

Mechanistic Variations and Rate Effects of Alkoxy and Thioalkoxy Substituents on Anionic Oxy-Cope Rearrangements

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Abstract: The effects of thiomethoxy and methoxy substituents on the rates and the mechanisms of anionic oxy-Cope rearrangements were investigated with density functional theory (B3LYP/6-31+G*). Thiomethoxy substituents at positions C4 or C6 of 3-oxido-1,5-hexadienes cause acceleration and promote heterolytic cleavage rather than concerted rearrangement, and the Cope product is formed via a stepwise pathway. The corresponding methoxy substituents impede heterolytic cleavage and slow the concerted rearrangement.

The enormous acceleration of Cope rearrangements of 3-hydroxy-1,5-hexadienes by deprotonation of the hydroxyl substituent has made the anionic oxy-Cope rearrangement a very useful synthetic transformation.^{1,2} Evans et al. have presented an explanation for this acceleration, based on the weakening of α -bonds in alkoxides.^{3,4} Recently, we showed that the anionic amino-Cope rearrangement proceeds by cleavage–recombination, rather than via a concerted pathway, and frequently the rearrangement does not occur because of competing cleavage. We provided a model to rationalize and differentiate acceleration from cleavage reactions.⁵ We have now studied the effect of substitution of thiomethoxy and methoxy substituents on the rates and the mechanisms of anionic oxy-Cope rearrangements; we have discovered a remarkable difference between these substituents and now provide explanations of a variety of puzzling data in the literature.

Evans et al. found that anionic oxy-Cope rearrangements of 1,5-diene-3-alkoxides with 4-thiophenoxy substituents are subject to a large rate acceleration, but fragmentation can also occur.³ Similar 1,5-diene-3-alkoxides with 4-methoxy substituents rearrange at a much lower rate.^{2,3} One of our groups found that thiophenoxy substituents at the C6 position of bicyclic divinyl carbinols accelerate rearrangements (Figure 1), but alkoxy substituents at the same position cause deceleration.⁶

Macdonald et al. observed anionic amino-Cope rearrangements of **1–3** (Figure 2). However, no product was observed for **4** (Figure 2).⁷ They suggested that a cleavage mechanism followed by an addition reaction are responsible for the product. The Meyers group prepared several N-allyl N-substituted amines and treated them with a strong base. The reactions gave

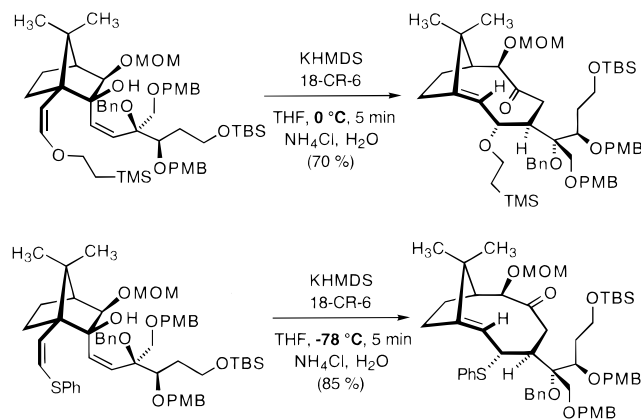


Figure 1. The top figure shows an anionic oxy-Cope rearrangement which occurs at 0 °C. The bottom figure shows a similar anionic oxy-Cope rearrangement with a sulfur substituent at C6. This reaction occurs at –78 °C.

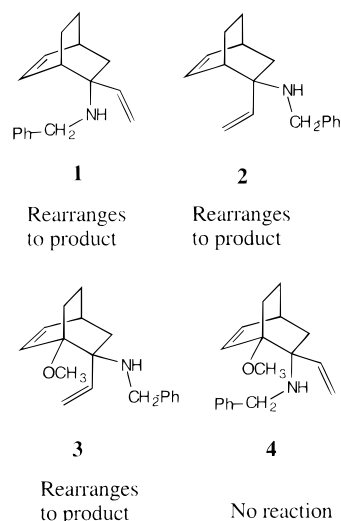


Figure 2. Properties for anionic amino-Cope rearrangements of endo and exo isomers with C4 unsubstituted or methoxy substituted.

dissociated and/or recombined addition products in the presence of THF. However, when the less polar solvent toluene was used,

