Chiral Diamines 4: A Computational Study of the Enantioselective Deprotonation of Boc-pyrrolidine with an Alkyllithium in the Presence of a Chiral Diamine

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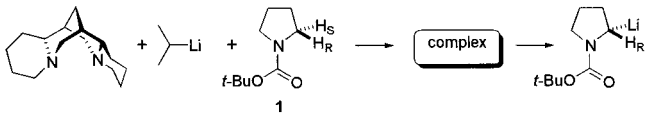
Abstract: The enantioselective deprotonation of *N*-Boc-pyrrolidine (**1**) with i-PrLi−(−)-sparteine has been studied at theoretical levels up through B3P86/6-31G*. Four low-energy intermediate complexes involving i-PrLi−(−)-sparteine and **1** were located via geometry optimizations; two of these complexes would lead to abstraction of the *pro*-S hydrogen from **1**, and the other two complexes would lead to loss of the *pro*-R hydrogen. The lowest-energy intermediate complex was found to lead to loss of the *pro*-S hydrogen as observed experimentally. Transition states for the deprotonations were located using the synchronous transit-guided quasi-Newton method. The calculated activation enthalpy for transfer of the *pro*-S hydrogen within the lowest-energy intermediate complex, 10.8 kcal/mol, is reasonable for a reaction that occurs at a relatively low temperature, and the calculated kinetic hydrogen isotope effect is in agreement with experimental data. The lower enantioselectivity observed experimentally for deprotonation of **1** using t-BuLi−(−)-sparteine is attributed to a transition-state effect due to increased steric interaction engendered by the bulky t-BuLi. Replacement of the *tert*-butoxycarbonyl group in **1** by a methoxycarbonyl is predicted to result in a slower deprotonation with somewhat decreased enantioselectivity. Asymmetric deprotonation of **1** using i-PrLi in combination with the C_2-symmetric diamine, (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane, was calculated to be much less selective than is the deprotonation mediated by (−)-sparteine as observed experimentally. The relative energies of the intermediate complexes were fairly well-reproduced by ONIUM calculations in which the sparteine ligand less its nitrogen atoms was treated by molecular mechanics and the remainder of the complex was treated by quantum mechanics.

Asymmetric deprotonation of a prochiral carbon by a chiral base to give a configurationally stable organolithium offers a conceptually simple route to enantioenriched products. Seminal investigations over the past decade by the groups of Hoppe[1] and Beak[2,3] have demonstrated that the 1:1 complex of a sec-alkyllithium and (−)-sparteine is remarkably efficient in effecting such enantioselective deprotonations particularly in the case of substrates, such as carbamates, that give a dipole-stabilized organolithium.[4] A prototypical and particularly well-studied example of such a process is the highly enantioselective deprotonation of *N*-(*tert*-butoxycarbonyl)pyrrolidine (Boc-pyrrolidine, **1**) by isopropyllithium−(−)-sparteine which, as illustrated below, proceeds with high selectivity (ee > 95%) for removal of the *pro*-S hydrogen.[4] Kinetic studies of this reaction by Gallagher and Beak have demonstrated that it involves formation of a thermodynamically favorable three-component complex of i-PrLi, sparteine, and **1** prior to rate-determining lithiation of the complexed Boc-pyrrolidine.[5] To date, the structure of the intermediate complex, which presumably plays a pivotal role in determining the stereochemistry of the deprotonation step, has not been determined.[6]



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In light of the obvious synthetic utility of asymmetric deprotonation methodology for the preparation of chiral targets, it seemed worthwhile to investigate the ability of ab initio molecular orbital theory to describe the enantioselective lithiation of **1**. Herein we report the results of a study demonstrating that modern computational methods can provide detailed insight into the factors responsible for the high enantioselectivity in

† Yale University.

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(1) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 1422. (b) Schwerdtfeger, J.; Hoppe, D. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 1505. (c) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1764. (d) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem*. **1999**, *64*, 8616. (e) Heinl, T.; Retzow, S.; Hoppe, D.; Fraenkel, G.; Chow, A. *Chem. Eur. J.* **1999**, *5*, 3464 and references therein.

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(4) For reviews, see: (a) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem*. **1994**, *66*, 1479. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res*. **1996**, *29*, 552. (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2283.

(5) Gallagher, D. J.; Beak, P. *J. Org. Chem*. **1995**, *60*, 7092.

(6) Beak has elegantly demonstrated[2b] that *i*-PrLi/(−)-sparteine exists in ethereal solution as an unsymmetrical, ether solvated dimer [(*i*-PrLi)$_2$·(−)-sparteine], but this structure need not be maintained in the pre-lithiation complex leading to deprotonation of **1**.

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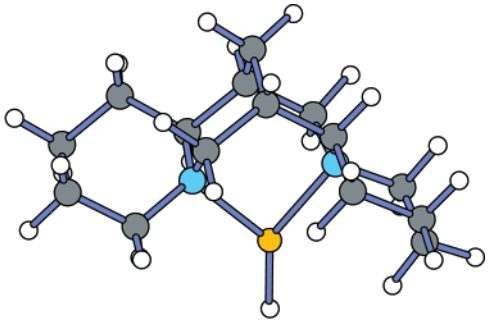

Figure 1. Structure of the lithium hydride−(−)-sparteine complex; nitrogen atoms are blue, lithium is orange.

the (−)-sparteine mediated deprotonation of **1**.[7] A related computational study of the asymmetric deprotonation of alkyl carbamates by an alkyllithium in the presence of the C_2-symmetric chiral diamine ligand, (*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane, has been reported by Wurthwein, Behrens, and Hoppe.[8]

Results and Discussion

We recently reported the results of a computational study of the conformational isomers of (−)-sparteine and the transition states for their interconversion.[9] There are four low-energy conformers of (−)-sparteine;[9,10] the lowest-energy conformation cannot form a bidentate complex, but the next higher-energy form is able to do so, and the structure of its lithium hydride complex (**2**) is shown in Figure 1.[9] This LiH−(−)-sparteine complex (**2**) served as the starting point for investigation of the enantioselective deprotonation of **1** by *i*-PrLi−(−)-sparteine.

The complex of *i*-PrLi/(−)-sparteine/Boc-pyrrolidine that is involved in the deprotonation presumably has an isopropyl group in place of the hydrogen in the structure depicted in Figure 1. Additionally, it was assumed that the carbonyl group of **1** was the fourth ligand forming a tetrahedral-like arrangement about the lithium. With regard to the view shown in Figure 1, the isopropyl group in the complex may be placed either in front of or behind the plane with **1** adopting the other position. Further, the pyrrolidine ring of **1** may be either on the right or the left of the lithium with the *tert*-butoxy group occupying the other position. Thus, there are four rudimentary structures (**A**−**D**) that must be considered.

