

## New Paradigm for Anionic Heteroatom Cope Rearrangements

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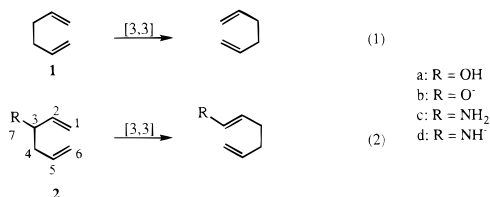
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[3,3]-Sigmatropic rearrangements such as the Cope rearrangement (eq 1) are reactions of synthetic and mechanistic importance.<sup>1</sup> This type of rearrangement is now generally considered to be concerted, after a long debate.<sup>2</sup> The oxy-Cope rearrangement (eq 2a) is a particularly synthetically useful analog of the Cope rearrangement.<sup>3</sup> Deprotonation of the hydroxy group in 3-hydroxy-1,5-hexadienes (eq 2b) results in an astounding rate acceleration of  $10^{10}$ – $10^{17}$ .<sup>4</sup> The anion-accelerated oxy-Cope rearrangement has been used in many natural product syntheses.<sup>5</sup>



Similar acceleration might be observed upon conversion of a 3-amino group<sup>6</sup> to an anion (eqs 2c,d), but there is only one report of an anion-accelerated amino-Cope rearrangement.<sup>7</sup> During a study to determine the stereochemistry of addition of allyl groups to  $\pi$ -systems, we prepared the *N*-allyl *N*-substituted amines **3**–**7** containing a chiral auxiliary<sup>8</sup> (see Supporting Information). Amide anions gave no rearranged products, but only dissociated and/or recombined addition products, or simply unreacted starting materials (Table 1). In one instance, the replacement of allyl for butyl in **4** (Table 1) was 98% complete.

A well-accepted model which explains the rapidity of the anionic oxy-Cope rearrangement gives no clue as to the origin of the failure of the anionic amino-Cope rearrangement. Evans and Baillargeon proposed that the substantial acceleration is related to the bond-weakening effect of the anionic alkoxy group on the adjacent C3–C4 bond.<sup>9a</sup> Steigerwald and Goddard used GVB theory to calculate the C–H bond strengths in methanol and methoxide.<sup>9b</sup> A 16.5 kcal/mol weakening of the C–H bond in methoxide was calculated, and the effect is large even in ion-

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**Table 1.** Attempted Anion-Accelerated Cope Rearrangements of 3-Amino-1,5-hexadiene Derivatives<sup>8</sup>

	conditions	results
<b>3</b>	KH/toluene, reflux overnight, MeI quench KH/DMF, RT, H <sup>+</sup>	no reaction deallylated imine
<b>4</b>	KH/toluene, RT, overnight <sup>t</sup> BuLi/THF, -78 → 0 °C	no reaction butyl addition product <sup>a</sup>
<b>5</b>	KH/toluene, RT → reflux <sup>t</sup> BuLi/THF, -78 °C → RT	no reaction deallylated imine
<b>6</b>	KH/toluene, RT → reflux <sup>t</sup> BuLi/THF, -78 °C → RT	no reaction decomposition
<b>7</b>	KH/toluene, RT → reflux <sup>t</sup> BuLi/THF, -78 °C → RT	no reaction no reaction

<sup>a</sup> Addition of 4 equiv of BuLi to the C=N link of **4** as determined by <sup>1</sup>H and <sup>13</sup>C NMR.

**Table 2.** Calculated Bond Dissociation Energies (BDE) at the UBecke3LYP/6-31+G\* Level

value	calcd <i>E</i> (kcal/mol)
BDE[H–CH <sub>2</sub> OH]	101.6
BDE[H–CH <sub>2</sub> O <sup>-</sup> ]	78.7
BDE[H–CH <sub>2</sub> OH] – BDE[H–CH <sub>2</sub> O <sup>-</sup> ]	<b>22.9</b>
BDE[H–CH <sub>2</sub> NH <sub>2</sub> ]	97.8
BDE[H–CH <sub>2</sub> NH <sup>-</sup> ]	73.2
BDE[H–CH <sub>2</sub> NH <sub>2</sub> ] – BDE[H–CH <sub>2</sub> NH <sup>-</sup> ]	<b>24.6</b>

paired systems; this theory has been widely accepted.<sup>9</sup> In an attempt to apply the theoretical model to the anionic amino-Cope rearrangement, we calculated the bond-weakening effect of methyl amide versus methylamine (Table 2). Calculations at the UBecke3LYP/6-31+G\* level<sup>10</sup> indicated that the bond-weakening effect of an NH<sup>-</sup> should be entirely comparable to that provided by O<sup>-</sup> (24.6 vs 22.9 kcal/mol), in spite of the experimental results for the amino-Cope rearrangement.