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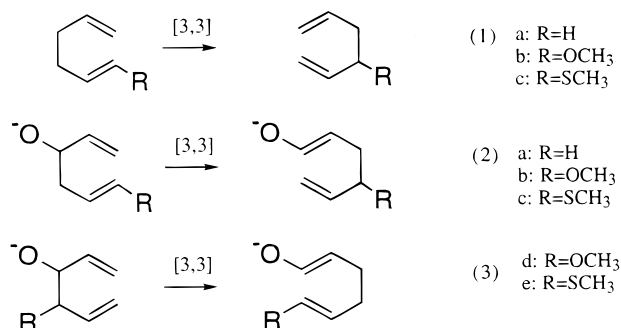
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Scheme 1. Systems Studied Computationally



no reaction occurred, not even at higher reaction temperatures.⁵ In a study by Macdonald et al. a 3-amino-1,5-diene with a thiophenoxy substituent at C4 was treated with strong base at -40°C . Rearranged product was formed when toluene was used as solvent.⁷

We have explored alkoxy and thioalkoxy substituent effects on the anionic oxy-Cope rearrangement, using hybrid density functional theory. Quantum mechanical computations were performed on the systems depicted in Scheme 1.

Computational Methods

All computations were performed with the B3LYP density functional and the 6-31+G* basis set using the Gaussian 94 program.⁸ The optimized stationary points were checked by means of frequency calculations. Unscaled frequencies were used to obtain zero-point energies. The location of global minima of the ground states and the products was guided by previous calculations on the anionic oxy-Cope rearrangement.⁵

Results and Discussion

Neutral and Anionic Oxy-Cope Rearrangements with a Methoxy Substituent at C4 or C6. The optimized geometries and the computed activation energies of the parent Cope rearrangement, previously published,⁹ is shown in Figure 3. The transition state of the parent reaction consists of two interacting delocalized allyl radicals with no charge polarization.⁵ A methoxy substituent at C6 does not change the transition-state geometry significantly and the activation energy changes very little.

By contrast, the anionic oxy-Cope rearrangement is very exothermic with an early transition state (Figure 4), constituting a weakly interacting acrolein and allyl anion.⁵ In the anionic oxy-Cope rearrangement, a methoxy substituent at either C4 or C6 has a significant effect on the transition-state geometry and the activation energy (Figures 5–7). The C3–C4 bond length stretches from 2.326 Å in the anionic oxy-Cope transition state (Figure 4) to 2.468 Å (C4 equatorial) (Figure 6) and 2.471 Å (C6) (Figure 7). The corresponding C1–C6 bond lengths shorten from 3.284 Å (anionic oxy-Cope) to 3.198 Å (C4 equatorial) and 3.066 Å (C6). The activation energy increases from 8.3 kcal/mol to 8.4 and 12.0 kcal/mol, respectively (Table 1). When the methoxy substituent at C4 is positioned in an axial

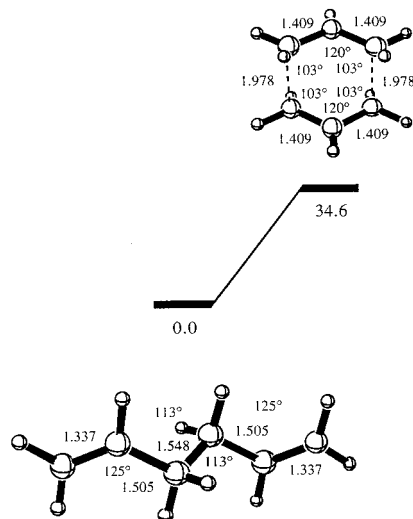


Figure 3. Stationary points located and geometry optimized of the Cope rearrangement using B3LYP/6-31+G* (previously published^{5,10}). Zero-point energies are included.

