Computational Study of the Mechanism of Isomerization of Allyl Alcohol into Homoallyl Alcohol by Lithium Amide

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Dedicated to Professor Lennart Eberzon on the occasion of his 65th birthday


Pathways for lithium amide catalyzed isomerization of lithiated allyl alcohol into lithiated homoallyl alcohol have been calculated using semiempirical (PM3), ab initio (HF, MP2) and DFT (B3LYP) methods. The rearrangement takes place in heterodimer complexes in which the two lithiums play different roles in different pathways via intermediates. In the proton transfer transition states the proton is about half transferred between carbon and nitrogen.

Despite the enormous synthetic usefulness of lithium organic reagents little is known about their reaction mechanisms. This is particularly true with respect to the specific role of the solvent in the reactions. Recently a study of solvent effects on stereoselective ring openings of meso-epoxides to chiral allyl alcohols by chiral lithium amides has been reported.1 It was discovered that upon changing the solvent from tetrahydrofuran (THF) to 2,5-dimethyltetrahydrofuran (DMTHF) or diethylether (DEE) further rearrangements to homoallyl alcohols were induced (Scheme 1).

The role of the solvent in this 1,3-proton transfer, the stereochemistry and other aspects of the detailed mechanism for this reaction have currently been investigated both experimentally and computationally. In this paper we report a computational study of a model system. It is shown in Scheme 2, and consists of the parent lithium amide (LiNH₂) (S1) as reactant catalyzing the rearrangement of the substrate lithiated cis-2-buten-1-ol (S2) into the product lithiated cis-3-buten-1-ol (P1).

Computational methods

All ab initio calculations were performed using the Gaussian 94 program,2 while semiempirical calculations were done using the SPARTAN program.3 Geometries were optimized at PM3,4±5 HF/6-31 + G(d)6±7 and at B3LYP/6-31 + G(d)8 levels of theory. All geometries were characterized as minima or saddle points on the potential energy surface (PES), by calculating the corresponding vibrational frequencies. For each transition state, its corresponding reaction pathway was followed to the connecting minimum structures using the intrinsic reaction coordinate (IRC)9 method. Reaction energies and activation barriers are calculated at the PM3, HF/6-31 + G(d), MP2/6-31 + G(d) and B3LYP/6-31

Scheme 1. Isomerization of the allylic alkoxide 1 to the homoallylic alkoxide 2 within the heterodimer complex 3 catalyzed by the chiral lithium amide 4.

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Results and discussion

Compound S1 forms, by a strongly exothermic reaction (−60.6 kcal mol\(^{-1}\)), heterodimer C1 with the substrate S2 (Scheme 3). The complex C1 is a ‘typical’ dimer complex, with the two lithiums forming bridges between the oxygen and the nitrogen, yielding a planar four-membered ring. Recently Williard and coworkers\(^{12}\) presented the first X-ray study of a complex between a lithium amide and a lithium alkoxide featuring a four-membered ring as in C1.

The shortest Li–C3 distance, Li1–C3, is calculated to be 3.12 Å, and therefore the interaction is negligible between the π-system of the double bond and the lithiums. The heterodimer product C5 (Scheme 4), on the other hand, shows a weak interaction between Li1 and C1 and C2, contributing to the slightly greater stability of C5 over C1.

Different pathways for the intramolecularly catalyzed rearrangement of C1 to C5 have been investigated, together with the non-catalyzed symmetry forbidden concerted 1,3-hydrogen transfer. The latter rearrangement, which makes use of the transition state TS1,

### Table 1. Calculated zero-point energy (ZPE) corrected relative energies [PM3, HF/6-31+G(d)/HF/6-31+G(d), MP2/6-31+G(d)/HF/6-31+G(d), B3LYP/6-31+G(d)/B3LYP/6-31+G(d) and zero-point energies (B3LYP/6-31+G(d)) (in kcal mol\(^{-1}\)).

