(m, 20H), 1.11 (s, 18H), 1.40 (s, 9H), 1.49 (s, 9H), 3.41 (d, $J = 12.9$ Hz, 4H), 3.75 (m, 6H), 3.94 (m, 2H), 4.06 (d, $J = 13.0$ Hz, 4H), 6.80 (d, 2H), 6.92 (d, 2H), 7.35 (s, 2H), 7.61 (s, 2H); 1,2-alternate: $\delta = 0.77$ (t, 12H), 0.90 (m, 4H), 1.44 (m, 4H), 1.48 (s, 36H), 2.91 (d, 2H), 3.55 (m, 4H), 3.62 (m, 4H), 3.63 (s, 4H), 3.97 (d, 2H), 7.12 (d, 4H), 7.22 (d, 2H).

[27] The binding constants are estimated using the Venus flytrap ($K_{ass} = 3\times10^{6}\,\mathrm{M}^{-1}$ for NO incarceration) according to a competition method described earlier, see E. Bosch, J. K. Kochi, *J. Org. Chem.* **1995**, *60*, 3172.

[28] In contrast, the model 2,6-dimethyl-4-*tert*-butylanisole (DMBA) results in a pale red-brown solution upon mixing with $NOSbCl_6$ ($K_{ass} \sim 700\,\mathrm{M}^{-1}$) in dichloromethane at 25 °C. X-ray structure analysis of a single crystal of DMBA complexed with NO^+ grown from a mixture of dichloromethane and hexane at −30 °C shows an approximately perpendicular orientation of NO poised centrally over the aromatic ring (see Experimental Section). This structure is similar to those observed previously with other single aromatic donors such as hexamethylbenzene (R. Rathore, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **1997**, *119*, 9393) and mesitylene (E. K. Kim, J. K. Kochi, *J. Am. Chem. Soc.* **1991**, *113*, 4962).

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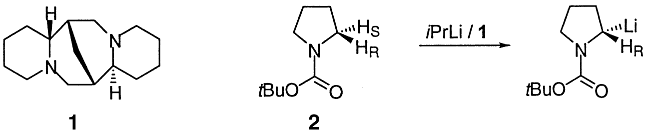
A Transition State for the Enantioselective Deprotonation of *N*-Boc-Pyrrolidine with Isopropyllithium/(−)-Sparteine**

Kenneth B. Wiberg* and William F. Bailey*

Over the course of the past decade, pioneering studies by the groups of Hoppe[1] and Beak[2] have demonstrated that the 1:1 complex of a *sec*-alkyllithium (such as *sec*-BuLi or *i*PrLi) and (−)-sparteine (**1**) is a remarkably efficient reagent for the highly enantioselective deprotonation that produce configurationally stable dipole-stabilized organolithium species.[3] A particularly simple example of such an asymmetric deprotonation is provided by the lithiation of *N*-Boc-pyrrolidine (**2**; Boc = *tert*-butyloxycarbonyl) with *i*PrLi/(−)-sparteine (Scheme 1). Beak et al. have shown that this kinetically controlled process proceeds with a remarkably high selectivity (95 ± 5 %)[2c] for abstraction of the *pro-S* hydrogen atom at C(2).[2, 3] Moreover, **1** appears to be the ligand of choice for such a deprotonation: A variety of structurally diverse chiral diamines have been screened as potential ligands for the asymmetric deprotonation of **2** but none was found to be nearly as effective as is **1**.[2d]



Scheme 1. Kinetically controlled deprotonation of *N*-Boc-pyrrolidine.

In light of the current interest in development of a transition state model that accounts for the ability of *sec*-alkyllithium/(−)-sparteine to effect highly enantioselective deprotonation,[3–5] it was of interest to investigate whether modern ab initio molecular orbital calculations could adequately describe the outcome of the asymmetric deprotonation of **2**. In this connection, we have recently reported a computational study of the conformational isomers of **1** and of the transition states for their interconversion.[6] We also have examined the complexes of **1** with both LiH and with *n*PrLi; in each of these cases, **1** behaves as a bidentate ligand and adopts a conformation that lies just above the lowest energy conformer for the uncomplexed ligand.[6] The structure of the LiH/(−)-sparteine complex is shown in Figure 1.