The divergent behavior of the oxy-anion and amino-anion was investigated with density functional (B3LYP/6-31+G\*) and MP2/6-31+G\* ab initio calculations.<sup>11</sup>

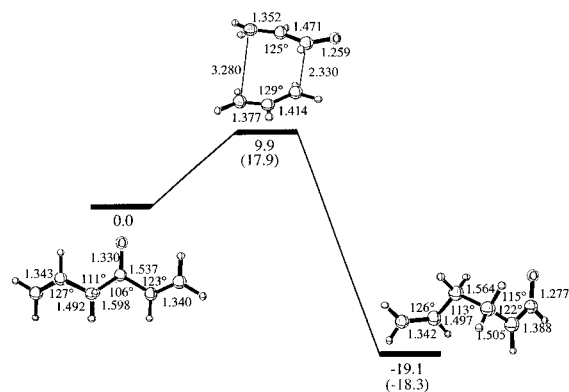
Figure 1 shows the stationary points found for the anionic oxy-Cope rearrangement. The reaction proceeds via a concerted pathway, with an activation energy of 9.9 kcal/mol. The overall reaction is 19 kcal/mol exothermic. The transition structure is quite early and dissociative; an intrinsic reaction coordinate calculation indicates no intermediates. The anionic amino-Cope substrate has an unexpectedly different energy surface (Figure 2), and proceeds via a stepwise mechanism. The initial barrier to reaction is 7.4 kcal/mol and leads to intermediate **9**, a complex of allyl anion and acrolein imine. The ion molecule complex, **9**, then recombines to form the rearranged product in an exothermic reaction (–21 kcal/mol).<sup>11</sup>

To further validate the results found at the B3LYP level, we mapped the energy surface at the RHF/6-31+G\* level and calculated energies at the MP2/6-31+G\* level. The energetics correlate with the B3LYP results (Figures 1 and 2), yielding a

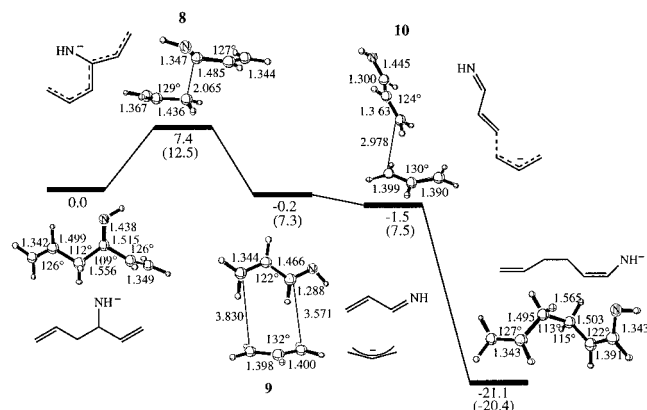
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**Figure 1.** Energies and structures of stationary points for the reaction of 3-O<sup>-</sup> 1,5-hexadiene at the Becke3LYP/6-31+G\* level. MP2/6-31+G\*/6-31+G\* energies are given in parentheses. Energies are in kcal/mol.



**Figure 2.** Energies and structures of stationary points for the reaction of 3-NH<sup>-</sup> 1,5-hexadiene at the Becke3LYP/6-31+G\* level.

concerted mechanism for the anionic oxy-Cope but a stepwise mechanism for the anionic amino-Cope.

In the anionic oxy case, one would expect the substrate to proceed to the rearranged product,<sup>12</sup> which is observed in solution and in the gas phase.<sup>13</sup> The anionic amino substrate, however, exhibits different behavior, unexpected in light of the Evans–Goddard (EG) model. Our calculations for the gas phase indicate the anionic amino substrate would probably proceed to the rearranged product in the absence of solvent, albeit via a stepwise pathway involving an amino-molecule complex intermediate. In solution, however, we would expect intermediate **9** to be substantially stabilized and dissociated, since **9** is an allyl anion weakly bound to acrolein imine. Therefore, the intrinsic stepwise pathway of the anionic amino substrate leads to dissociation rather than rearrangement in solution. Experimental results are in accord; anionic oxy-Cope substrates yield rearranged products, while anionic amino-Cope substrates usually yield dissociated products.<sup>8,13,14</sup> The rare amino substrates which do rearrange are bicyclic species which cannot dissociate and are restrained geometrically to recombine after the first step.<sup>7</sup>

Is there a simple model that can be used to understand and predict both acceleration and cleavage? The EG hypothesis is that the reactions are concerted but facilitated by weakening bond strength. Our calculations show that this assumption cannot be made for all anionic [3,3] sigmatropic rearrangements. However, a corollary to the EG model results in a new paradigm to understand these reactions. The homolysis model provides a

(12) The second transition state, **10**, is lower than **9**, since a lower energy ion–dipole complex is present on the potential surface.

