

Concerted Rearrangement versus Heterolytic Cleavage in Anionic [2,3]- and [3,3]-Sigmatropic Shifts. A DFT Study of Relationships among Anion Stabilities, Mechanisms, and Rates

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The anionic [2,3] sigmatropic Wittig rearrangements of deprotonated 4-hetero-1-pentenes and the anionic [3,3] sigmatropic Cope rearrangements of 3-substituted-1,5-hexadienes were explored by using density functional calculations. While the deprotonated anionic 3-hydroxy-1,5-hexadiene (**2a**), 3-thiohydroxy-1,5-hexadiene (**2c**), and 3-formamidy-1,5-hexadiene (**2d**) Cope substrates undergo concerted rearrangements, the deprotonated anionic 3-amino-1,5-hexadiene (**2b**) and 3-methyl-1,5-hexadiene (**2e**) Cope substrates follow nonconcerted cleavage/recombination pathways. We have also found that the gas-phase Wittig (**1a**), aza-Wittig (**1b**), and carba-Wittig (**1c**) reactions proceed via nonconcerted cleavage/recombination pathways. These results are compared with previous results on the Cope rearrangements of deprotonated anionic 3-hydroxy-1,5-hexadiene and 3-amino-1,5-hexadiene anions. A previously established model that heterolytic and homolytic bond dissociation energies can be used to predict how anionic amino- and oxy-Cope substrates will react is generalized to account for the reactivity of other Cope substrates as well as for the Wittig rearrangements. There is also a relationship between the basicity of the anionic substituent in the Cope rearrangement and the reaction pathway: the more basic the substituent anion, the less stable it is, and the more likely it is that cleavage will occur. A first step toward studying these reactions in solution was also taken by calculating energetics for some of the rearrangements with a lithium counterion present.

Introduction

The [2,3]-Wittig rearrangement of the deprotonated 4-hydroxy-1-pentenes (eq 1a) and the anionic oxy-Cope rearrangement (eq 2a) have been found to be of large use in organic synthesis, in part due to their high stereo- and regioselectivity.^{1,2} These reactions are believed to proceed in solution via concerted mechanisms involving five-membered- and six-membered-ring transition states, respectively.^{3–5}

The corresponding aza-Wittig (eq 1b) reaction and the anionic amino-Cope reaction (eq 2b) have attracted much less interest, and only a few examples of these transformations have been reported in the literature.^{5,6} Generally, the stereo- and regioselective control of these reactions

is poorer than that of the Wittig and the anionic oxy-Cope rearrangements. For example, the Coldham group reported that the trans-metalation of an allylic amine with methylolithium gave no aza-[2,3]-Wittig rearranged product, but instead yielded a product mixture (Figure 1).^{5c} It was suggested that these products form via [1,2]-rearrangements.

In an attempt to utilize the anionic amino Cope synthetically, Meyers et al. prepared *N*-allyl-*N*-substituted amines and subjected these to KH/toluene or BuLi/THF at $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$.^{7a} No rearranged product was observed; instead, only dissociated and/or recombined addition products or simply unreacted starting material was obtained (Figure 2).

In this study, we have investigated the [2,3]-pericyclic rearrangements of **1a–c** and the [3,3]-sigmatropic shifts

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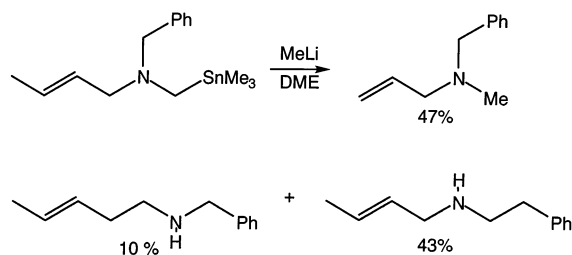


FIGURE 1. An attempted aza-Wittig rearrangement studied by the Coldham group.

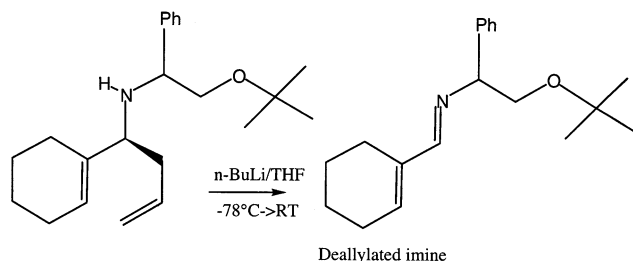
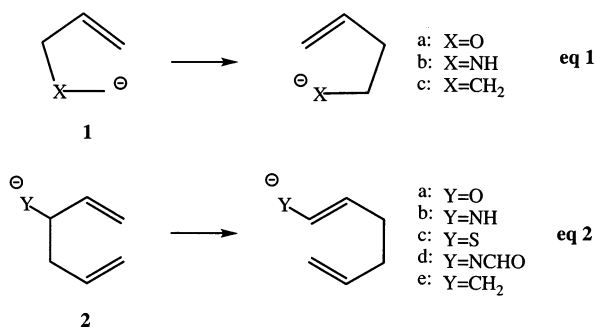