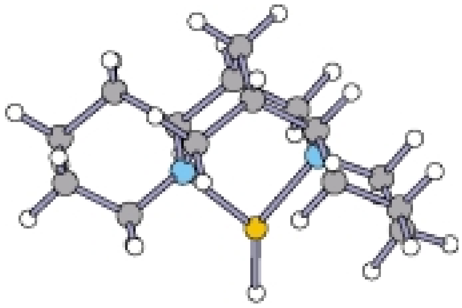


Figure 1. The LiH complex of (−)-sparteine; nitrogen atoms are blue, lithium is orange.

On the reasonable assumption that the deprotonation reaction depicted in Scheme 1 involves precomplexation of the base, ligand, and substrate,[3, 7] the reactive species would have an isopropyl group in place of the hydrogen atom shown in Figure 1 and the carbonyl group of **2** would presumably serve as a fourth ligand, which gives a near-tetrahedral arrangement around the lithium atom. Thus, with respect to the view portrayed in Figure 1, the *i*Pr group may be either forward or behind the plane and **2** takes the other position. Similarly, the pyrrolidine ring of **2** may be either to the right or the left of the lithium atom and the *tert*-butoxy group occupies the other position. Given these preliminaries, there are four potential structures to be examined.

Because of the very large size of the complexes ($C_{27}H_{50}N_3O_2Li$ = 83 atoms), the initial geometry optimizations were initially carried out at the STO-3G level and refined at the HF/3-21G level.[8] While this theoretical level sometimes gives unsatisfactory relative energies, it is known that it usually gives quite good geometries.[9] Of the four structures examined, the lowest energy complex **3**, depicted in Figure 2, had the shortest distance (3.10 Å) between the

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[**] Chiral Diamines, Part 2. This investigation was supported by a grant from the National Institutes of Health. Part 1: ref. [6].

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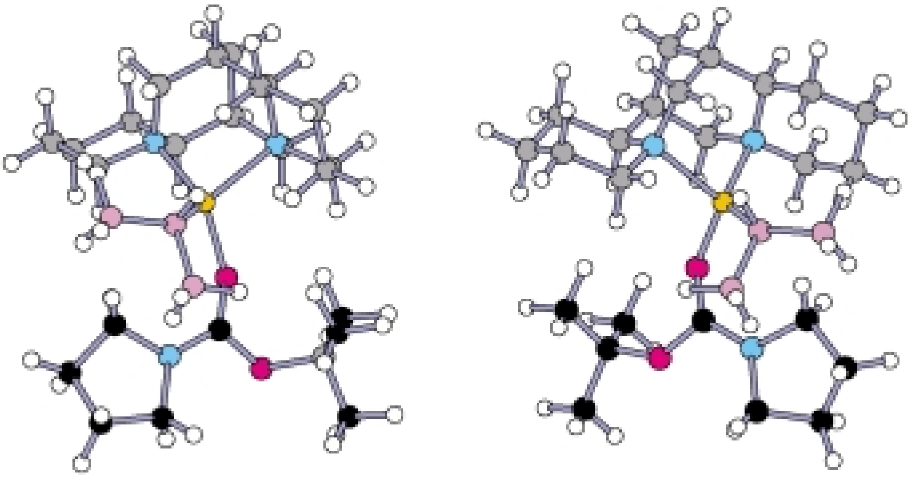

3 4

Figure 2. The lowest energy complexes, **3** and **4**, of (−)-sparteine/*i*PrLi/*N*-Boc-pyrrolidine; the oxygen atoms are red and the isopropyl carbon atoms are purple, other colors are as Figure 1.

carbanionic isopropyl center and an *α*-proton on the pyrrolidine ring; details are summarized in Table 1.[10] A transition state for proton transfer from the bound pyrrolidine in **3** to the bound *i*PrLi was located using the synchronous transit-guided quasi-Newton method of Schlegel et al.[11] to give the structures in Figure 3. It is apparent from a cursory examination that proton transfer within **3** leads to abstraction of a *pro-R* hydrogen atom from bound **2**; this is clearly contrary to the experimental result.[2, 3]

Table 1. Diastereoisomeric (−)-sparteine/*i*PrLi/*N*-Boc-pyrrolidine complexes and transition states for the proton transfer.