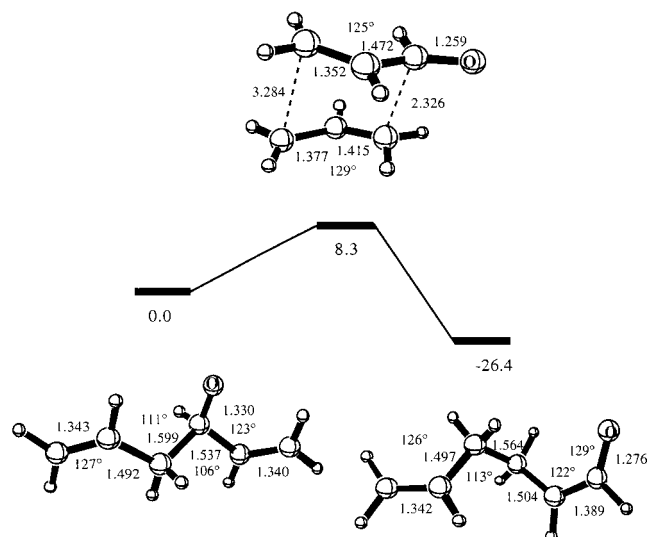


Figure 4. Stationary points located and geometry optimized of the anionic oxy-Cope rearrangement using B3LYP/6-31+G* (previously published^{5,10}). Zero-point energies are included.

orientation (Figure 5), the C1–C6 bond is also 0.1 Å longer than the corresponding bond in the anionic oxy-Cope rearrangement, while the difference in the C3–C4 bond length is very small. The activation energy of the C4 methoxy-substituted (axial) anionic oxy-Cope rearrangement is 9.3 kcal/mol.

The results from the computations indicate that methoxy substituents at C4 and C6 slow the anionic oxy-Cope rearrangement. The intrinsic reaction coordinate (IRC) calculation shows that anionic oxy-Cope rearrangements with a methoxy substituent at C6 follow a concerted asynchronous mechanism; as with the parent anionic oxy-Cope, the transition state is nearly dissociative but is not an energy minimum.

Neutral and Oxy-Cope Rearrangements with a Thiomethoxy Substituent at C4 or C6. A thiomethoxy substituent at C6 has a small effect on the neutral Cope rearrangement, increasing the activation barrier from 34.6 kcal/mol to 37.4 kcal/mol. In the anionic oxy-Cope rearrangement, however, a dramatic change occurs. Early and asynchronous chair transition states were located and geometry optimized with C3–C4 bond lengths of 2.110 Å (the thiomethoxy substituent at C4, equatorial position (Figure 8)), 2.033 Å (the thiomethoxy substituent at

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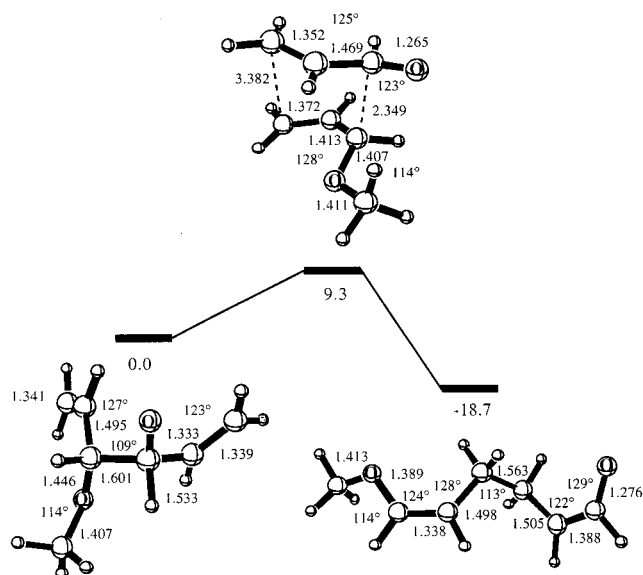


Figure 5. Stationary points located and geometry optimized of the anionic oxy-Cope rearrangement with a methoxy substituent at C4 (axial position) using B3LYP/6-31+G*. Zero-point energies are included.

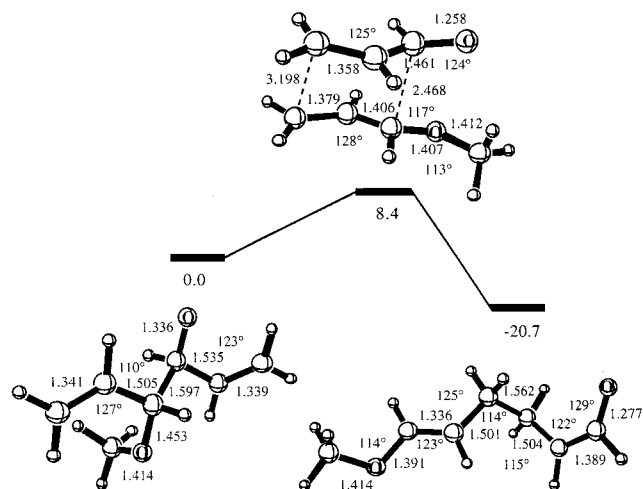


Figure 6. Stationary points located and geometry optimized of the anionic oxy-Cope rearrangement with a methoxy substituent at C4 (equatorial position) using B3LYP/6-31+G*. Zero-point energies are included.