Although complexes **A**−**D** are quite large, they have some significant advantages with regard to conformational issues: (a) the largest ligand, (−)-sparteine, is fairly rigid;[9] (b) the isopropyl ligand has two identical appendages (the methyl groups), and these will surely maintain a staggered conformation; (c) the amide group in **1**, O═C−N−CH_2, will have torsional angles close to 0° or 180°; (d) the *t*-Boc group in **1** will surely adopt the Z-conformation as found with most esters;[11] (e) the conformational behavior of pyrrolidine is similar to that of cyclopentane, and there should be a very low barrier to conformational change.

The four primary structures described above (**A**−**D**) were then examined in more detail. In light of the large size of the complexes ($C_{27}H_{50}NO_2Li$, 83 atoms), initial geometry optimizations were carried out at the STO-3G level and this was followed by HF/3-21G optimizations. Although this theoretical level sometimes gives unsatisfactory relative energies, it is known that it usually gives quite good geometries.[12] The lowest-energy complex identified in this iteration (arbitrarily termed **C**) also had the shortest distance (3.10 Å) between the isopropyl carbon and an α-proton on the pyrrolidine ring. Complexes **A** and **D** had the isopropyl group positioned too far from a pyrrolidine hydrogen to allow proton transfer, and complex **B** was found to lie significantly higher in energy than the other three species. The energies and proton-transfer distances for these complexes (**A**−**D**) are summarized in Table 1.

Table 1. Initial *i*-PrLi/(−)-Sparteine/Boc-pyrrolidine Complexes

	complex			
	A	**B**	**C**	**D**
i-Pr group	back	front	front	back
pyrrolidine	left	right	left	right
C···H dist[a]	5.89	4.12	3.10	5.89
HF/3-21G	−1364.56023	−1364.55482	−1364.56160	−1364.56109
E_{rel} (kcal/mol)	0.9	4.3	0.0	0.3

[a] Distance (Å) between *i*-PrLi carbon and nearest C(2)−H of Boc-pyrrolidine (**1**).

Table 2. Calculated Energies of Modified *i*-PrLi/(−)-Sparteine/Boc-pyrrolidine Complexes

	complex			
	A′(5)	**C (3)**	**C′ (4)**	**D′ (6)**
hydrogen removed	*pro*-R	*pro*-R	*pro*-S	*pro*-S
$\Delta\Delta H$ (HF/3-21G)[a]	3.3	3.9	0.0	2.9
$\Delta\Delta H$ (B3P86/6-31G*)[a]	2.7	3.1	0.0	3.1
$\Delta\Delta G$ (B3P86/6-31G*)[b]	2.4	2.5	0.0	2.9

[a] Difference in calculated total energies, kcal/mol. [b] Corrected for both the differences in ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K (the temperature at which the deprotonations were conducted).

Additional starting structures were obtained by rotating the pyrrolidine unit about the Li−O bond in both **A** and **D** so as to bring the reacting α-hydrogens closer to the isopropyl group, and this was followed by reoptimization to give two new complexes, **A′** and **D′**. In complex **C**, the isopropyl group was located proximate to the *pro*-R hydrogen of the pyrrolidine ring. Since, as noted above, it is the *pro*-S hydrogen of **1** that is preferentially removed,[4] a rotation was performed to bring the *pro*-S hydrogen of **1** into this position. This, in turn, resulted in a severe steric interaction between a hydrogen on the sparteine ligand and the *tert*-butoxy group of **1**, but the close contact could be relieved by rotating the latter. Geometry optimization led to complex **C′**. The energies of these modified complexes (**A′**−**D′**) are given in Table 2 along with an indication of which pyrrolidine α-hydrogen was nearest to the isopropyl group. Additional calculations of this type were performed, but no lower-energy structures were found. Henceforth, for the sake of clarity, the four lowest-energy structures will be designated **3**−**6** as indicated in Table 2 (viz.; **A′** = **5**, **C** = **3**, **C′** = **4**, **D′** = **6**). The structures of these complexes are shown in Figure 2. It should be noted that complexes **3** and **5** would be expected to result in preferential removal of the *pro*-R hydrogen of **1**, while complexes **4** and **6** would presumably lead to removal of the *pro*-S hydrogen.

It may be noted that in all of these complexes, the central isopropyl hydrogen is directed toward the sparteine, and the

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(11) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 618−619 and references therein

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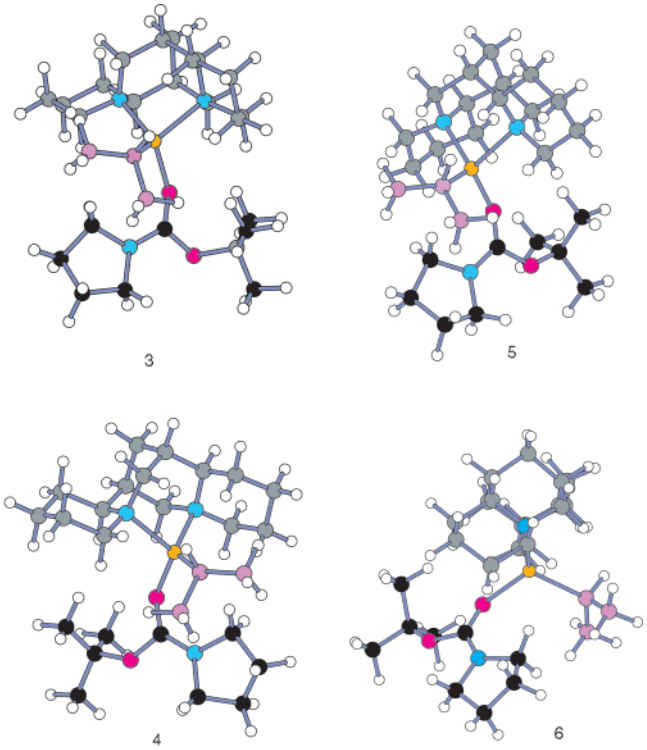

Figure 2. Structures of the *i*-PrLi/(−)-sparteine/Boc-pyrrolidine intermediate complexes (**3**−**6**); the oxygen atoms are red, the sparteine carbons are gray, the Boc-pyrrolidine carbons are black, the isopropyl carbon atoms are purple, other colors as in Figure 1.

methyls are near the pyrrolidine. Structures in which the isopropyl group was rotated to bring the methyl groups close to the sparteine were found to have relatively high energies, and the methyl groups rotated away from the sparteine during geometry optimization. This results from the short nonbonded distances between the methyl hydrogens and sparteine when these groups are brought close to each other. This will also be seen in the reaction using *t*-BuLi instead of *i*-PrLi which is discussed below.