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**Table 3.** Homolytic and Heterolytic Bond Dissociation Energies at the Becke and UBecke3LYP/6-31+G\* Levels (kcal/mol)

reaction	homo	hetero	homo – hetero
BDE [H–CH <sub>2</sub> OH]	101.6		
BDE [H–CH <sub>2</sub> O <sup>-</sup> ]	78.7	41.0 <sup>a</sup>	37.7
BDE [H–CH <sub>2</sub> NH <sub>2</sub> ]	97.8		
BDE [H–CH <sub>2</sub> NH <sup>-</sup> ]	73.2	22.3 <sup>a</sup>	50.9
3-oxy-1,5-hexadiene anion	30.1	27.8	2.3
3-amido-1,5-hexadiene anion	25.7	11.6	14.1

<sup>a</sup> The heat of formation of H<sup>-</sup> is in error by 47.4 kcal/mol, as estimated from the heterolysis of H<sub>2</sub>. This error is most likely due to the self-interaction energy (e.g., Johnson, B. G.; Gonzales, C. A.; Gill, P. M. W.; Pople, J. A. *Chem. Phys. Lett.* **1994**, *221*, 100). 47.4 kcal/mol was subtracted from the computed heterolytic dissociation energies to obtain these values.

reasonable guide to the ease of concerted rearrangements, because the transition states are essentially interacting delocalized radicals; a low homolytic energy leads to a low-energy transition state for the concerted process. The cleavage predicted for the anionic amino-Cope system is, however, heterolytic, and a C–H heterolytic bond cleavage is a valid model for this process. The homolytic and heterolytic bond dissociation energies for methanol, methoxide, methylamine, and methyl amide were calculated at the UB3LYP/6-31+G\* level (Table 3). The results are remarkably close for methanol and methoxide to the Evans–Baillargeon thermochemical estimates in 1978!<sup>9a</sup> In the oxy case, the bond weakening due to homolytic cleavage is 22.9 kcal/mol. The Cope analog undergoes a concerted rearrangement via a transition state resembling two interacting allyl radicals. In the amino case, however, there is an additional 5.5 kcal/mol bond weakening for homolytic bond cleavage, but the heterolytic cleavage is facilitated by 18.7 kcal/mol! Thus, the anionic amino-Cope system cleaves heterolytically.

True to the prediction from the simple model system, calculations on the homolytic and heterolytic cleavage of the 1,5-hexadiene substrates themselves show that heterolytic bond cleavage is much more favored for the anionic amino-Cope case than that for the anionic oxy system (Table 3). The calculated bond dissociation energies predict that heterolytic C3–C4 bond breaking is slightly favored for the anionic oxy system, but this energy difference is expected to reverse upon coordination of the O<sup>-</sup> by solvent or metal cation. There is a much larger preference for heterolysis in the anionic amino-Cope systems. Cleavage should occur in the gas phase or solution. This preference for the heterolytic C3–C4 bond cleavage of the anionic amino-Cope system can be traced to the relatively small electron affinity (EA) of acrolein imine. Acrolein has a small positive EA of 0.03 eV;<sup>14</sup> the EA of acrolein imine is unknown, but the calculated EA of acrolein imine at the UBecke3LYP/6-31+G\* level is an unfavorable –0.33 eV. The oxy anion can undergo homolysis to form the relatively stable acrolein radical anion. With the imine, this process is unfavorable, and heterolysis is more favorable.

Our calculations indicate that anionic oxy-Cope substrates react via a concerted pathway, whereas anionic amino-Cope substrates react via a stepwise heterolytic cleavage pathway. These results establish a new paradigm: homolytic and heterolytic cleavage of simple model molecules can be used to predict whether a substrate will undergo concerted reaction or heterolytic cleavage. Further applications are in progress.

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**Supporting Information Available:** Experimental data for 3–7 (4 pages). See any current masthead page for ordering and Internet access instructions.