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Chiral diamines. Part 3: Effect of ligand structure on the enantioselective deprotonation of *N*-Boc-pyrrolidine with *i*-PrLi: a computational comparison of (–)-sparteine and (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane[†]

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Abstract

The deprotonation *N*-Boc-pyrrolidine by *i*-PrLi–(*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane has been studied at the HF/3-21G and B3P86/6-31G* theoretical levels. The two lowest energy complexes of the *N*-Boc-pyrrolidine–*i*-PrLi–diamine ligand, as well as the transition states leading to proton transfer, were found to be similar in both geometry and energy in accord with experimental findings. The results are compared to those for the analogous but enantioselective (–)-sparteine-mediated deprotonation.

Enantioselective deprotonations via chiral diamine–alkyllithium complexes have received considerable study by the groups of Beak[1] and Hoppe.[2,3] The asymmetric deprotonation of *N*-Boc-pyrrolidine (**1**) by a 1:1 complex of a *sec*-alkyllithium and (–)-sparteine (**2**) is a prototypical example of such a process.[3] Beak has shown, as illustrated below, that this kinetically controlled lithiation proceeds with very high selectivity (>95%) for removal of the *pro-S* hydrogen.[4] In striking contrast to the ability of sparteine to mediate the highly enantioselective deprotonation of **1**, the C_2-symmetric diamine,[5] (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**3**), is totally ineffective as a ligand.[4]

Given the growing importance of asymmetric deprotonation as a route to enantioenriched compounds, it was of interest to investigate the ability of modern MO calculations to account for the disparate behavior of **2** and **3** when used as ligands for a *sec*-alkyllithium in the lithiation of **1**. In connection with this, we have recently reported a computational study of the deprotonation of **1** by (–)-sparteine–*i*-PrLi in which the low energy complexes of substrate **1**, *i*-PrLi, and ligand **2** were determined and the transition states for proton abstraction were located.[6] The most stable complex, which lies some 3.1 kcal/mol lower in energy than the alternative aggregate, was found to lead to the experimentally observed preference for removal

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[†] Dedicated to Harry H. Wasserman on the occasion of his 80th birthday: a friend, colleague, scholar, artist and musician.

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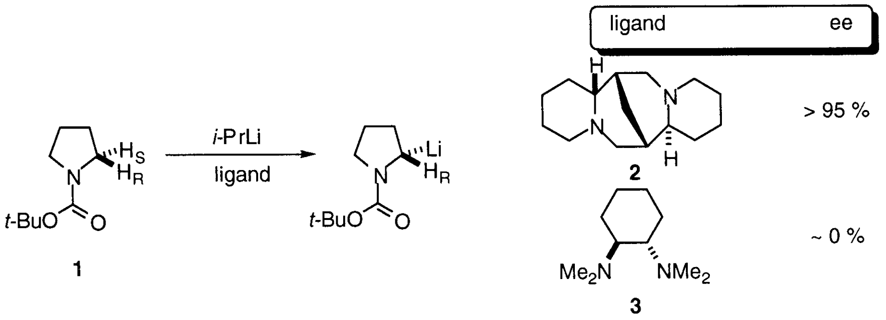

of the *pro-S* hydrogen of **1** and the calculated activation energy for the process (11 kcal/mol)[6] was quite reasonable for a reaction that occurs at low temperature. Herein we report the results of an analogous investigation of the deprotonation of **1** by the (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**3**)–*i*-PrLi reagent.

The two lowest energy complexes, **A** and **B**, of **1** with *i*-PrLi–**3** were located by an initial HF/3-21G geometry optimization, followed by the use of the B3P86/6-31G* theoretical level for the final geometry optimizations.[7] The energies of complexes **A** and **B**, depicted in Fig. 1, are given in Table 1. The zero-point energies, and the correction from 0 K (corresponding to the calculations) to 195 K (–78°C), were obtained from HF/3-21G calculations of vibrational frequencies scaled by 0.917. The transition states for proton transfer were located at the HF/3-21 level using the quasi-Newton synchronous transit method of Schlegel.[8] The vibrational frequencies were calculated and in each case there was just one imaginary frequency corresponding to removal of H(2). This was followed by a B3P86/6-31G* optimization to a transition state using the calculated force constants as the starting point. The energies of the transition states, **A-TS** leading to removal of H_R and **B-TS** leading to removal of H_S, are given in Table 1.