C4, axial position (Figure 9)), 2.100 Å (the thiomethoxy substituent at C6) (Figure 10). The activation energies decrease from 8.3 kcal/mol for the parent anionic oxy-Cope rearrangement, to 5–6 kcal/mol for 4- or 6-thiomethoxy-substituted cases (Table 1). The forming bond length is 3.5 Å, so long that it is unlikely there is any significant interaction between the termini. Indeed, conformational isomers of these transition states were found for both the 4- and 6-thiomethoxy cases. These are essentially the same in energy and lead to acrolein plus the thiomethoxyallyl anion. These transition state structures are also shown in Figures 8–10. This demonstrates that cleavage is likely with thiomethoxy substituents. Thus, the thiomethoxy substituent stimulates cleavage and stabilizes the thiomethoxy allyl anion.

The intrinsic reaction coordinate (IRC) calculation shows for the anionic oxy-Cope rearrangement with a thiomethoxy substituent at C6 that a concerted mechanism is followed; despite the absence of an intermediate, the reaction is completely asynchronous: the C3–C4 bond cleaves, and subsequently, the C1–C6 bond is formed. The reason the IRC calculation suggests a concerted mechanism is that the energy barrier for recombina-

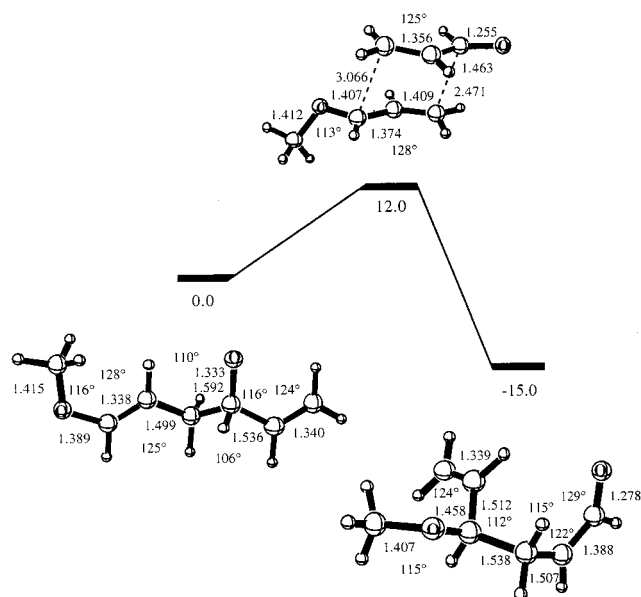


Figure 7. Stationary points located and geometry optimized of the anionic oxy-Cope rearrangement with a methoxy substituent at C6 using B3LYP/6-31+G*. Zero-point energies are included.

Table 1. Computed Energies of Activation of the Anionic Oxy-Cope Rearrangements with Methoxy and Thiomethoxy Substituents at C4 and C6^a

reactant	transition state		product rearrangement
	rearrangement	cleavage	
6-SMe	5.0	4.6	-13.1
4-SMe SYN	5.6	6.0	-25.4
4-SMe ANTI	5.3	5.0	-20.9
6-OMe	12.0		-15.0
4-OMe SYN	9.3		-18.7
4-OMe ANTI	8.4		-20.7

^a The energies are relative to the methoxy- and thiomethoxy-substituted 3-oxido-1,5-hexadienes and are computed with B3LYP/6-31+G*. Zero-point energies are included (kcal/mol).