	Species[a]			
	3	**3-TS**	**4**	**4-TS**
HF/3-21G[b]	−1364.56160	−1364.52160	−1364.56792	−1364.53232
proton transfer distance [Å]	3.10		2.66	
ZPE[c] [kcal mol^{-1}]	464.8	461.1	465.0	461.8
B3P86/6-31G* [b]	−1385.87094	−1385.84627	−1385.87620	−1385.85355
E_{rel} [kcal mol^{-1}]	3.1		0.0	
ΔH^{+}[d] [kcal mol^{-1}]		11.8		11.0

[a] See Figures 2–4. [b] Energies are given in Hartrees (1 H = 627.51 kcal mol^{-1}). [c] Zero-point energies. [d] At 0 K; the correction to 195 K did not change the results.

Consideration of the structure of complex **3** (Figure 2) led to the realization that it is possible to rotate the pyrrolidine unit so that the *pro-S* hydrogen would lie closer to the carbanionic center of *i*PrLi. Not surprisingly, this led to a severe steric interaction between a hydrogen atom on (−)-sparteine and the *tert*-butoxy group of **2** but this could be relieved through a rotation of the latter.[12] Geometry optimization, performed as described above, gave a slightly lower energy complex **4** (Figure 2) with a shorter distance (2.66 Å) for the proton transfer (Table 1). More significantly, the transition state for transfer of the *pro-S* hydrogen from the bound pyrrolidine within **4**, located as described above and depicted in Figure 4, was found to have a substantially lower energy (Table 1) than the transition state for transfer of the *pro-R* hydrogen within complex **3**.

In order to obtain more satisfactory relative energies, B3P86/6-31G* geometry optimizations[13] were carried out for **3** and **4** (Figure 2) as well as for their transition states (**3-TS** and **4-TS**, Figure 3 and 4). Vibrational frequencies were calculated at the HF/3-21G level and scaled by 0.917.[9b] These results are summarized in Table 1. The calculated energies, corrected for the differences in zero-point energies, lead to an activation enthalpy for the transfer of the *pro-S* hydrogen atom of the pyrrolidine moiety within the more stable complex (**4**) of 11.0 kcal mol^{-1}. Conversely, transfer of the *pro-R* hydrogen from the pyrrolidine ring of complex **3**, which is some 3.1 kcal mol^{-1} less stable than **4**, is calculated to require an activation enthalpy of 11.8 kcal mol^{-1}. These are quite rea-

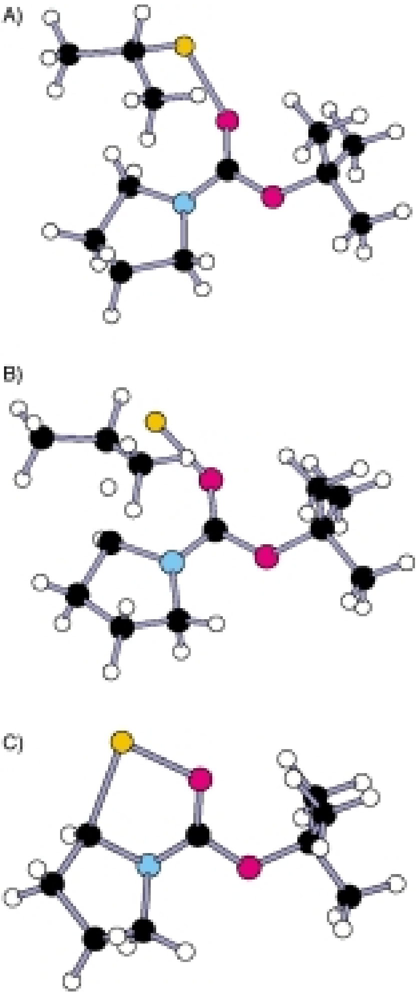

Figure 3. Proton transfer within complex **3**: A) complex **3** with (−)-sparteine removed; B) transition state (**3-TS**) for the transfer of the *pro-R* hydrogen; C) product of the reaction; atomic colors are as Figure 2.