FIGURE 2. Cleavage reaction occurring instead of an anionic amino-Cope rearrangement of a *N*-allyl-*N*-substituted amine conducted at $-78\text{ }^{\circ}\text{C}$ in KH/toluene or BuLi/THF.

SCHEME 1



of **2a–e** (Scheme 1) in the gas phase using density functional theory. The results are discussed in light of previously published theoretical studies on the anionic amino- and oxy-Cope rearrangements.^{7–9} As a first step toward the examination of the solution-phase behavior of these substrates, the energetics of rearrangement and cleavage/recombination pathways in the presence of a lithium counterion were also calculated. These results are discussed and compared with the corresponding gas-phase results in the absence of Li⁺.

Computational Methods

All geometry-optimized structures and computed energies were determined with the B3LYP functional and the split valence 6-31+G* basis set. The optimized geometries were established as minima or transition structures by means of frequency calculations. Transition structures were found to have one imaginary frequency, while ground-state, intermediate, and product geometries only have real frequencies. The

nonscaled frequencies were used to compute zero-point energies (ZPE). All calculations were performed with the Gaussian 98 program.¹⁰

Results

The Wittig, the Aza-Wittig, and the Carba-Wittig Rearrangements in the Gas Phase, No Counterion.

The negatively charged ground-state, transition-state, and product structures of the Wittig rearrangement were geometry optimized. A transition state leading to cleavage was located and found to be 2.6 kcal/mol higher in energy than the ground state (Figure 3A). A concerted rearrangement transition state could not be located for the bare carbanion. This is in accord with a previously published MP2/6-31+G//6-31+G study.³ Next the recombination step was investigated. No intermediate complex between the allyl anion and formaldehyde was found. However, the energy of the allyl anion and the formaldehyde at infinite distance was computed to be 16.3 kcal/mol (no ZPE correction) lower than that of the reactant, see box in Figure 3A. Attempts were also made to find a transition state recombining the formaldehyde with the allyl anion. This was done by means of constrained geometry optimizations where the distance between one of the terminal allyl anion carbon atoms and the carbonyl carbon of the formaldehyde was constrained in intervals ranging from 1.9 to 2.7 Å. We were unable to locate a transition state for the recombination reaction, presumably since this step is very fast. It appears that the allyl anion–formaldehyde complex is not a minimum, but a flat region on the surface. When the orbitals involved in bond formation are aligned, collapse to the alkoxide product occurs without a barrier. The reaction is concerted in the sense of having only a single transition state, but is clearly stepwise in terms of sequential bond cleavage and bond formation. Therefore, the parent Wittig reaction in the gas phase involves dissociation followed by recombination (Figure 3A).

The computed activation energy for cleavage of the aza-Wittig amine (**1b**) is also only 2.6 kcal/mol (Figure 3B). A corresponding rearrangement transition state could not be located. Thus, these calculations indicate that the aza-Wittig substrate will also react via cleavage/recombination in the gas phase.

The all-carbon substrate for a hypothetical Wittig rearrangement—what we call a carba-Wittig substrate—**1c** was also examined computationally (Table 1, Figure 3C). As with the Wittig and the aza-Wittig cases, calculations show that cleavage occurs with a very low barrier of 2.4 kcal/mol, followed by fast recombination.

The Anionic Oxy-, Amino-, Thiooxy-, Formamidyl-, and Methyl-Cope Rearrangements in the