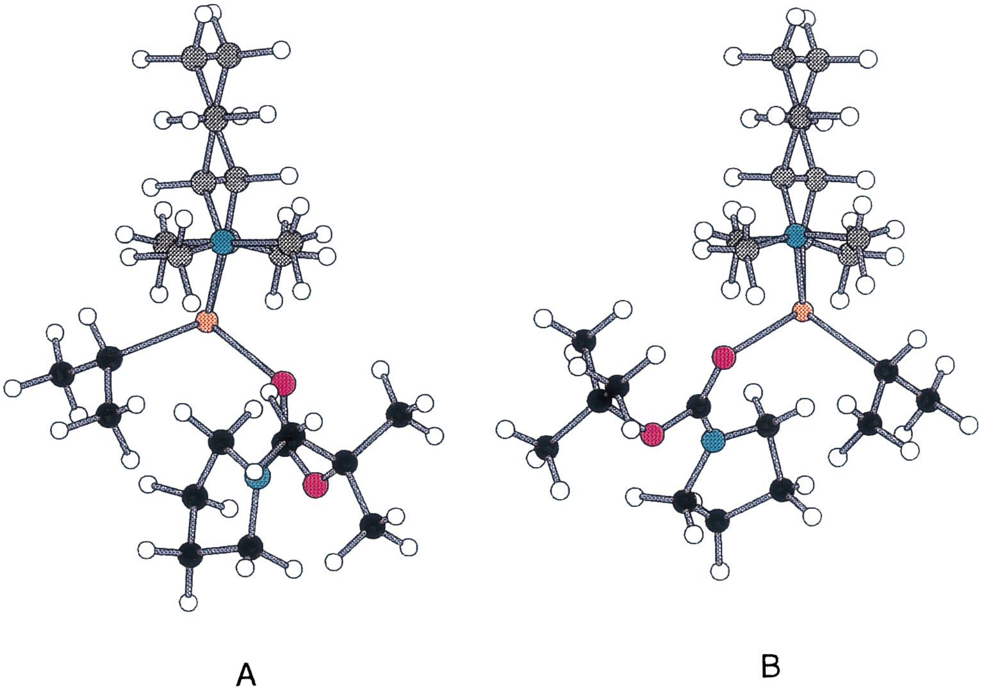

Figure 1. Lowest energy complexes, **A** and **B**, of *N*-Boc-pyrrolidine (**1**)/*i*-PrLi/(*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**3**); the nitrogen atoms are blue, the lithium is orange, and the oxygens atoms are red

Table 1
Diastereoisomeric (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**3**)/*i*-PrLi/*N*-Boc-pyrrolidine (**1**) complexes and transition states for proton transfer

	Species[a]			
	A	**A-TS**	**B**	**B-TS**
HF/3-21G[b]	−1173.91994	−1173.99422	−1173.92074	−173.88776
ZPE (kcal/mol)	413.3	410.3	413.4	410.3
Hcorr (kcal/mol)	16.7	16.3	16.6	16.3
B3P86/6-31G*[b]	−1192.27528	−1192.25392	−1192.27597	−1192.25556
E_{relative} (kcal/mol)	0.4		0.0	
$\Delta H^{\ddagger}$ (kcal/mol)		10.8		10.0

[a] See Fig. 1.

[b] Energies are given in Hartrees (1H = 627.51 kcal/mol).

The results of these calculations indicate that complex **B**, which leads to the removal of the *pro*-S hydrogen of **1**, is only 0.4 kcal/mol lower in energy than complex **A**, which leads to removal of the *pro*-R hydrogen. More to the point, the difference in transition state energies ($\Delta\Delta H^{\ddagger}$) is only ~1 kcal/mol. Both of these values are much smaller than those found in the earlier study for (−)-sparteine induced deprotonation of **1**.[6] The reason for the differing behavior of complexes derived from ligands **2** and **3** can be easily appreciated by examination of the structures of the relevant complexes.

