.9	H_R	3.43	2.4	2.8
BR1m	39.5	−178.5	0.0	H_S	4.92	2.7	1.8
ZBR1m	35.0	−179.5	−3.1	H_S	2.54	0.0	0.0
BR2	−42.2	−18.9	−13.2	H_R	3.60	5.2	
BR2m	42.9	−25.2	−8.0	H_S	2.73	1.5	1.5
C	36.0	−22.5	−10.8	H_S	2.57	2.9	2.8
Cm	−42.3	−18.8	−13.2	H_R	3.50	5.1	4.5
ZC	42.4	−25.6	−7.8	H_S	2.71	1.5	1.5
CR2	28.9	179.0	−4.5	H_S	2.79	2.2	2.3
CR2m	−31.0	−179.4	2.0	H_R	3.47	2.8	1.9
ZCR2m	−32.9	−179.7	1.8	H_R	4.25	2.9	2.8
ZCR2	35.0	−179.5	−3.1	H_S	2.54	0.0	0.0

[a]Hydrogen in **2** (Scheme 1) closest to the *i*-PrLi anion in the complex. [b]B3LYP/6-31G* enthalpy change at 298 K, in kcal/mol, with respect to the lowest energy complex. [c]B3LYP/6-311+G* enthalpy change at 298 K, in kcal/mol, with respect to the lowest energy complex.

Table 2. Calculated Transition States Derived from the Ground-State Complexes and Relative Energies (kcal/mol) with Respect to the Lowest Energy Form

complex	τ1	τ2	τ3	hydrogen[a]	ΔH(1)[b]	ΔH(2)[c]	cm^{-1}[d]
A	−33.9	−24.9	−5.4	H_R	3.6	3.8	1407i
ZA	−32.5	−4.0	−28.8	H_R	3.9	3.6	1399i
Am	36.0	−24.9	−8.1	H_S	4.2	4.0	1406i
AR2	−35.4	−174.4	−0.3	H_R	1.5	1.5	1413i
ZAR2	−33.7	−179.3	−0.1	H_R	1.7	1.4	1406i
B	−37.1	24.0	9.1	H_R	3.8	3.5	1405i
Bm	23.9	25.1	7.3	H_S	4.5	4.1	1402i
ZBm	36.7	27.8	4.7	H_S	2.3	2.2	1421i
BR1	−35.3	−174.4	−0.3	H_R	1.5	1.5	1431i
BR1m	29.7	177.5	−4.4	H_S	2.5	2.4	1407i
BR2m	42.5	−28.1	−5.1	H_S	2.5	2.3	1423i
C	36.1	−24.9	−8.1	H_S	4.2	4.0	1406i
Cm	−33.9	−24.9	−5.4	H_R	3.0	3.3	1408i
ZC	42.5	−28.1	−5.1	H_S	2.5	2.3	1423i
CR2	29.7	177.5	−4.4	H_S	2.5	2.4	1412i
CR2m	−35.4	−174.4	−0.3	H_R	1.5	1.5	1412i
ZCR2	35.0	179.5	−2.9	H_S	0.0	0.0	1432i

ZC = BR2m, CR2 = BR1m, CR2m =, AR2 = BR1

[a]Hydrogen in **2** (Scheme 1) closest to the *i*-PrLi anion in the complex. [b]B3LYP/6-31G* enthalpy change at 298K, in kcal/mol, with respect to the lowest energy complex. [c]B3LYP/6-311+G* enthalpy change at 298K, in kcal/mol, with respect to the lowest energy complex. [d]Transition state imaginary frequencies.

hydrogen in **2** is in very reasonable agreement with the 95:5 er reported for this lithiation.[5]

CONCLUSIONS

The rather convoluted computational analysis of the asymmetric lithiation of **2** presented above may seem a rather arcane disambiguation. However, there are two features of the investigation that are of general interest. It is significant that theoretical calculations can reproduce small differences (∼1.5 kcal/mol) in activation enthalpies that replicate experimental observations for these large (88 atoms) and conformationally flexible systems. However, of more importance is the unexpected finding that the conformations of the *N*,*N*-diisopropyl groups in the amide moiety of **2** can have a large effect on the enantioselectivity of the lithiation. In most systems studied to date, protecting groups are chosen to minimize conformational complexity. The present observations suggest that in some cases where the enantiomeric selectivity is low, introduction of less symmetrical protecting groups may lead to increased, or even reversed, enantioselectivity.

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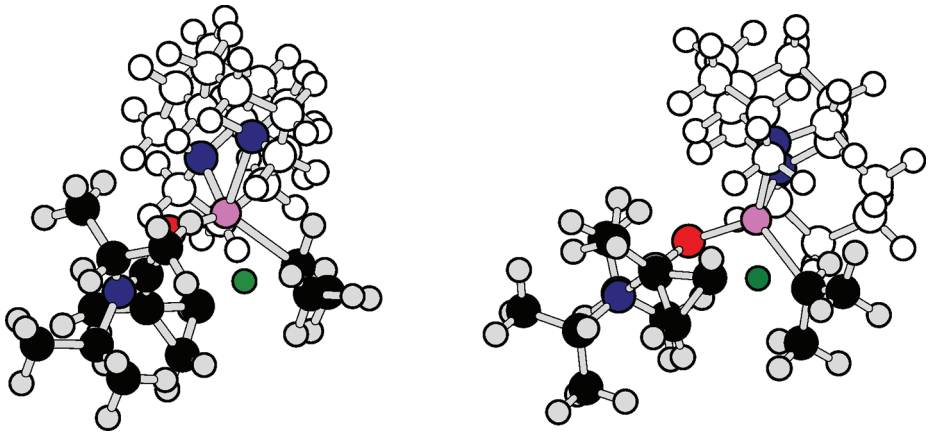

Figure 4. Low energy transition states for abstraction of H_S (left) and H_R (right). The sparteine component is shown as open circles and the hydrogen being transferred is shown in green.

EXPERIMENTAL SECTION

All of the calculations were carried out using Gaussian-09.[6]

ASSOCIATED CONTENT

Supporting Information

Summary of the calculations including computed energies, imaginary frequencies for the transition states, and computed atomic coordinates for conformers **A**–**C** and for the lowest energy transition states leading to abstraction of H_R and H_S. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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