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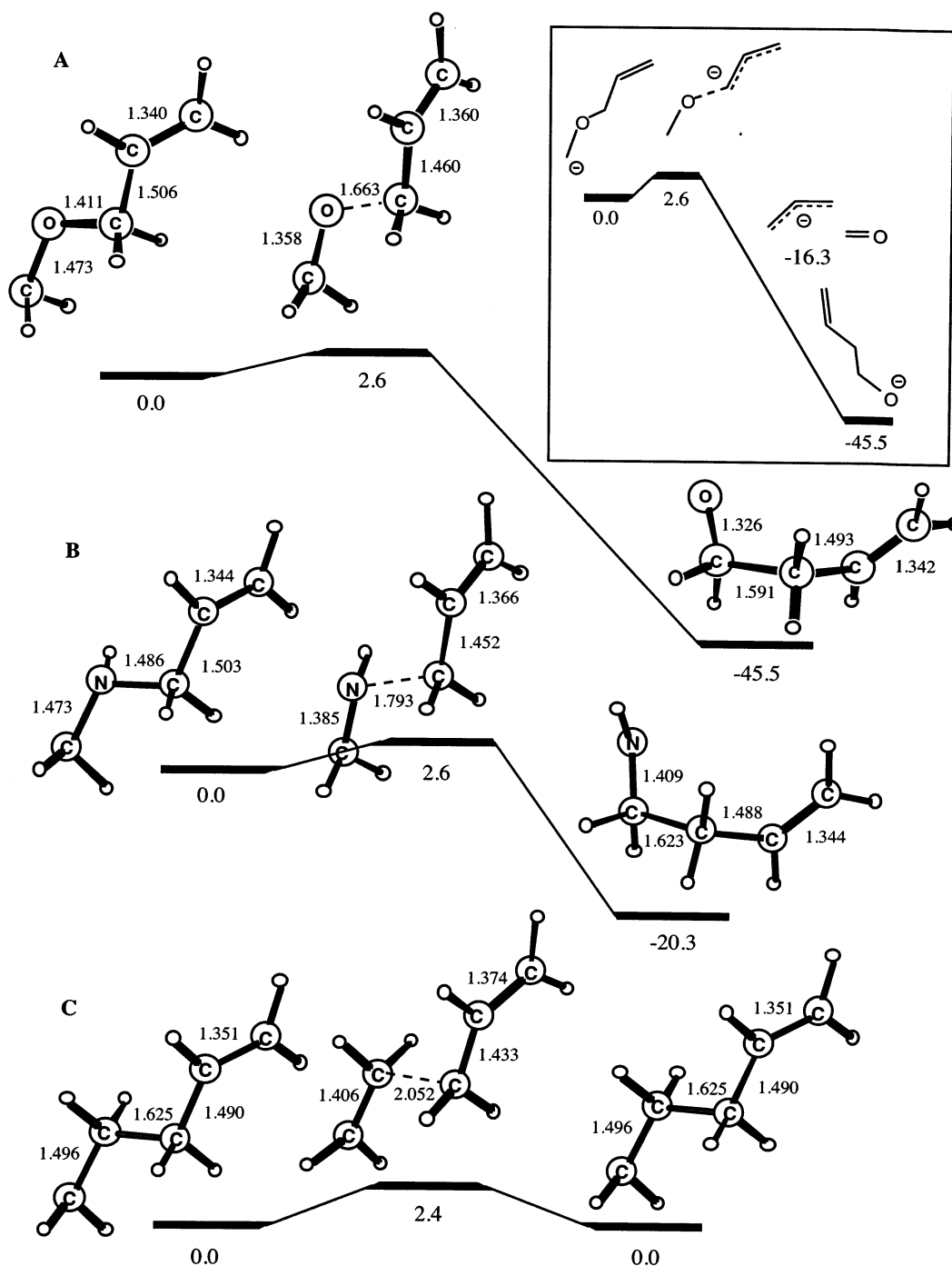


FIGURE 3. Ground state, rate-limiting transition state and rearranged product geometries optimized in the gas phase for the nonconcerted Wittig rearrangement (A), the nonconcerted aza-Wittig rearrangement (B), and the nonconcerted carba-Wittig rearrangement (C), using B3LYP/6-31+G*. Zero-point energies are included and bond lengths are in Å.

Gas Phase, No Counterion. Previous computations have shown that while the anionic oxy-Cope rearrangement (eq 2a) should follow a concerted pathway with a low barrier (8.3 kcal/mol), the anionic amino-Cope rearrangement (eq 2b) will proceed via a cleavage/recombination pathway, with a barrier of 5.9 kcal/mol.^{7a,11} The gas-phase experimental work on the anionic oxy-Cope rearrangement and a vast body of synthetic work in solution are consistent with the rapid rearrangements

of anionic oxy substrates.¹¹ The computational prediction of cleavage for the anionic amino substrate is also consistent with experiments by Meyers et al.^{7a}