Transition states for proton transfer within complexes **3**, **4**, **5,** and **6** were located at the HF/3-21G level using the synchronous transit-guided quasi-Newton method of Schlegel, et al.[13] To obtain more satisfactory relative energies, the B3P86/6-31G* energies for **3, 4**, **5**, and **6** were calculated via geometry optimizations starting with the HF/3-21G structures; their transition states, **3-TS**, **4-TS**, **5-TS**, and **6-TS**, were calculated in the same fashion using the HF/3-21G calculated force constants in the initial step. In each case there was just one imaginary frequency corresponding to removal of an α-hydrogen from **1**. The calculated frequencies obtained at the HF/3-21G level were scaled by 0.917; zero-point energies (ZPE) and the corrections to the enthalpy and free energy on going from 0 K (corresponding to the calculations) to 195 K (−78 °C, the temperature at which the deprotonations are typically conducted) were then obtained using these frequencies. The results of these calculations are summarized in Table 3; a summary of the calculated total energies and the corrections to 195 K may be found in Table S1 of the Supporting Information. It will be seen in the Tables that the relative enthalpies and free energies generally differ little, indicating that the entropy changes are small. It should be noted that the enthalpy corrections to 195 K are probably more reliable than the corresponding free-energy corrections.[14]

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Table 3. Calculated Transition-State Energies for Proton Transfer within the *i*-PrLi/(−)-Sparteine/Boc-pyrrolidine Complexes

	complex			
	5-TS	**3-TS**	**4-TS**	**6-TS**
hydrogen removed	*pro*-R	*pro*-R	*pro*-S	*pro*-S
$\Delta\Delta H$ (HF/3-21G)[a]	4.3	6.6	0.0	3.6
$\Delta\Delta H$ (B3P86/6-31G*)[b]	4.5	4.5	0.0	4.2
$\Delta\Delta G$ (B3P86/6-31G*)[b]	3.2	3.6	0.0	4.1
$\Delta H^{\ddagger}$ (B3P86/6-31G*)[b]	12.6	12.2	10.9	12.0
$\Delta G^{\ddagger}$ (B3P86/6-31G*)[b]	12.3	12.6	11.5	12.7

[a] Difference in calculated total energies, kcal/mol. [b] Corrected for both the differences in ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K (the temperature at which the deprotonations were conducted), see text.

The structures of the two lowest-energy transition states, **4-TS** leading to removal of the *pro*-S hydrogen and **5-TS** leading to removal of the *pro*-R hydrogen, are depicted in Figure 3 sans sparteine for clarity of presentation. The calculated energies (Table 3), corrected for both the difference in zero-point energies and the change in the enthalpy on going to 195 K (−78 °C), lead to an activation enthalpy for transfer of the *pro-S* hydrogen of the ligated pyrrolidine within the more stable complex (**4**) of 10.9 kcal/mol. Conversely, transfer of the *pro-R* hydrogen from the pyrrolidine ring of complex **5**, which is some 2.7 kcal/mol less stable than **4** (Table 2), is calculated to have an activation enthalpy of 12.6 kcal/mol. These activation energies are quite reasonable for a reaction that occurs at a relatively low temperature. On the assumption that **4** and **5** are in equilibrium, the difference in transition-state enthalpies is 4.5 kcal/mol ($\Delta\Delta H$ in Table 3*)*, and the difference in transition-state free energies is 3.2 kcal/mol. These relatively large energy differences are fully in accord with the high enantioselectivity that has been observed experimentally for deprotonation of **1**.[4]

Beak has recently noted that the distance between the oxygen of the carbamate carbonyl group and the proton that is preferentially removed in such deprotonations appears to be an important factor in the success of carbamate-directed lithiations, and a distance of 2.78 Å was suggested as optimal.[3] In this connection, it is of interest to note that the calculated distance between the carbonyl oxygen and the *pro*-S hydrogen of **1** is 2.64 Å in the ground state of the intermediate complex (**4**) and 2.80 Å in the transition state (**4-TS**).

An important feature of the transition states illustrated in Figure 3 is the development of a "bond" between lithium and the α-pyrrolidine carbon as the proton is being transferred to the isopropyl carbon and the bond from the latter to the lithium is being broken. This interaction, which serves to retain the

(14) The enthalpy correction depends only on a constant term times the temperature for both the translational and rotational parts. The vibrational part is the main source of error, and most of the error is associated with the very low frequencies which are not well described in the ab initio calculations. The complexes in this study have on the order of 10 frequencies under 100 cm^{-1}. With closely related molecules, one might anticipate that much of the error will cancel when differences in enthalpy are calculated. The free energy, on the other hand, is dependent on the rotational constants for the molecule being studied, and for large molecules the assumption of a classical model for rotation may lead to errors. In addition, the free-energy vibrational terms are more sensitive to the low calculated vibrational frequencies than is the enthalpy term. Cf. Janz, G. J. *Estimation of Thermodynamic Properties of Organic Compounds*; Academic Press: New York, 1958. It should also be noted that only the free energies of rearrangement are significant for processes that occur in solution. For processes such as A + B = C, the changes in free-energy terms corresponding to translation and rotation are not well defined for the condensed phase.

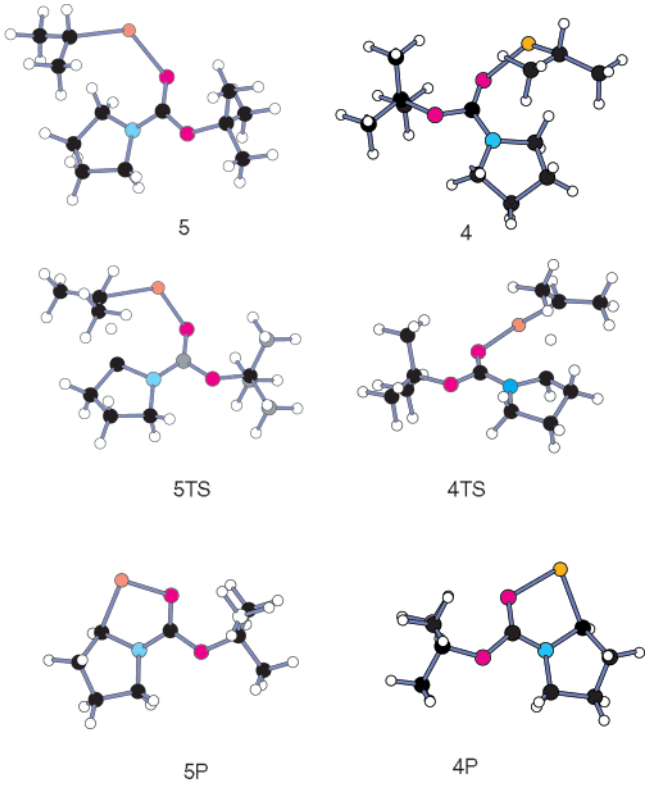
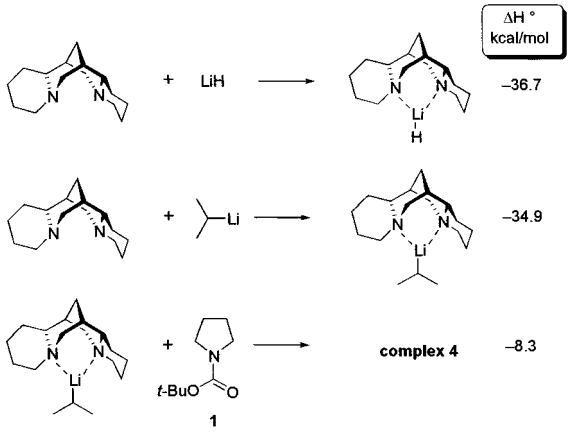


