Transition States and Activation Barriers for [3,3]-Sigmatropic Shift of Allyl Azides

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Abstract
CBS-QB3 and density functional theory studies of the [3,3]-sigmatropic rearrangements of several allylic azides indicate that this reaction is a concerted process that proceeds via a half-chair transition state. The activation barriers for rearrangements of hydroxyl azides are lower than those of the corresponding aliphatic azides. The epoxidations and phenyl azide cycloadditions of allylic azides were also studied.

Keywords: Azide, [3,3]-sigmatropic rearrangement, cycloaddition, DFT

1. Introduction
Since the first report of the Claisen rearrangement, numerous hetero [3,3]-sigmatropic rearrangements have been observed. An early study by Gagneux, Winstein and Young indicated that allylic azides can equilibrate to form a mixture of regio isomers. Either \( \alpha \)- or \( \gamma \)-methallyl azide rapidly generate an equilibrium mixture of the two isomers. The rates and equilibrium constants of the rearrangement were measured. Three mechanisms can be envisioned: (1) a concerted pericyclic [3,3]-sigmatropic rearrangement, (2) a dissociative process involving radical pair or ion-pair formation, or (3) an associative pathway through a diradical (Scheme 1). These mechanisms have been explored for a variety of Claisen and Cope process.

Winstein and co-workers demonstrated that the rates of the rearrangement increase only slightly with an increased solvent polarity. In addition, the rearrangements exhibit negative entropies of activation which point to covalent bonding in the transition state. These observations are indicative of very little charge separation in the transition state, and it has been generally assumed that the equilibration occurs via a cyclic transition state. The effect of pressure on the equilibration of \( \alpha \)- and \( \gamma \)-methylallyl azide was reported by le Noble. The rearrangement was assumed to occur through a cyclic transition state. Several experimental examples of allylic azide isomerization which support this notion.

Recently Sharpless \textit{et al.} have reported selectivity in the trapping of equilibrating allylic azides. When mixtures were submitted to cycloadditions with phenylacetylene in presence of copper as catalyst (Figure 1), or
epoxidation with MCPBA, different products were trapped. Since both steric and electronic effects can influence reactivity of azides and olefins, they studied different allylic azides. They noticed in hydroxylated allyl azides the OH group could significantly modulate the equilibrium in these dynamic systems.

**Scheme 1**

**Primary vs Secondary Azides**

\[
\begin{align*}
X=H & \quad 2a, 67\% \\
X=OH & \quad 3a, 45\%
\end{align*}
\]

\[
\begin{align*}
X=H & \quad 2b, 33\% \\
X=OH & \quad 3b, 55\%
\end{align*}
\]

**Primary vs Tertiary Azides**

\[
\begin{align*}
X=H & \quad 4a, 70\% \\
X=OH & \quad 5a, 55\% \\
& \quad (47\% \text{ trans}, 8\% \text{ cis})
\end{align*}
\]

\[
\begin{align*}
X=H & \quad 4b, 30\% \\
X=OH & \quad 5b, 45\% \\
& \quad (91\% \text{ trans}, 9\% \text{ cis})
\end{align*}
\]

**Secondary vs Tertiary Azides**

\[
\begin{align*}
X=H & \quad 6a, 65\% \\
X=OH & \quad 7a, 82\%
\end{align*}
\]

\[
\begin{align*}
X=H & \quad 6b, 35\% \\
X=OH & \quad 7b, 18\% \\
& \quad (32\% \text{ trans}, 3\% \text{ cis})
\end{align*}
\]

(cis not detected)

**Figure 1.** The allylic azide rearrangements and catalytic cycloaddition of allylic azides with phenylacetylene.
Density functional theory has been used to describe the mechanism of the allylic azide rearrangement, as well as competition with azide-alkyne cycloadditions\textsuperscript{12} and epoxidations of 2a and 2b.\textsuperscript{13} The influence of steric and electronic effects on reactivity for parent aliphatic azides and their closely related hydroxylated derivatives were also explored.