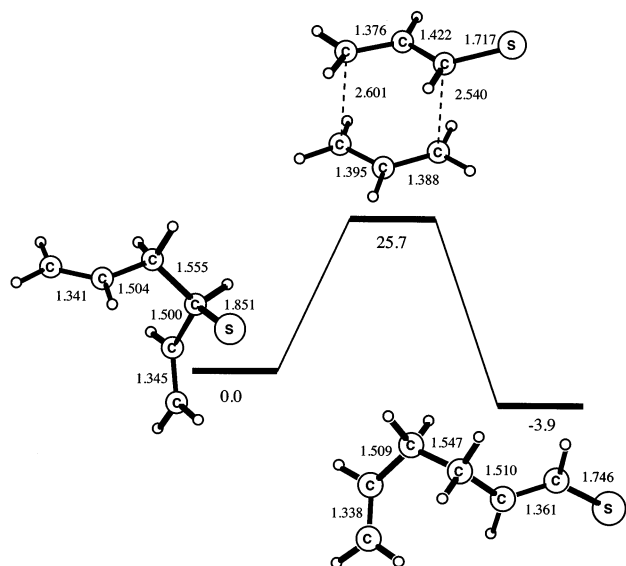
To more fully understand this rearrangement, the energetics of the anionic thiooxy- (**2c**), formamidyl- (**2d**), and methyl-Cope (**2e**) rearrangements were examined. The anionic thiooxy-Cope rearrangement proceeds via a concerted pathway, with a relatively high barrier (25.7 kcal/mol, Table 1, Figure 4). The anionic formamidyl-Cope rearrangement also follows a rearrangement pathway, and is considerably faster than the anionic thiooxy-

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TABLE 1. Energies (kcal/mol) of the Rate Limiting Transition States and Products Relative to the Respective Ground States of Anionic [2,3]- and [3,3]-Sigmatropic Rearrangements^a

	calcd gas-phase proton affinity (ΔH)	TS rearrang	TS cleavage	ΔH_{rxn}
1a (Wittig)	405	12.0 ^c	2.6	-45.5
1b (aza-Wittig)	410	22.2 ^c	14.8 ^c	-47.4 ^c
1c (carba-Wittig)	411	29.4 ^c	2.6	-20.3
2c (anionic thiooxy-Cope)	341	25.7	14.9 ^c	-25.2 ^c
2d (anionic formamidyl-Cope)	350	20.6	2.4	0.0
2a (anionic oxy-Cope)	361	8.3 ^b	13.3 ^c	0.0 ^c
2b (anionic amino-Cope)	382	31.8 ^c		-3.9
2e (anionic methylido-Cope)	402		5.9 ^b	-12.0
			4.6	-21.8

^a The energies were computed at the B3LYP/6-31+G* level of theory. Zero-point energies are included. ^b References 7 and 11. ^c A lithium cation is included.

**FIGURE 4.** Stationary points and optimized geometries in the gas phase for the anionic thiooxy-Cope rearrangement, using B3LYP/6-31+G*. Zero-point energies are included and presented bond lengths are in Å.

Cope rearrangement (20.6 kcal/mol, Table 1, Figure 5), but it is still slower than the anionic oxy-Cope rearrangement (8.3 kcal/mol).^{7a} The anionic methyl-Cope rearrangement, in contrast, prefers a nonconcerted cleavage pathway with an extremely low barrier of 4.6 kcal/mol (Table 1, Figure 6).

The Wittig, the Aza-Wittig, and the Carba-Wittig Rearrangements with a Lithium Counterion. Most of the solution-phase reactions described herein are carried out in relatively nonpolar solvents, so the metal cation will be associated with the anion. Consequently, the first step toward a description of the solution-phase behavior of these rearrangements is to include a metal cation such as lithium. Ground states of the Wittig and the aza- and carba-Wittig reactions were geometry optimized where the lowest energies were obtained in which the lithium ion binds to the localized negative charge of the terminal carbon anion and also coordinates to the p-bond of the olefin part of the substrate (see Figures 7A–9A).

The computed activation barrier of the Wittig rearrangement of **1a** with a lithium counterion present (see