Figure 3. Structures of the two lowest-energy complexes and transition states leading to deprotonation of Boc-pyrrolidine; **4-TS** leads to removal of the *pro*-S hydrogen and **5-TS** leads to removal of the *pro*-R hydrogen. The sparteine ligand has been removed for clarity; colors as in Figure 2.

configuration at C(2) of **1**, is just what would be expected for a kinetically controlled deprotonation.[5]

What then is the origin of the energy difference between the transition states derived from complexes **4** and **5**? An examination of all calculated nonbonded distances within the range of 2−3 Å between the (−)-sparteine ligand and the bound *i*-PrLi and *N*-Boc-pyrrolidine units provides an insight into the nature of the interactions responsible for the relative energies. In general, the steric interactions were distributed over both the sparteine group and the reactants. For complexes **4** and **5**, the short distances (viz., 2.1−2.3 Å) between hydrogens on the sparteine ligand and hydrogens of the *i*-PrLi as well as those of the *tert*-butoxy group of bound **1** were examined. Complex **4** had two of these distances (2.28 and 2.30 Å), whereas complex **5** had three of these distances, two of which were quite short (2.18, 2.19, and 2.29 Å). On going to transition state **4-TS**, the short nonbonded distances in **4** are about the same (2.24 and 2.29 Å). Transition state **5-TS** retains very short nonbonded interactions (2.18 and 2.29 Å) between a sparteine hydrogen and one from the *tert*-butoxy group. Consequently, it is not surprising that **4** has a lower energy than **5** and that **4-TS** has a lower energy than **5-TS**.

Binding Energies of Complexes. The B3P86/6-31G* energies calculated in the course of this study (Table S1) may be used to estimate the sizable binding energies involved in forming the complexes. As illustrated below, the binding enthalpy for the (−)-sparteine−lithium hydride complex amounts to 36.7 kcal/mol.[9] Complexation of the larger *i*-PrLi ligand in an η_2-fashion with (−)-sparteine is calculated to be exothermic by 34.9 kcal/mol at 195 K (−78 °C) after correction for differences in ZPE. Reaction of this *i*-PrLi−(−)-sparteine complex with **1** at −78 °C to give the most stable intermediate complex (**4**) releases a further 8.3 kcal/mol. It might be noted that formation of the other intermediate complexes are also thermodynamically quite favorable: the B3P86/6-31G* calculated enthalpies, corrected for ZPE differences as well as for the enthalpy change on going to 195 K, for formation of **3**, **5**, and **6** from *i*-PrLi + (−)-sparteine + **1** are −39.8, −40.4, and −40.0, respectively. These calculated values are, of course, for monomeric *i*-PrLi, and the organolithium is undoubtedly aggregated in solution,[15] as is the sparteine−*i*-PrLi complex.[2b] Nonetheless, the magnitude of the binding energies leaves little doubt that the intermediate complex is quite stable thermodynamically, as suggested by the kinetic data reported by Beak.[5]



The overall energy change on going from the most stable intermediate complex (**4**) to the product complex (**4P**) may be obtained from the data summarized in Table S1. At the HF/3-21G level, the proton-transfer reaction, illustrated in Figure 3, is exothermic with $\Delta H° = -21.2$ kcal/mol, and at the B3P86/6-31G* level it is calculated to have $\Delta H° = -18.6$ kcal/mol. This result is fully consonant with the high yields that are a hallmark of this chemistry.

Kinetic Hydrogen Isotope Effects. The structures of the transition states, **4-TS** and **5-TS**, in which the proton is approximately half transferred, suggests that the kinetic hydrogen isotope effect should be relatively large. Since the activation energy is small and the proton is transferred over a considerable distance, one might expect that tunneling effects may be small. Thus, the isotope effect may be derived from the calculated vibrational frequencies as shown below, where $u_i = \nu_i{*}1.439/T$.[16]

$$\frac{k_H}{k_D} = \frac{\nu^{\pm}_{L(H)}}{\nu^{\pm}_{L(D)}} \prod_i^{3n-7\pm} \frac{u^{\pm}_{i(H)}}{u^{\pm}_{i(D)}} \times \frac{\exp -0.5u^{\pm}_{i(H)}}{\exp[-0.5u^{\pm}_{i(D)}]} \times \frac{1-\exp[-u^{\pm}_{i(D)}]}{1-\exp[-u^{\pm}_{i(H)}]} \times \prod_i^{3n-6} \frac{u_{i(D)}}{u_{i(H)}} \times \frac{\exp[-0.5u^{\pm}_{i(D)}]}{\exp[-0.5u_{i(H)}]} \times \frac{1-\exp[-u_{i(H)}]}{1-\exp[-u^{\pm}_{i(D)}]}$$

Here, the first product is over the $3n - 7$ vibrational frequencies of **4**TS and **4**d_1TS, whereas the second product is over the $3n - 6$ frequencies of **4** and **4**d_1. With complex **4** and its transition state, the preexponential factor, $\nu_L^{\ddagger}(H)/\nu_L^{\ddagger}(D)$, is 1.377, and at 195 K, the exponential part gives 8.82, leading to a calculated isotope effect (k_H/k_D) of 12.2 at −78 °C. The corresponding

