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

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

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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 ($LiNH_2$) (S1) as reactant catalyzing the rearrange-

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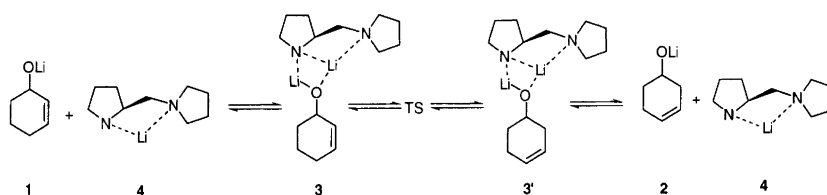
Scheme 1. Isomerization of the allylic alkoxide **1** to the homoallylic alkoxide **2** within the heterodimer complex **3** catalyzed by the chiral lithium amide **4**.

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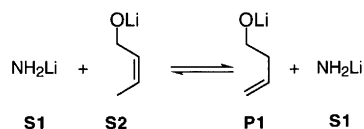
Scheme 2. Model system for the computational study of the isomerization of an allylic alkoxide (**S2**) into a homoallylic alkoxide (**P1**) catalyzed by a lithium amide (**S1**).

+G(d) levels, and also corrected for differences in zero point energy, ΔZPE. Test calculations with the addition of diffuse and polarization functions on hydrogens gave no significant changes in structures or relative energies, confirming a previous study on a similar system.[10] Generally in the text, referred relative energies (kcal mol^{-1}), and bond distances (Å) are calculated at B3LYP/6-31+G(d)//B3LYP/6-31+G(d)+ΔZPE level. All heterodimeric complexes were found to have very low lying vibrational modes. As previously described,[11] relative energies are considered to be less affected by this error. Calculated relative energies of optimized minima and transition state structures are given in Table 1.

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 slighly 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})].

Compound	PM3	HF/6-31+G(d)	MP2/6-31+G(d)	B3LYP/6-31+G(d)	ZPE[a]
S1+S2	53.3	61.9	65.2	60.6	14.7+64.8(0)
P1+S1	58.2	59.9	62.1	57.9	14.7+64.9(0)
C1	0.0	0.0	0.0	0.0	82.3(0)
C2	21.4	29.1[b]	23.4[b]	26.4	82.6(0)
C3	20.3	30.2	23.9	25.6	82.1(0)
C4	21.4	29.1[b]	23.4[b]	24.4	82.4(0)
C5	−2.2	−1.4	−3.8	−0.8	81.9 (0)
TS1	79.6	103.5	84.3	82.3	78.4(1)
TS2	47.4	49.0	33.9	33.2	79.7(1)
TS3	46.2	49.5	35.7	35.2	79.3(1)
TS4	29.1	—[b]	—[b]	26.2	82.2(1)
TS5	26.8	38.0	30.8	32.6	82.1(1)
TS6	55.7	66.4	50.8	51.3	78.7(1)
TS7	47.7	54.8	38.9	37.8	79.0(1)

[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.
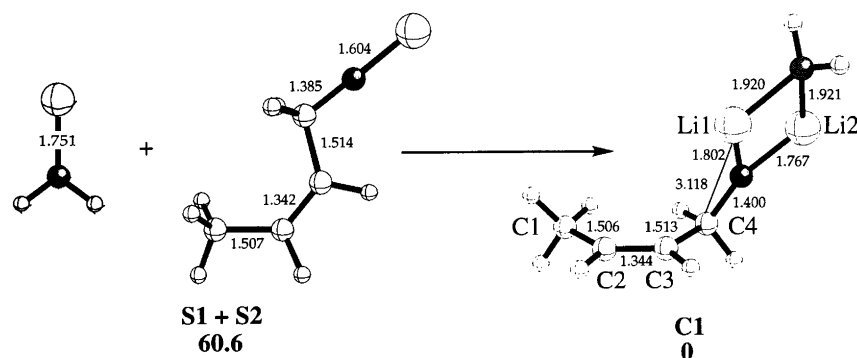
Scheme 3. Complexation of lithium amide (**S1**) and the lithium alkoxide **S2** yielding the heterodimer complex **C1**.

C1   TS1   C5
0   82.3   -0.8
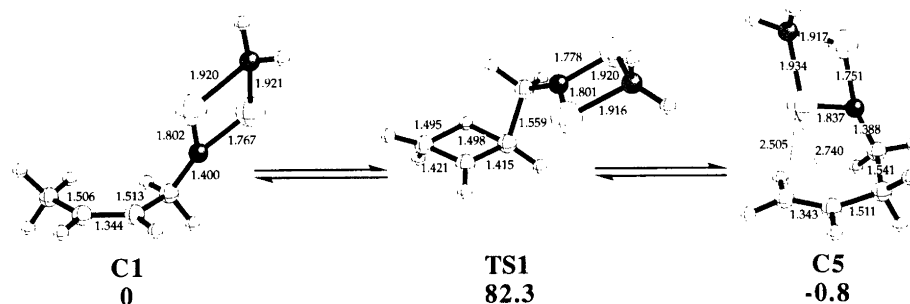
Scheme 4. Concerted 1,3-hydrogen shift via **TS1**.