2. Computational Methods

All calculations were performed with Gaussian 03.\textsuperscript{14} The hybrid B3LYP functional\textsuperscript{15} in conjunction with the 6-31G(d) basis set\textsuperscript{16} was used for the optimization of all of the stationary points in the gas phase. Frequency calculations were used to characterize all of these as minima or first-order saddle points. All reactions and activation enthalpies reported were zero-point energy (ZPE) corrected with unscaled frequencies. IRC calculations\textsuperscript{17} were used to confirm the connections between the reactants, products and transition states. High accuracy CBS-QB3\textsuperscript{18} calculation were also carried out for small systems.

3. Results and Discussion

The possible pathways have been computed for the simplified allylic azide rearrangement. DFT calculations confirm that the allylic azide rearrangement proceeds through a six-centered half-chair transition state. The activation barrier for the allylic transformation in 1a is 22.6 kcal/mol. The heterolytic process requires 50 kcal/mol. No transition state corresponding to diradical formation could be found. Both CBS-QB3 and DFT calculations predict the same activation barrier. Figure 2 shows the transition structure TS1 for the [3,3]-sigmatropic shift 1a. Bond distances for the developing and breaking bonds in the transition structure are 2.06 Å.

![Figure 2](image-url)

**Figure 2.** Calculated transition structure TS1 for allylic azide rearrangement of 1a. Bond lengths and relative enthalpies are in Å and kcal/mol. The value in parenthesis is the CBS-QB3 result.

3.1. Primary vs. secondary azides

The reaction profiles for allylic azide rearrangements of cis and trans isomers of 1-azidobut-2-ene 2 is shown in Figure 3. The activation barriers for interconversion of trans-2a and cis-2a to corresponding secondary azides 2b and 2b-1 are 21.5 and 21.6 (difference between 24.4 and 1.9 for cis isomer) kcal/mol, respectively. Both reactions are endothermic by 0.9 and 1.4 kcal/mol. The endothermicity of the reactions is the result of increased steric interaction in secondary azides in comparison to primary azides, especially in 2b-1.

The electronic effects on allylic azide rearrangement were also studied by substituting one of the hydrogen of the methyl group by a hydroxyl group. Hydroxyl azide trans-3a is more stable than cis-3a by 1.4 kcal/mol. The
activation barriers for allylic azide rearrangements of trans-3a and cis-3a are 20.0 and 20.9 (differences between 24.4 and 1.9) kcal/mol respectively. The lower activation barrier in the case of hydroxylated derivative TS3 in contrast to parent system TS2 can be explained by the formation of an internal hydrogen bond which stabilizes the transition structures. The stationary points for azide rearrangement of hydroxylated derivative 3 is shown in Figure 5. Both isomerization of trans-3a and cis-3a are exothermic (because of stronger hydrogen bonds in 3b and 3b-1).

The B3LYP/6-31G* calculations underestimates the relative enthalpies of 3b in compare to CBS-QB3 (-1.1 kcal/mol). Calculations indicate that about 83% of azides is in primary form for the parent system 2a. In comparison more than 99% of azides belongs to secondary isomer in the hydroxylated derivative. Both experiment
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Equations 1-3 were used to explore the origin of the relative stability of primary allylic azides trans-2a and 3a over secondary azides 2b and 3b. The relative enthalpies of the isomer point out that the position of the double bond is the key factor that determines the stability of primary azides. But the internal hydrogen bonding can alters the ratio.

\[
\begin{align*}
0.0 & \rightleftharpoons 5.3 \\
0.0 & \rightleftharpoons 4.1 \\
0.0 & \rightleftharpoons 2.1 
\end{align*}
\]

To study the reactivity of isomerization of allylic azides 2a and 2b in compare to cycloaddition of azides with terminal alkynes such as phenylacetylene and epoxidation of alkene with a peracid (HCO₃H) further calculations were performed to locate their transition states (Figure 6 and 7). The activation barriers for the concerted reaction of trans-2a and 2b with phenylacetylene leading corresponding 1,2,3-triazole were found to be 20.4 and 21.3 kcal/mol (relative to 2b), respectively. The lowest energy optimized transition structures for cycloaddition reactions (TSc1 and TSc2) are shown in Figure 7. Both reactions are highly exothermic. In 2004, Sharpless et al. performed a DFT study to revealed the mechanistic pathway of catalytic azide-alkyne cycloaddition. They reported that the dramatic rate increase observed in the copper-catalyzed synthesis of 1,2,3-