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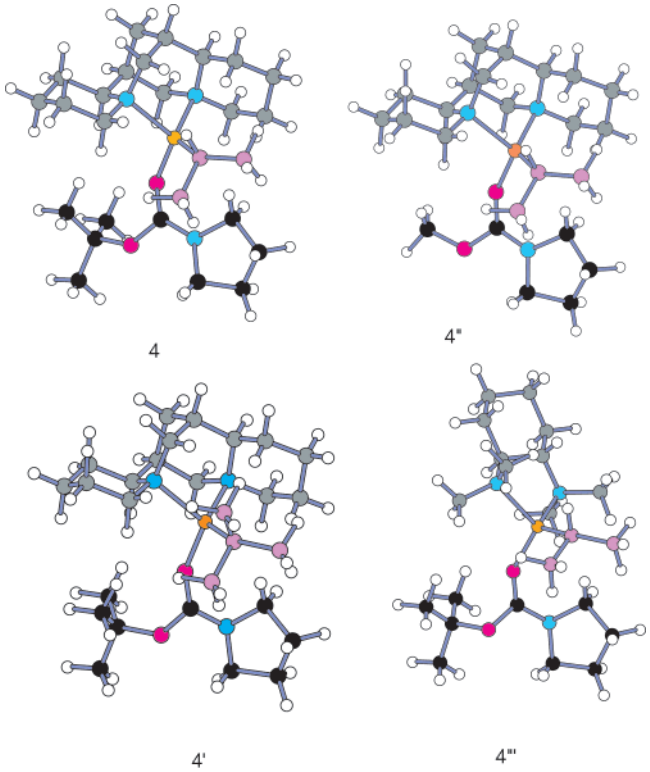


Figure 4. Structures of the lowest-energy intermediate complexes; colors as in Figure 2.: *i*-PrLi + (−)-sparteine + Boc-pyrrolidine (**4**); *t*-BuLi + (−)-sparteine + Boc-pyrrolidine (**4′**); *i*-PrLi + (−)-sparteine + *N*-(Methoxycarbonyl)pyrrolidine (**4″**); *i*-PrLi + (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane + Boc-pyrrolidine (**4‴**).

value at 298 K (25 °C) is 5.3. Given the assumptions inherent in the calculation, the result is in reasonable agreement with the k_H/k_D of >30 obtained by Gallagher and Beak from a competition experiment employing **1** and 2,2,5,5-tetradeuterio-**1** conducted at −78 °C.[5]

Lithiation of *N*-Boc-Pyrrolidine with *t*-BuLi−(−)Sparteine. As noted above, lithiation of 1 with a secondary alkyllithium, such as *i*-PrLi or *sec*-BuLi, in the presence of (−)-sparteine is highly enantioselective.[4] Perhaps not surprisingly, the less basic *n*-BuLi−sparteine reagent has been found to be totally ineffective in removing a proton from 1.[17] The behavior of *t*-BuLi−(−)-sparteine in this reaction is, however, something of a conundrum. Beak has observed that deprotonation of 1 using *t*-BuLi−(−)-sparteine in either cyclopentane or diethyl ether proceeds in lower yield than the analogous reaction with the *sec*-alkyllithium−(−)-sparteine reagent and gives product that is essentially racemic.[17] The simplest rationalization of this result is the one proposed by Beak: the bulky *t*-BuLi−(−)-sparteine reagent does not complex with the Boc-pyrrolidine.[17] As detailed below, this explanation may not be correct.

The estimated binding enthalpy for the *t*-BuLi−(−)-sparteine complex, calculated from the B3P86/6-31G* energies and corrected for ZPE differences as well as for the enthalpy change on going to 195 K (−78 °C), is −35.5 kcal/mol. This value is similar to that calculated for the corresponding *i*-PrLi complex. More to the point, reaction of the *t*-BuLi−(−)-sparteine complex with **1** at −78 °C to give the most stable intermediate complex (4′), which leads to loss of the *pro*-S hydrogen (Figure 4), is calculated to be *exothermic* by 4.5 kcal/mol. Formation of the two other low-energy intermediate complexes, **3′**, and **5′**, from

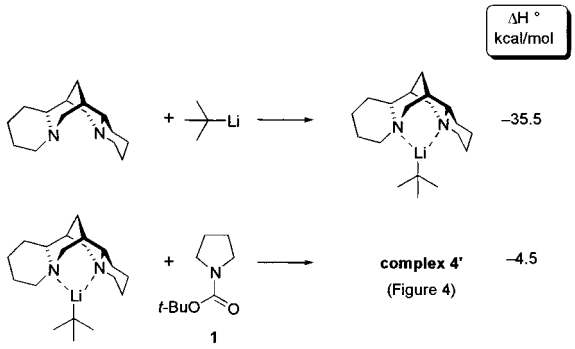
(17) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

Table 4. Calculated Energies of the *t*-BuLi/(−)-Sparteine/Boc-pyrrolidine Complexes

	complex			
	5′	**3′**	**4′**	**6′**
$\Delta\Delta H$ (HF/3-21G)[a]	2.0	1.6	0.0	0.4
$\Delta\Delta H$ (B3P86/6-31G*l)[b]	0.5	1.4	0.0	1.2
$\Delta\Delta G$ (B3P86/6-31G*)	0.4	2.5	0.0	2.0
	5′-TS	**3′-TS**	**4′-TS**	
$\Delta\Delta H$ (HF/3-21G)[a]	−1.2	1.9	0.0	
$\Delta\Delta H$ (B3P86/6-31G*)[b]	3.3	0.8	0.0	
$\Delta\Delta G$ (B3P86/6-31G*)	2.7	1.7	0.0	
$\Delta H^{\ddagger}$ (B3P86/6-31G*)[b]	18.9	15.0	15.7	
$\Delta G^{\ddagger}$ (B3P86/6-31G*)[b]	18.1	15.0	15.8	

[a] Difference in calculated total energies, kcal/mol. [b] Corrected for both the differences in ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K (the temperature at which the deprotonations were conducted), see text.

t-BuLi + (−)-sparteine + **1** is also thermodynamically favorable and leads to removal of the *pro*-R hydrogen: the B3P86/6-31G* calculated enthalpies, corrected for ZPE differences as well as for the enthalpy change on going to 195 K, are −38.3 and −36.6, respectively. It would appear that there should be no difficulty in forming such an intermediate complex. However, it should be noted that the free-energy change for the formation of complexes **3′**−**5′** would be expected to be significantly less favorable than the enthalpy change.[18]



Of the three low-energy intermediate complexes involving *t*-BuLi (**3′**, **4′** and **5′**), that leading to removal of the *pro*-S hydrogen (**4′**, Figure 4) is calculated to be more stable than complex **3′** or **5′**, which leads to abstraction of the *pro*-R hydrogen (Table 4). Although **5′** has a low relative energy, its optimized structure is different than the others with an approximately planar lithium bonded to sparteine and *t*-BuLi with the *N*-Boc-pyrrolidine being relatively far removed (O···Li distance = 4.9 Å). As a result, it has a high activation energy (Table 4) and will not be further considered.