<table>
<thead>
<tr>
<th>Compound</th>
<th>PM3</th>
<th>HF/6-31+G(d)</th>
<th>MP2/6-31+G(d)</th>
<th>B3LYP/6-31+G(d)</th>
<th>ZPE(^a)</th>
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<tbody>
<tr>
<td>S1+S2</td>
<td>53.3</td>
<td>61.9</td>
<td>65.2</td>
<td>60.6</td>
<td>14.7 + 64.8(0)</td>
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<tr>
<td>P1+S1</td>
<td>58.2</td>
<td>59.9</td>
<td>62.1</td>
<td>57.9</td>
<td>14.7 + 64.9(0)</td>
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<tr>
<td>C1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>82.3(0)</td>
</tr>
<tr>
<td>C2</td>
<td>21.4</td>
<td>29.1(^b)</td>
<td>23.4(^b)</td>
<td>26.4</td>
<td>82.6(0)</td>
</tr>
<tr>
<td>C3</td>
<td>20.3</td>
<td>30.2</td>
<td>23.9</td>
<td>25.6</td>
<td>82.1(0)</td>
</tr>
<tr>
<td>C4</td>
<td>21.4</td>
<td>29.1(^b)</td>
<td>23.4(^b)</td>
<td>24.4</td>
<td>82.4(0)</td>
</tr>
<tr>
<td>C5</td>
<td>−2.2</td>
<td>−1.4</td>
<td>−3.8</td>
<td>−0.8</td>
<td>81.9(0)</td>
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<td>TS1</td>
<td>79.6</td>
<td>103.5</td>
<td>84.3</td>
<td>82.3</td>
<td>78.4(1)</td>
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<td>TS2</td>
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<td>49.0</td>
<td>33.9</td>
<td>33.2</td>
<td>79.7(1)</td>
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<tr>
<td>TS3</td>
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<td>49.5</td>
<td>35.7</td>
<td>35.2</td>
<td>79.3(1)</td>
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<td>TS4</td>
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<td>−0.0</td>
<td>26.2</td>
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<td>TS5</td>
<td>26.8</td>
<td>38.0</td>
<td>30.8</td>
<td>32.6</td>
<td>82.1(1)</td>
</tr>
<tr>
<td>TS6</td>
<td>55.7</td>
<td>66.4</td>
<td>50.8</td>
<td>51.3</td>
<td>78.7(1)</td>
</tr>
<tr>
<td>TS7</td>
<td>47.7</td>
<td>54.8</td>
<td>38.9</td>
<td>37.8</td>
<td>79.0(1)</td>
</tr>
</tbody>
</table>

\(^a\)Number of imaginary frequencies given in parentheses. \(^b\)Optimization at HF/6-31+G(d) level gave the same minimum structure for C2 and C4 and thus no TS in between them.

Scheme 3. Complexation of lithium amide (S1) and the lithium alkoxide S2 yielding the heterodimer complex C1.
is shown in Scheme 4. The calculated barrier is 82.3 kcal mol\(^{-1}\), which is comparable to that of 1,3-sigmatropic rearrangement of 2-pentene (105 kcal mol\(^{-1}\) at the HF/3-21G//HF/3-21G level).\(^{13}\) Obviously such a route is unfavourable for our model reaction.

In the mechanism shown in Scheme 5 the amide nitrogen is employed as a base to perform the 1,3-proton transfer catalytically. The two lithiums in the heterodimer C1 are different, and they play different roles in the rearrangements C1 to C2 and C1 to C3. Compounds C2 and C3 are both intermediates on pathways to the heterodimer C5. The pathway C1 to C3 is a one-step process via transition state TS3. In this activated complex the proton is somewhat more than half-transferred from C1 to the amide nitrogen. Li1 is coordinated strongly to the former amide nitrogen and the oxygen anion and only weakly to the former double-bond \(\pi\)-system in the allylic anion-like moiety. Li2 is also coordinated strongly to the oxygen anion but less strongly to the carbanionic C1 carbon and the former amide nitrogen. Possibly repulsion between the proton being transferred and Li2 is the cause for the non-linear arrangement of C1, H and N. This indicates the absence of an agostic effect.