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 amidic nitrogen. Li1 is coordinated strongly to the former amidic nitrogen and the oxyanion and only weakly to the former double-bond π-system in the allylic anion-like moiety. Li2 is also coordinated strongly to the oxyanion but less strongly to the carbanionic C1 carbon and the former amidic 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 oxyanion and the π-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 oxyanion.

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 π-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 amidic-like nitrogen and the oxyanion. In sharp contrast Li2 is only coordinated to the oxyanion. 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 amidic nitrogen and the oxyanion. Li2 on the other hand
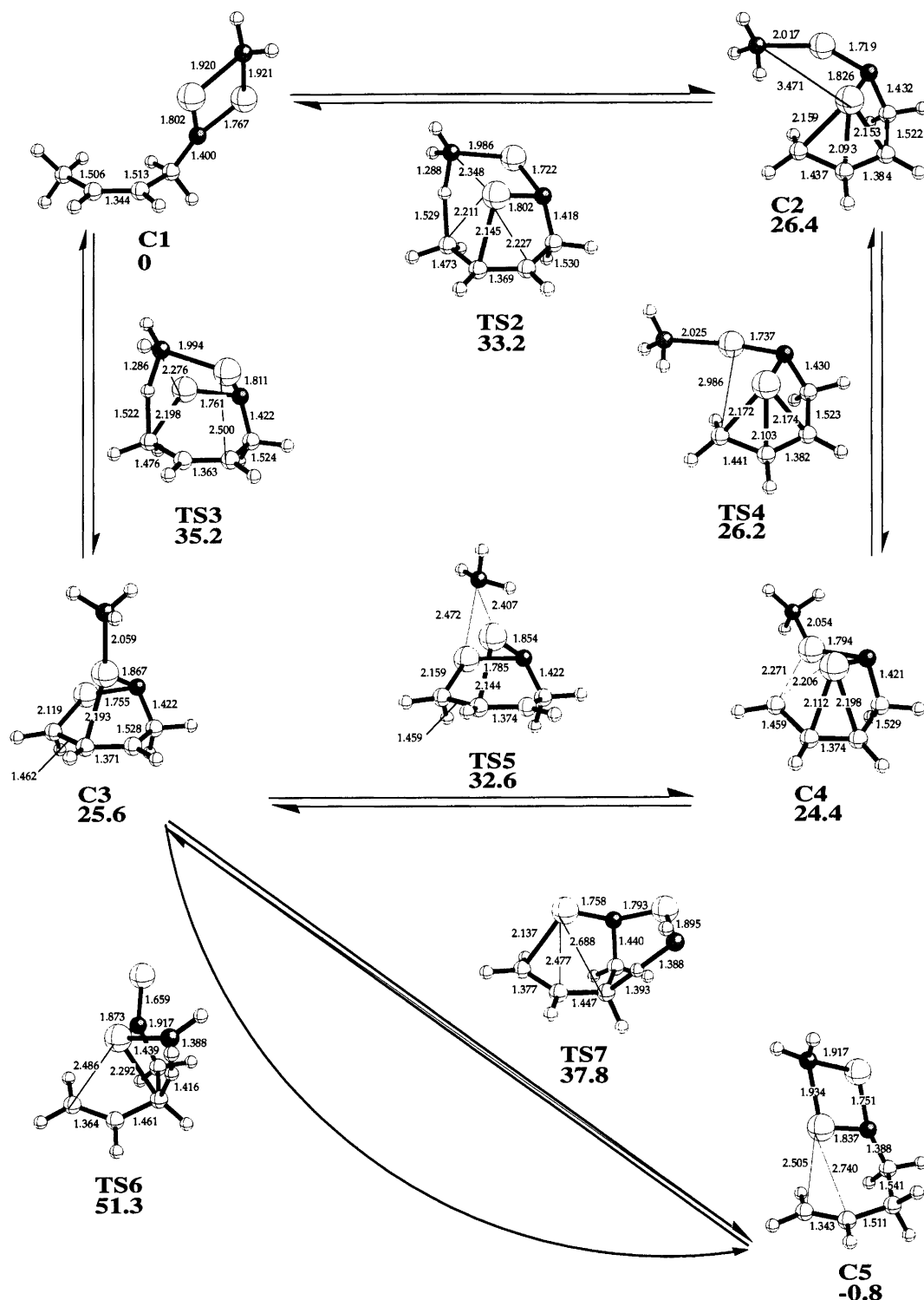
Scheme 5. Calculated mechanism for the formation of the homoallylic alkoxide **C5** from the allylic alkoxide **C1**. Energies of structures and bond distances are also displayed.

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 amidic 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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