**Figure 6.** Relative enthalpies for cycloaddition and epoxidation reactions of trans-2a and 2b in presence of phenylacetylene and performic acid. Energies are in kcal/mol.

triazoles in the reaction of methylacetylene with methyl azide. They calculated the activation barrier is 11 kcal/mol.
lower than in the corresponding uncatalyzed concerted cycloaddition reaction. The transition states and activation energies are shown in Figure 7. The activation energies for the transformation trans-2a and 2b to their corresponding products are 8.8 and 10.3 kcal/mol, respectively, which is substantially lower than the activation enthalpies for isomerization. The transition structure for the epoxidation of trans-2a is highly synchronous and the C-O bonds formations distances are almost 2.06 Å.

![Transition states](image)

Figure 7. Computed transition states of reactions of 2a and 3a with phenylacetylene and performic acid. Relative enthalpies and bond lengths are in kcal/mol and Å.

3.2. Primary vs tertiary azides.

Figure 8 shows the stationary points for isomerization of primary azide 4a to tertiary azide 4b. The activation

![Reaction profile](image)

Figure 8. Reaction profile for allylic azide rearrangements of 4a. Relative enthalpies and bond lengths are in kcal/mol and Å.
enthalpy for rearrangement of primary azide 4a to tertiary azide 4b is 22 kcal/mol. The secondary azide 4b is 2.4 kcal/mol higher in energy than 4b. In the hydroxylated derivative 5a, the two isomers cis and trans have the same stability and each one constitute 50% of all the existing isomers in gas phase. This fact can be attributed to the strong internal hydrogen bond between OH and N in cis isomer. The rearrangement of both cis and trans isomers need the same activation barrier (19.5 kcal/mol). Transition structure trans-TS5 gives the major product 5b-1, it is 1.7 kcal/mol less in energy than other isomeric form 5b-2.

![Diagram](image)

**Figure 9.** Calculated stationary points for allylic azide rearrangements of cis and trans-5a. Relative enthalpies and bond lengths are in kcal/mol and Å.

### 3.3. Secondary vs tertiary azides.

A similar study was carried out to locate the transition states of allylic azide rearrangement of secondary azide 6a and its hydroxylated derivative 7a to their corresponding trans tertiary azides 6b and 7b. The rearrangement of 6a and 7a are predicted to have the same activation enthalpies (20.2 kcal/mol). Figure 10 and 11 displays the calculated stationary points involved in the isomerization of 6a to trans-6b and 7a to 7b, respectively. The reaction enthalpies are 1.2 and 3.7 kcal/mol, respectively. The larger relative stabilization of the reactant by the hydroxyl substituant in 7a as compared to the product is the result of strong internal hydrogen bonding between the hydroxyl group and

![Diagram](image)

**Figure 10.** Reaction profile for allylic azide rearrangements of 6a. Relative enthalpies and bond lengths are in kcal/mol and Å.
Figure 11. Calculated stationary points for allylic azide rearrangements of 7a. Relative enthalpies and bond lengths are in kcal/mol and Å.

nitrogen. The thermodynamic for both reactions indicate that secondary azides are favored over tertiary azides. In addition, the most stable isomers in both aliphatic and hydroxylated systems (6a and 7a), respectively account for 88% and 99% of all possible isomers.

4. Conclusions

Here, we have used CBS-QB3 and B3LYP density functional calculations to investigate the mechanism of the allylic azide rearrangement. The concerted reaction is highly favored and reactions proceeds through a six-centered half-chair transition state. The conversion of primary aliphatic azides to corresponding secondary or tertiary azides requires about 22 kcal/mol, this is about 2 kcal/mol than the activation enthalpy required for the isomerization of secondary azide 6a to tertiary azide 6b. All of these reactions are endothermic. The stability of aliphatic azides follows in the order decreased stability primary> secondary>tertiary. The hydroxyl group facilitates the rearrangement by about more than 2 kcal/mol except for rearrangement of secondary azide 7a to tertiary azide 7b (0.3 kcal/mol). The trend of stability of hydroxylated allylic azides are not similar to aliphatic ones and the secondary azides are stable than primary isomers.

References and Notes