The complex **4′** is calculated to be only 1.4 kcal/more stable than **3′** that leads to abstraction of the *pro*-R hydrogen (Table 4). Moreover, the activation enthalpies at −78 °C, corrected for differences in ZPE, calculated for *pro*-S deprotonation via **4′-TS,** $\Delta H^{\ddagger}$ = 15.7 kcal/mol, and for *pro*-R deprotonation via **3′-TS**, $\Delta H^{\ddagger}$ = 15.0 kcal/mol, are both significantly larger than the 10.9 kcal/mol activation enthalpy found for *pro*-S deprotonation within the *i*-PrLi complex discussed above. The free-energy changes are similar. The small difference in transition

(18) As indicated in ref 14, it is difficult to calculate the free-energy change in solution. It is also possible that the complexes are formed from a sparteine−*t*-BuLi dimer, similar to the corresponding *i*-PrLi dimmer, in which case $\Delta G \approx \Delta H$. It was not possible to calculate the energy of this dimer because of its size.

state energies for **3′** and **4′** (~1 kcal/mol, Table 4), is most likely the reason for a lack of selectivity observed by Beak in the deprotonation of **1** using *t*-BuLi−(−)-sparteine.[17]

The origin of the higher activation enthalpy for deprotonation from within the *t*-BuLi intermediate complex (**4′**) is apparent from an analysis of the calculated structure of the complex. An examination of the *i*-PrLi complexes in Figure 2 shows that the central hydrogen of the isopropyl group is oriented to point toward the sparteine residue. This arrangement presumably minimizes steric interactions. When the hydrogen is replaced by methyl, forming a *tert*-butyl group, it perforce faces the sparteine residue (**4′**, Figure 4), and as the proton transfer occurs, the *tert*-butyl group must rotate in a fashion that brings the methyl closer to the sparteine residue. An analogous rotation must also occur within the *i*-Pr complex (**4**), but in this case the smaller hydrogen does not engender such a large steric interaction. In short, the much larger methyl group in the *t*-BuLi complex vis-à-vis the *i*-PrLi complex leads to a larger steric interaction in the transition state for the former reaction, and this results in a higher activation energy for the deprotonation.

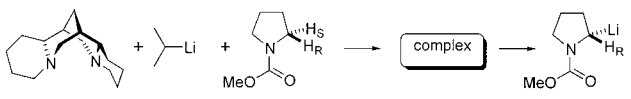
Steric interactions within the *t*-BuLi intermediate complexes also lead to an increase in energy of the complexes themselves. This can be appreciated most easily by reference to the following reaction, calculated to be endothermic by 3.2 kcal/mol.

Steric interactions within the most stable *t*-BuLi intermediate complex (**4′**) are also apparent from a comparison, summarized below, of the longer internuclear distances calculated for this species with those of the corresponding distances in the more stable *i*-PrLi intermediate complex (**4**).

	internuclear distances, Å		
	Li−O	Li−N	Li−C
i-PrLi complex **4**	2.084	2.200,2.187	2.153
t-BuLi complex **4′**	2.150	2.224,2.269	2.214

Lithiation of *N*-(Methoxycarbonyl)pyrrolidine. In light of the high enantioselectivity observed in deprotonation of Boc-pyrrolidine (**1**) by (*i*-PrLi)−(−)-sparteine, it is of interest to inquire as to the role of the Boc-group. Is the bulky *tert*-butoxy group needed to achieve high enantioselectivity? This question was explored computationally by replacing the *tert*-butoxy groups in complexes **3**−**5** with methoxy and reoptimizing the structures following the procedure described above. The energies of the resulting complexes (**3″**, **4″**, and **5″**) as well as their transition states (**3″-TS**, **4″-TS**, and **5″-TS**) are given in Table 5.

Not surprisingly, formation of the intermediate complexes are thermodynamically quite favorable: the B3P86/6-31G* calculated enthalpies, corrected for ZPE differences as well as for the enthalpy change on going to −78 °C, for formation of **3″**, **4″**, and **5″** from *i*-PrLi + (−)-sparteine + *N*-(methoxycarbonyl)pyrrolidine (**7**) are −43.3, −46.4, and −43.7, respectively.

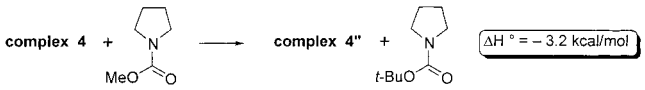


The structure of the most stable complex, **4″**, which leads to removal of the *pro*-S hydrogen of the pyrrolidine, is depicted in Figure 4. Cursory inspection of the structure of **4″** reveals that the methoxy group lies in a relatively unhindered position. Complex **5″**, leading to removal of the *pro*-R hydrogen, is calculated to be 2.6 kcal/mol less stable than **4″** (Table 5). The calculated activation enthalpy for transfer of the *pro*-S hydrogen within complex **4″**, $\Delta H^{\ddagger} = 12.2$ kcal/mol, as well as for transfer of the *pro*-R hydrogen from within complex **5″**, $\Delta H^{\ddagger} = 12.6$ kcal/mol, are both slightly larger than that for the corresponding Boc-pyrrolidine complexes **4** and **5**. The higher activation energies calculated for deprotonation of *N*-(methoxycarbonyl)-pyrrolidine by *i*-PrLi−(−)-sparteine is largely a consequence of the lower steric energy of the methoxy complexes vis-à-vis the Boc-containing complexes. This can be best appreciated by consideration of the following isodesmic reaction, calculated to be exothermic by −3.2 kcal/mol.

Table 5. Calculated Energies of the *i*-PrLi/(−)-Sparteine/*N*-(Methoxycarbonyl)Pyrrolidine Complexes

	complex		
	5″	**3″**	**4″**
$\Delta\Delta H$ (HF/3-21G)[a]	2.3	2.6	0.0
$\Delta\Delta H$ (B3P86/6-31G*l)[b]	2.0	2.3	0.0
$\Delta\Delta G$ (B3P86/6-31G*l	1.3	1.6	0.0
	5″-TS	**3″-TS**	**4″-TS**
$\Delta\Delta H$ (HF/3-21G)[a]	3.0	4.6	0.0
$\Delta\Delta H$ (B3P86/6-31G*)[b]	3.1	4.2	0.0
$\Delta\Delta G$ (B3P86/6-31G*)	2.7	3.7	0.0
$\Delta H^{\ddagger}$ (B3P86/6-31G*[b]	12.7	13.3	11.5
$\Delta G^{\ddagger}$ (B3P86/6-31G)	13.3	14.0	12.0

[a] Difference in calculated total energies, kcal/mol. [b] Corrected for both the differences in ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K (the temperature at which the deprotonations were conducted), see text.