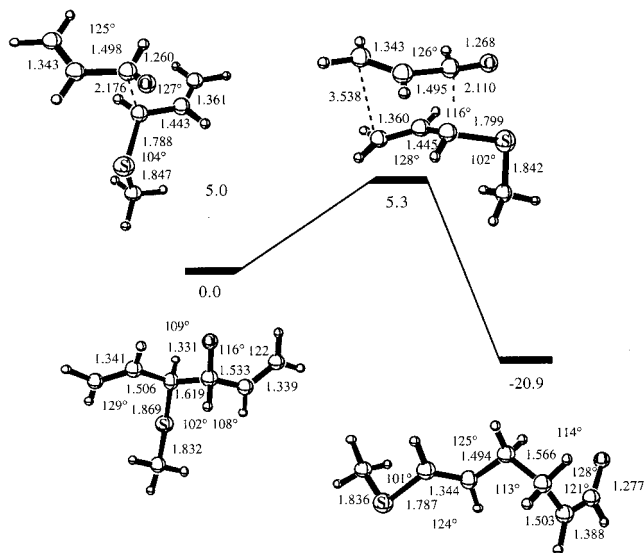


Figure 8. Stationary points located for the anionic oxy-Cope rearrangement with a thiomethoxy substituent at C4 (equatorial position) and geometry optimized with B3LYP/6-31+G*. Zero-point energies are included.

tion of the allyl anion and thiomethoxyacrolein is negligible. Thus, the cyclic and the cleavage transition states found are conformers which react according to a cleavage mechanism.

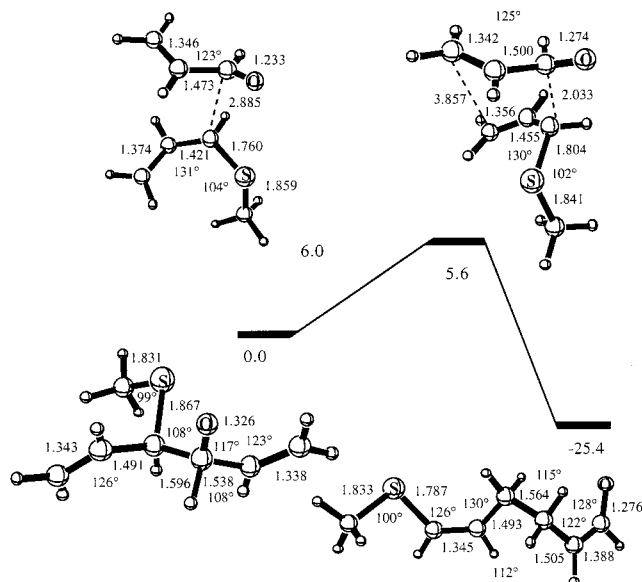


Figure 9. Stationary points located for the anionic oxy-Cope rearrangement with a thiomethoxy substituent at C4 (axial position) and geometry optimized with B3LYP/6-31+G*. Zero-point energies are included.

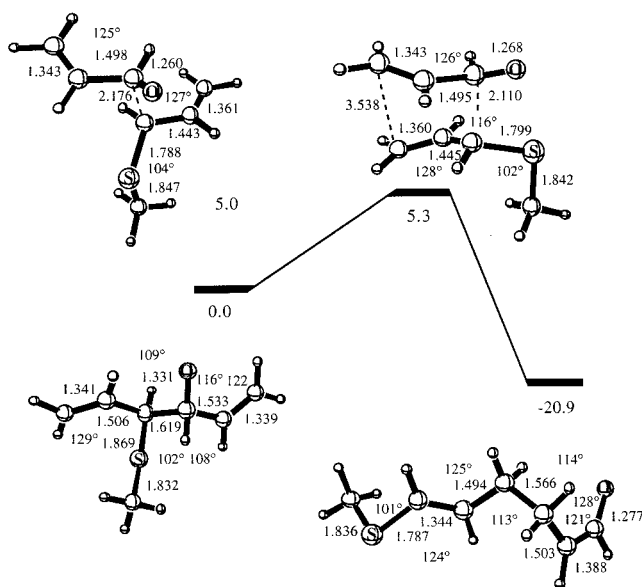


Figure 10. Stationary points located for the anionic oxy-Cope rearrangement with a thiomethoxy substituent at C6 and geometry optimized with B3LYP/6-31+G*. Zero-point energies are included.

No transition states involving cleavage could be found for the parent, the anionic oxy-Cope rearrangement, or its methoxy-substituted counterparts.