Complete transfer of the proton results in the intermediate C3, which contains a partially developed allylic anionic part. Li1 coordinates to ammonia, the oxygen anion and the \(\pi\)-system of the former double bond of the allylic anion moiety. Li2 on the other hand coordinates only to C1, which has a hybridization intermediate between sp\(^2\) and sp\(^3\), and the oxygen anion.

The pathway C1 to C2 makes use of the activated complex TS2. In this complex the proton is somewhat more than half-transferred from C1 to the nitrogen. The allyl anion is only partially developed in the transition state, as indicated by the hybridization at C1, which is between sp\(^2\) and sp\(^3\), and the longer C1–C2 bond compared with the C2–C3 bond. Both Li1 and Li2 are coordinated strongly with the amide nitrogen. Li1 interacts weakly with the former double bond \(\pi\)-system, and stabilizes the transition state by coordinating strongly to both the carbanionic carbon and the nitrogen. Complete transfer of the proton to the nitrogen results in the intermediate C2 which contains an allylic anionic moiety.

Li1 is coordinated to carbons C1, C2 and C3 as well as to the oxygen, but not to the amine nitrogen. Li2, on the other hand, is only coordinated to the amine nitrogen and the oxygen anion. The intermediate C2 is found to be present on a shallow part of the potential energy surface, and rearranges essentially without any barrier via TS4 to another slightly more stable intermediate C4. Applying corrections for difference in zero-point energy makes TS4 even lower in energy than the reactant C2. The intermediate C4 has a structure similar to that of C2, but in C4 Li2 also coordinates to the allyl anionic carbon C1. At the HF/6-31+G(d) level C2 and C4 could not be separated as two different intermediates.

We have not discovered any direct route from C4 to the rearranged heterodimer C5. However, C4 can easily rearrange to the intermediate C3 by ammonia rearrangement from Li2 to Li1 via transition state TS5. This pathway via C2, TS4, C4 and TS5 to C3 has lower barriers than the direct route from C1 to C3.

The intermediate C3 may rearrange directly via two different parallel one-step reactions making use of the transition states TS6 and TS7 to the heterodimer product C5 as indicated in Scheme 5. In TS6, which has a much higher energy than TS7, the proton is somewhat less than half-transferred from the ammonia nitrogen to the C3 carbanionic carbon, which has a hybridization intermediate between sp\(^2\) and sp\(^3\), and is part of an allylic anion-like moiety. Li1 is, in addition to C1, C2 and C3, coordinated to the amide-like nitrogen and the oxygen anion.

In sharp contrast Li2 is only coordinated to the oxygen anion. This lack of bonding explains the high energy of TS6. It is noteworthy that the proton transfer is not facilitated by Li coordination to C3 and N, between which the proton is being transferred, as it is in TS2 and TS3. Despite this the C3–H–N arrangement appears to be non-linear.

The other pathway to C5 is via TS7 and this activated complex has considerably lower energy than TS6. In TS7 the proton in flight is close to being half-transferred from coordinated ammonia to C3. The arrangement of the amide-like nitrogen, the proton and the carbanionic C3, which has a hybridization intermediate between sp\(^2\) and sp\(^3\), is close to linear. Li1 only coordinates to the amide nitrogen and the oxygen anion. Li2 on the other hand
Scheme 5. Calculated mechanism for the formation of the homoallylic alkoxide C5 from the allylic alkoxide C1. Energies of structures and bond distances are also displayed.

coordinates preferentially to C1 in the allylic anion-like moiety and the oxyanion, less strongly to C2, only weakly to C3, and not to the amide nitrogen. TS7 is the rate-limiting transition state in the rearrangement of C1 to C5. The calculated activation barriers for the isomerization are higher than the experimentally observed ones. Preliminary calculations, including solvation, indicate larger stabilization of the transition states than the initial state heterodimer complex C1. This lowers the activation barriers.
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References


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