Making the assumption that **4″** and **5″** are in equilibrium, the difference in transition state energies for removal of the *pro*-S versus *pro*-R hydrogen in complexed **1** is $\Delta\Delta H = 3.1$ kcal/mol (Table 5) or $\Delta\Delta G = 2.7$ kcal/mol. These results (Table 5) suggest that replacement of the Boc-group in **1** by a methoxycarbonyl should result in a slightly slower reaction with somewhat lower enantioselectivity. Experimental verification of this prediction is problematic since the organolithium reagent would most likely add to the methyl carbamate more rapidly than it would deprotonation the pyrrolidine.[3]

Why is *C*$_2$-Symmetric *trans*-1,2-Bis(*N*,*N*-dimethylamino)-cyclohexane Ineffective as a Ligand for the Enantioselective Deprotonation of 1 ?[19] One particularly interesting feature of the chemistry discussed above is that C_2-symmetric, chiral diamines,[20] such as *trans*-1,2-bis(*N*,*N*-dimethylamino)cyclohexane and isosparteine, give poor enantioselectivities when used in combination with a *sec*-alkyllithium for deprotonation of **1**.[21] Beak's group has screened a few dozen structurally diverse chiral ligands to assess their utility for the asymmetric deprotonation of **1**, but none were found to be as satisfactory as is (−)-sparteine in providing product of very high ee.[2c] Indeed, while (−)-sparteine is the most effective ligand for promoting

(19) A preliminary account of this portion of the investigation has appeared, see: Wiberg, K. B.; Bailey, W. F. *Tetrahedron Lett.* **2000**, *41*, 9365.

(20) For a discussion of the benefits of using C_2-symmetric, chiral ligands in asymmetric syntheses, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(21) It should be noted that Hoppe's group has obtained quite high enantioselectivities in the asymmetric deprotonation of alkyl and indenyl carbamates by *sec*-butyllithium in the presence of certain C_2-symmetric chiral diamines.[1e, 8]

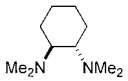
Table 6. Calculated Relative Energies of the *i*-PrLi/(*S*,*S*)-1,2-Bis(*N*,*N*-dimethylamino)cyclohexane/Boc-pyrrolidine Complexes (kcal/mol)

	complex	
	3‴	**4‴**
ΔΔH (HF/3-21G)[a]	0.5	0.0
ΔΔH (B3P86/6-31G*)[a]	0.4	0.0
ΔΔG (B3P86/6-31G*)[b]	0.5	0.0
	3‴-TS	**4‴-TS**
ΔΔ*H* (HF/3-21G)[a]	2.2	0.0
ΔΔ*H* (B3P86/6-31G*)[a]	1.1	0.0
ΔΔ*G* (B3P86/6-31G*)[b]	1.2	0.0
Δ*H*‡ (B3P86/6-31G*)[b]	10.2	9.5
Δ*G*‡ (B3P86/6-31G*)	10.8	10.1

[a] Difference in calculated total energies. [b] Corrected for both the differences in ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K (the temperature at which the deprotonations were conducted), see text.

asymmetric lithiation of **1**, *trans*-1,2-bis(*N*,*N*-dimethylamino)-cyclohexane is certainly among the worst: The C_2-symmetric diamine does promote lithiation of 1 at −78 °C, but the product is totally racemic.[2c]

The disparate behavior of (−)-sparteine and *trans*-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane as ligands for the asymmetric deprotonation of **1** was investigated by exploring the structure and energetics of intermediate complexes formed from *i*-PrLi, Boc-pyrrolidine (**1**), and (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)-cyclohexane (**8**). The two lowest-energy complexes of *i*-PrLi + **1** + **8** were obtained by replacing the (−)-sparteine ligand in complexes **4** and **5** with ligand **8** and reoptimization of the structures following the procedure described above. The energies of the resulting intermediate complexes (**3‴** and **4‴**), as well as the transition states for proton transfer within the complexes (**3‴-TS** leading to transfer of the *pro*-R hydrogen and **4‴-TS** leading to transfer of the *pro*-S hydrogen), corrected for differences in ZPE as well as the change in enthalpy on going from 0 K to −78 °C, are summarized in Table 6**.**



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The *i*-PrLi/(*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**8**)/Boc-pyrrolidine (**1**) complexes are quite stable: the binding energies are calculated to be 43.3 kcal/mol for **3‴** and 43.7 kcal/mol for **4‴**. However, the two complexes differ in enthalpy by only 0.4 kcal/mol (ΔΔ*G* = 0.5 kcal/mol, Table 6). Moreover, the difference in transition state energies is a mere ∼1 kcal/mol (Table 6). These ground-state and transition-state energy differences are much smaller than those found for the deprotonation of **1** mediated (−)-sparteine.

The reason for the differing behavior of complexes derived from (−)-sparteine and the C_2-symmetric diamine (**8**) can be easily appreciated by reference to the structures of the relevant complexes. Examination of Figure 5, which shows complexes **3‴** and **4‴** in a view wherein the nitrogens of the diamine ligand (**8**) are superimposed, demonstrates that nonbonded interactions are quite similar in both complexes. Consequently, the small difference in energy between **3‴**and **4‴** is not surprising. By way of comparison, the two lowest-energy intermediate complexes involving (−)-sparteine (**4** and **5**) are also shown in Figure 5 from the same perspective (viz., with the nitrogen atoms of the ligand superimposed).

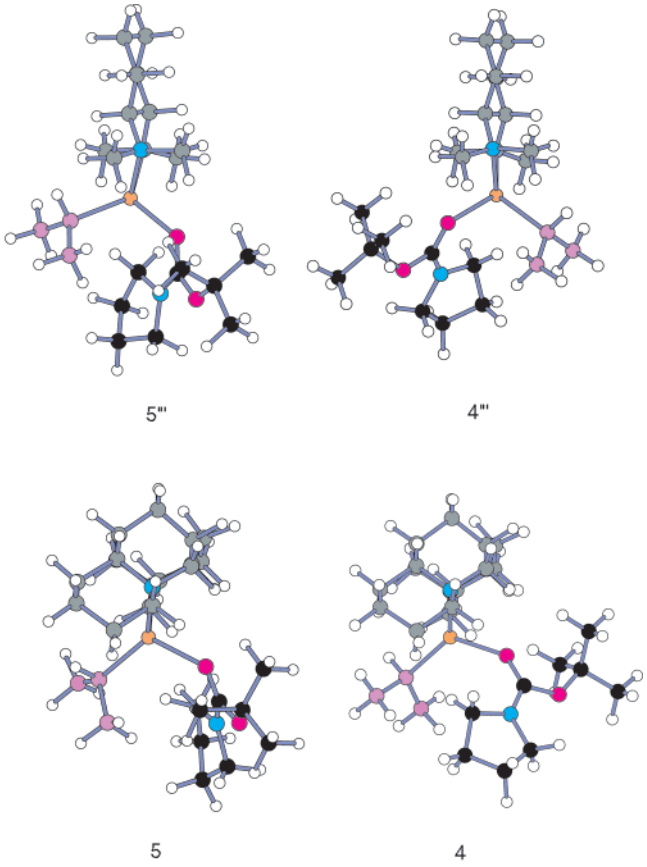

Figure 5. Comparison of thestructures of the lowest-energy intermediate complexes of *i*-PrLi/(*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane/Boc-pyrrolidine (**4‴** and **5‴**) and the corresponding (−)-sparteine complexes (**4** and **5**) with nitrogen atoms superimposed; colors as in Figure 2.