Stabilization of Anions and Radicals by Hydroxy and Thiol Substituents. To assess the substituent effects on radical and anionic stabilization, B3LYP/6-31+G* calculations were used to compute heterolytic and homolytic bond dissociation energies of H-CH₂OH and H-CH₂SH. The reactions are given in Table 2. Schleyer et al. studied a similar system, with RHF and MP2 calculations.¹⁰ The thiol substituent stabilizes the methyl anion by 19.0 kcal/mol, while the hydroxy substituent stabilizes the methyl anion by only 3.9 kcal/mol. These

Table 2. Computed Homolytic and Heterolytic Bond Dissociation Energies for the Formation of Hydroxy- and Thiol-Substituted Methyl Radicals and Anions, and Methoxy- and Thiomethoxy-Substituted Allyl Radicals and Anions^a

reaction	radical	anion
H-CH ₂ OH	-5.6	-3.9
H-CH ₂ SH	-4.3	-19.0
1-methoxypropene	-2.4	3.1
3-methoxypropene	-8.0	-2.4
1-thiomethoxypropene	-2.9	-13.5
3-thiomethoxypropene	-6.0	-16.6

^a The energies are relative to the homolytic and heterolytic bond dissociation energies of methane and propene. Zero-point energies are included (kcal/mol).

substituents stabilize the methyl radical by 4.3 and 5.6 kcal/mol, respectively, below that of methane.

The computations show that thiol and hydroxy substituents stabilize methyl anions and methyl radicals. The thiol substituent, however, stabilizes the anion to a much higher extent than the hydroxy substituent does. The large stabilizing effect by the RS substituent is caused by polarizability of the SR bond.¹⁰ The hydroxy substituent stabilizes the methyl radical slightly more than the thiol substituent does.

Calculations were also applied to the heterolytic and homolytic bond dissociation energies of propene and substituted propenes to form the corresponding allyl anions and radicals. The reactions are given in Table 2. The formation of the 1-thiomethoxy allyl anion from 3-thiomethoxypropene is easier by 16.6 kcal/mol, than creation of the allyl anion from propene. From *anti*-1-thiomethoxypropene, the energy of formation is 13.5 kcal/mol lower. The methoxy group stabilizes the allyl anion by only 2.4 kcal/mol relative to 3-methoxypropene, but destabilizes it by 3.1 kcal/mol when formed from 1-methoxypropene. Again, the thiomethoxy stabilizes the allyl anion to a very large extent, while methoxy slightly stabilizes or even destabilizes the allyl anion.

The computed homolytic bond dissociation energies, relative to propene, for the formation of allyl radicals are -6.0 kcal/mol (from 3-thiomethoxypropene), -2.9 kcal/mol (from 1-thiomethoxypropene), -8.0 kcal/mol (from 3-methoxypropene), and -2.4 kcal/mol (from 1-methoxypropene). Both thiomethoxy and methoxy substituents stabilize the allyl radical to about the same extent. The enol ether and enol thioether (1-methoxypropene and 1-thiomethoxypropene) are both stabilized by the resonance-donating methoxy and thiomethoxy substituents. Consequently, it is thermodynamically more favorable to form the allyl anion from propene than from 1-methoxypropene.

Prediction of Cleavage or Cope Rearrangement Based on Computed Homolytic and Heterolytic Bond Dissociation Energies of Thiomethoxy and Methoxy-Substituted 3-Oxy-1,5-hexadienes. Recently we presented a model that explains and predicts the outcome of anionic oxy- and amino-Cope rearrangements.⁵ On the basis of the heterolytic and homolytic bond cleavage of the C3-C4 bond of the Cope reagent, the reaction is predicted to proceed via a stepwise mechanism which includes bond cleavage to acrolein (or amino-acrolein) and the allyl anion, or along an asynchronous concerted rearrangement mechanism. Since the transition state of a concerted Cope rearrangement is considered to consist of two weakly interacting radicals, a low homolytic bond dissociation energy favors rearrangement. A low heterolytic bond dissociation energy, on the other hand, results in bond cleavage. Subsequent combination of the fragments can lead, formally, to the same product. This hypothesis was tested on the thiomethoxy- and the

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Table 3. Computed Homolytic and Heterolytic Bond Dissociation Energies for Cleavage of the C3–C4 Bond of 4- and 6-Methoxy-3-oxido-1,5-hexadiene and 4- and 6-Thiomethoxy-3-oxido-1,5-hexadiene Anions at the B3LYP/6-31+G* Level (kcal/mol)^a

reaction	homo	hetero	homo - hetero
6-OMe	24.4	28.5	-4.1
4-OMe SYN	19.4	23.4	-4.1
4-OMe ANTI	19.6	23.7	-4.1
6-SMe	25.3	13.1	12.1
4-SMe SYN	21.7	9.6	12.1
4-SMe ANTI	21.9	9.8	12.1

^a Zero-point energies are included.

methoxy-substituted Cope reagents. The computed energies are presented in Table 3.