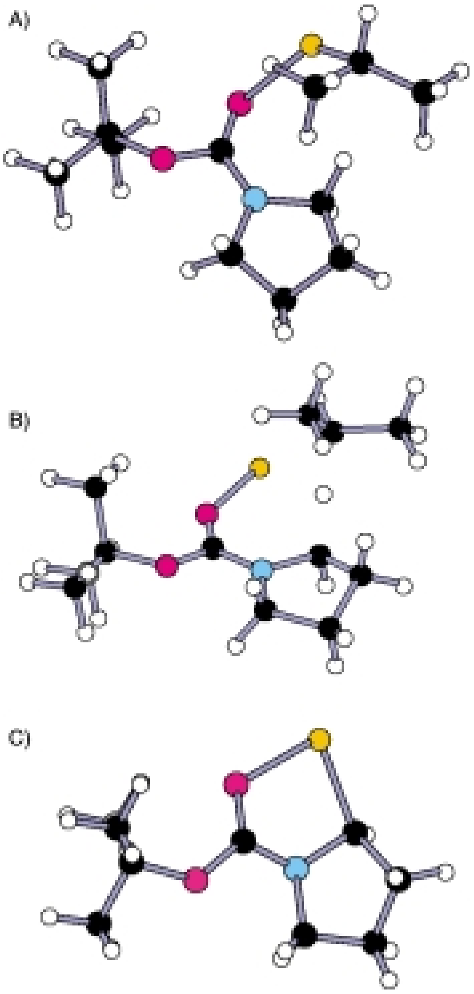

Figure 4. Proton transfer within complex **4**: A) complex **4** with (−)-sparteine removed; B) transition state (**4-TS**) for the transfer of the *pro-S* hydrogen; C) product of the reaction; atomic colors are as Figure 2.

sonable activation energies for a reaction that occurs at a relatively low temperature. An important feature of both transition states is the development of a bond between the lithium and the α-pyrrolidine carbon atoms as the proton is transferred (Figures 3 and 4). This is precisely what is expected for a kinetically controlled asymmetric deprotonation.[2, 3]

What is the origin of the difference in energy between the transition states derived from **3** and **4**? This question was explored by examination of all calculated nonbonding distances within the range of 2 to 3 Å between the (−)-sparteine unit and the bound *i*PrLi and *N*-Boc-pyrrolidine units. For both complexes, there are several short distances (namely, 2.1 – 2.2 Å) between hydrogen atoms on the sparteine ligand and those on the *i*PrLi, as well as those of the *tert*-butoxy group of bound **2**. The distances are, however, shorter in **3** than **4**, leading to the difference in energy. This difference persists in the transition states derived from **3** and **4**.

Since all of the important interactions appear to be steric in origin, it should be possible to model the complexes by molecular mechanics using suitable parameters for a four-coordinate lithium center that can be derived from the present calculations. This is being investigated and will be reported subsequently along with calculations for related systems.

Received: January 20, 2000 [Z 14573]

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[7] Beak et al.[2b] has elegantly demonstrated that *i*PrLi/(−)-sparteine exists in an ethereal solution as an unsymmetrical, ether-solvated dimer $[(i\mathrm{PrLi})_2\cdot(-)\text{-sparteine}]$ but this structure clearly need not be maintained in the deprotonation of **2**.

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[12] Structures were constructed, examined, and adjusted prior to geometry optimization using Gaussview. The structures of the other three initial complexes were also modified by rotation about single bonds in order to move the bound *i*PrLi closer to the α-carbon of the pyrrolidine ring; geometry optimization for these structures did not lead to species with energies lower than those found for **3** or **4**.

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