Fig. 1, which shows complexes **A** and **B** in a view wherein the nitrogens of the diamine ligand **3** are superimposed, demonstrates that non-bonded interactions are quite similar in both complexes. Consequently, the small difference in energy between **A** and **B** is not surprising. By way of comparison, the lowest energy complexes (**C** and **D**) of *N*-Boc-pyrrolidine (**1**)/*i*-PrLi/(−)-sparteine (**2**) are depicted in Fig. 2 from the same perspective (with nitrogen atoms of **2** superimposed).[9] It is clear that steric interactions are quite different in the two sparteine complexes: the lower energy complex, **D**, which leads to the experimentally observed removal of H_S of **1**, was found to be 3.1 kcal/mol more stable than the alternative structure, **C**, which leads to removal of H_R.

The computational results presented above demonstrate that ab initio methods are capable of reproducing the dramatic difference in efficacy between (−)-sparteine (**2**) and (*S*,*S*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**3**) as ligands for the enantioselective lithiation of *N*-Boc-pyrrolidine (**1**) by an *i*-PrLi–diamine complex. The larger question, of course, is whether this approach to understanding the role of chiral diamine ligands in asymmetric deprotonation has predictive value that might guide ligand development. It seems clear from the results to date, for example, that a C_2-symmetric *trans*-1,2-bis(*N*,*N*-dialkylamino)cyclohexane bearing branched *N*-alkyl groups would be more efficient than **3** as a chiral adjuvant for asymmetric deprotonation, but designing an optimal ligand using ab initio methods would be a computationally intensive endeavor. For this reason, we are exploring the possibility of modeling substrate–RLi–ligand complexes by molecular mechanics using parameters derived from the ab initio calculations.

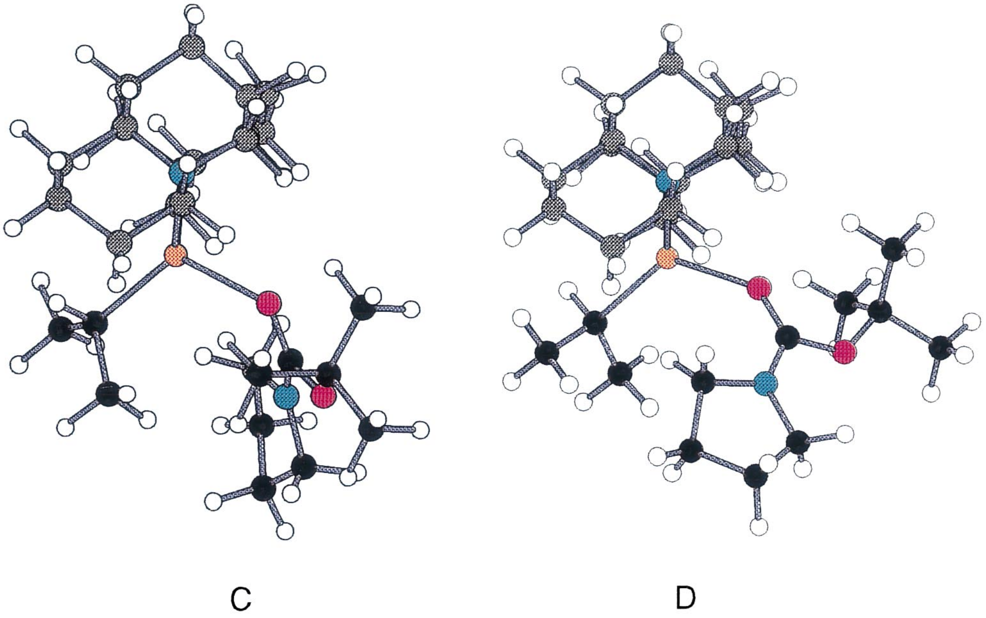

Figure 2. Lowest energy complexes, **C** and **D**, of *N*-Boc-pyrrolidine (**1**)/*i*-PrLi/(–)-sparteine (**2**) with nitrogen atoms superimposed; colors are as in Fig. 1

Acknowledgements

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