For all the methoxy substituents at C4 or C6 the homolytic BDE is lower than the heterolytic, whereas the opposite is true for thiomethoxy substituents. Our calculations suggest that substituted anionic oxy-Cope rearrangements follow different mechanisms depending on the substituents. A methoxy substituent decelerates the reaction and promotes a concerted and homolytic mechanism, while a thiomethoxy substituent accelerates the reaction via a stepwise cleavage mechanism. This is nicely predicted by the model. The computed heterolytic bond dissociation energies of the thiomethoxy-substituted Cope reagents are 12.1 kcal/mol lower than the homolytic bond dissociation energies. Thus, heterolytic cleavage is preferred over the concerted rearrangement. The computed homolytic bond dissociation energies of the methoxy-substituted Cope reagents are lower than the heterolytic ones by 4.1 kcal/mol, suggesting that concerted rearrangement is the preferred route.

Comparisons with Experimental Data. Evans et al. demonstrated that 4-thiophenoxy-3-hydroxy-1,5-hexadienes undergo anionic rearrangements under much milder conditions than the alkoxy-substituted counterparts. However, cleavage of the thiophenoxy-substituted dienes competes with rearrangement.³ Our results show that the 1-thiomethoxyallyl anion is stabilized. This anion should be even more stabilized in a polar solvent, and thus cleavage should be favored. In a nonpolar solvent, on the other hand, the weakly solvated metal cations will bind more strongly to the oxy anion, and rearrangement rather than cleavage will be favored. When 4-hydroxy-4-methyl-5-thiophenoxyhepta-2,6-diene was treated with Et₂O and KH at 25 °C, it underwent Cope rearrangement, but in the more polar solvent THF and employing the more electronegative alkali metal NaH, predominant cleavage occurred.³ The alkoxy-substituted dienes rearranged at considerably higher temperatures, and no frag-

mentation was observed.³ The computations showed that the methoxy-substituted anionic oxy-Cope rearrangements proceed via concerted rearrangement pathways, as in accordance with experiments.

We observed rapid anionic oxy-Cope rearrangement of a divinyl camphor derivative with a vinyl sulfide substituent in C6 position at -78 °C (Figure 1). An analogous vinyl ether compound had to be heated to 0 °C before any reaction occurred (Figure 1). In both studies acceleration was observed with the sulfur substituents. Evans et al. observed cleavage, while we found a rearranged product.^{3,6} Our computations show no significant difference between thioalkoxy substituents at C4 or C6. This example likely involves cleavage and recombination leading to rearrangement because the reactant is bicyclic. When cleavage of the C3–C4 bond occurs, the fragments are held in proximity so that the C1–C6 bond can form, and the rearranged product is formed.

Macdonald et al. found that isomers **1–3** (Figure 1) rearrange, while isomer **4** does not. We suggest that this is because the methoxy substituent suppresses cleavage.⁷

Only starting material was observed when toluene was used as solvent for an anionic amino-Cope rearrangement reaction.⁵ Macdonald et al. performed a similar anionic amino-Cope rearrangement with a thiomethoxy substituent in toluene. The reaction was rapid at -78 °C. The yield was, however, only 20%.⁷ This can be explained by the ability of the thiomethoxy group to stabilize allyl anions, which promotes cleavage but with poor recombination, explaining the low yield.

Conclusions

This study shows that anionic oxy-Cope rearrangements with thiomethoxy substituents at positions C4 or C6 proceed via an accelerated stepwise mechanism. The corresponding methoxy substituents cause the reaction to proceed via a decelerated, but still concerted mechanism. The results in this study can rationalize and explain several experimental data in anionic oxy-Cope rearrangements. With a proper choice of substituents the oxy-Cope rearrangement can be tuned to proceed either to rearrangement or fragmentation of the starting material.

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