Steric Interactions in the (−)-Sparteine Intermediate Complexes. An examination of the nonbonded distances in complexes **3**−**6** revealed that they were greatest in complex **4**, suggesting that the principal factors determining the relative energies of the complexes were steric in origin. If this is the case, the relative energies should be reproduced by a molecular mechanics calculation, provided that the important electronic interactions are also taken into account.

The ONIUM model of Morokuma et al.[22] provides a way in which to test this hypothesis. Following this paradigm, the molecule is separated into two parts; the "high level part" is treated at one level of theory, and the "low level part" is treated using a lower level of theory. The coupling between the two parts has been worked out in detail.[22] In the present case, we have chosen to treat the high level part at the HF/3-21G level, and to treat the low level part using molecular mechanics. Three molecular mechanics force fields have been integrated into this model: the UFF of Goddard, et al.,[23] the Amber force field,[24] and the Dreiding force field.[25] The Amber force field does not

(22) (a) Maseras, F.; Morokuma, K. *J. Comput. Chem.* **1995**, *16*, 1170. (b) Matsubara, T.; Sieber, S.; Morokuma, K. *Int. J. Quantum Chem.* **1996**, *690*, 1101. (c) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morukuma, K. *J. Phys. Chem.* **1996**, *100*, 19357. (d) Humbel, S.; Sieber, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 1959. (e) Dapprich, S.; Komaromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *THEOCHEM* **1999**, *462*, 1.

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Table 7. Results of ONIUM Calculations[a]

complex	calc energy	E_{rel}, ONIUM	E_{rel}, HF/3-21G
3	−789.03433	3.0	4.0
4	−789.04140	0.0	0.0
5	−789.03397	4.7	3.2
6	−789.03396	4.7	2.9

[a] E_{rel} in kcal/mol.

currently have the parameters needed to describe a tetracoordinate lithium, and the Dreiding force field appeared to give steric energies which were unreasonable large. Therefore, all of the calculations were carried out using UFF.[23]

The high level part included the Boc-pyrrolidine (**1**), *i*-PrLi, and the nitrogen atoms of sparteine that are coordinated with lithium. The low level part included all of the atoms of the sparteine ligand except for the two nitrogens. It should be noted that the use of fewer atoms in the high level part was found to be unsatisfactory. For example, when the *tert*-butyl group of **1** was included in the low level part, it tended to rotate to a position midway between the ester E and Z conformers. When only a portion of the pyrrolidine ring was included in the high level part, it tended to rotate during geometry optimization to place the low level part near the isopropyl group.

The four complexes **3**−**6** were examined in this fashion, giving the results shown in Table 7. The relative energies calculated in this way are compared with those directly calculated using HF/3-21G, and the results are encouraging (Table 7). Complex **4** is found to have the lowest energy in each case, and although there is not complete agreement between the two sets of calculations, the energies are quite similar.

The ONIUM model deserves further study as a relatively rapid and inexpensive method for screening a variety of chiral ligands for use in asymmetric deprotonations. In addition to using HF/3-21G and molecular mechanics, the model also provides the opportunity to examine the reacting system at higher theoretical levels such as B3P86/6-311+G* while using HF/3-21G to describe the ligand system. The results of these ongoing studies will be reported at a later time.

Summary

The results described above demonstrate that modern computational methods may be used to gain detailed understanding of the factors responsible for the very high enantioselectivity observed in the asymmetric deprotonation of Boc-pyrrolidine (**1**) by the *i*-PrLi−(−)-sparteine reagent. The etiology of the enantioselectivity appears to be predominantly a steric phenomenon: the major repulsive steric interactions present in the ground state of the most stable, three-component intermediate complex (**4**) are relieved on going to the transition state for transfer of the *pro*-S hydrogen (**4-TS**). The corresponding ground state of the intermediate complex that leads to removal of the *pro*-R hydrogen (**5**) is more congested, hence less stable, than is **4**, and since at least some of these interactions persist in the transition state for transfer of the *pro*-R hydrogen (**5-TS**), the activation energy is consequently higher. The failure of (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**8**) to effect enantioselective deprotonation of **1** when used in combination with *i*-PrLi is attributable to the fact that there is little steric difference between the two sides of the C_2-symmetric diamine in the intermediate complex.

The failure of *t*-BuLi−sparteine to effect enantioselective deprotonation of **1** appears to be a consequence of the higher activation enthalpy for proton transfer within the intermediate complexes (**3′**−**5′**) rather than the failure of *t*-BuLi−sparteine to form a stable complex with **1**. The results of these studies further suggest that the bulky *tert*-butoxycarbonyl (Boc) group should be more effective than a smaller methoxycarbonyl in promoting high levels of enantioselection in the deprotonation of **1** by *sec*-alkyllithium−sparteine.

It might be noted that it was not obvious at the inception of this study that the most stable intermediate complex (**4**) would correspond to the proton transfer process having the lowest activation energy; it was equally probable a priori that ground state destabilization might result in a lower activation energy. Should this observation prove to be general for deprotonations mediated by other chiral ligands, the ONIUM model discussed above holds great promise as a method for the rapid evaluation of a range of structurally diverse ligands for enantioselective deprotonation of Boc-pyrrolidine and other substrates.

Computational Methods

Calculations were performed using Gaussian 99.[26] In the case of the B3P86/6-31G* geometry optimizations, the long execution times led us to use a relaxed criterion for convergence: namely, a predicted change in energy of less than 1×10^{-5} Hartrees (0.005 kcal/mol).

Acknowledgment. The work at Yale was supported by a Grant from the National Institutes of Health; the work at UCONN was supported by a Grant from Procter & Gamble Pharmaceuticals, Mason, Ohio.

Supporting Information Available: A summary of the calculations, including calculated absolute energies, zero-point energies, as well as detailed structural data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0107733

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