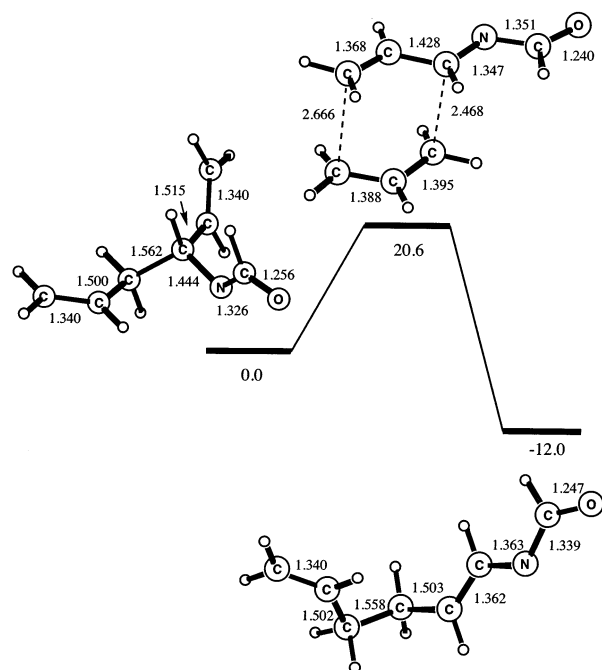
**FIGURE 5.** Stationary points and optimized geometries in the gas phase for the anionic formamidyl-Cope rearrangement, using B3LYP/6-31+G*. Zero-point energies are included and presented bond lengths are in Å.

Figure 7A) at the B3LYP/6-31+G* level is 12.0 kcal/mol (Table 1). This value is in reasonable agreement with the computed value (16.2 kcal/mol) at the MP2/6-31+G//6-31+G level previously published.³ The computed barrier to cleavage (see Figure 7B) is higher (14.8 kcal/mol, Table 1). This is in agreement with experiments, which give exclusively the rearranged product.

The computed activation barrier to rearrangement (22.2 kcal/mol) of the aza-Wittig reaction with Li⁺ (see Figure 8B) is considerably higher than that of the corresponding cleavage/recombination pathway (see Figure 8A), with a rate-limiting transition state 14.9 kcal/mol higher in energy than the ground-state energy. This clearly demonstrates that cleavage/recombination is preferred, which is in agreement with experiments. The carba-Wittig reaction, presented in Figure 9A, is even more prone to undergo cleavage than the aza-Wittig reaction is, and it cleaves with a barrier of 13.3 kcal/mol.

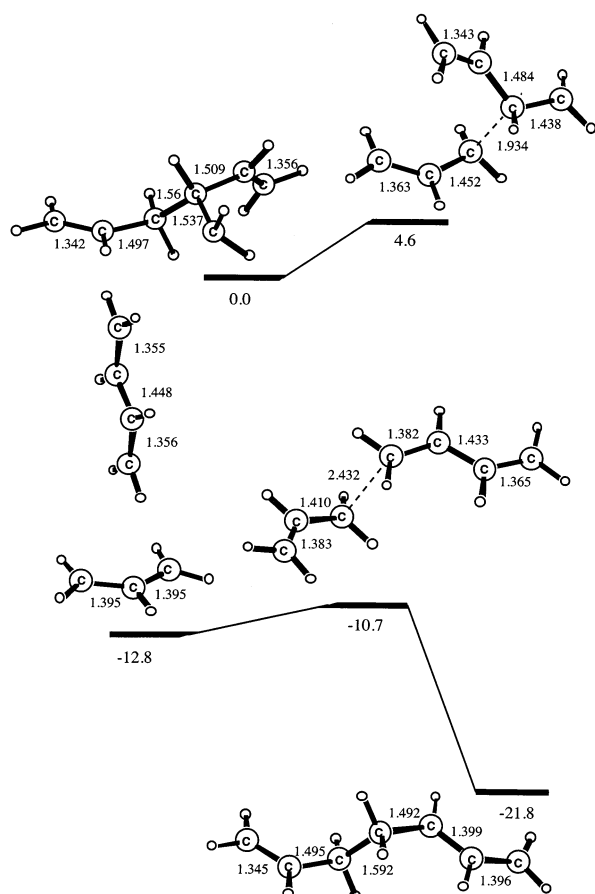


FIGURE 6. Stationary points and optimized geometries in the gas phase for the anionic methyl-Cope rearrangement, using B3LYP/6-31+G*. Zero-point energies are included and presented bond lengths are in Å.

Because of the low electronegativity of carbon, no rearrangement occurs but cyclization of the carbanion five-membered ring can occur and the barrier for this process was computed to be 29.4 kcal/mol, see Figure 9B.

The Anionic Oxy-Cope Rearrangement with a Lithium Counterion. Calculations were also performed with a lithium ion coordinated to the oxyanion in the anionic oxy-Cope rearrangement. The computed barrier is 31.8 kcal/mol, which is much higher than that of the gas-phase anionic oxy-Cope reaction. The transition-state geometry of this rearrangement together with the ground state and rearranged product are presented in Figure 10. The transition-state structure is very different from that computed without the lithium ion,^{7a} resembling the transition-state structure of the neutral, parent Cope rearrangement.¹²

Discussion

Rearrangements in the Gas Phase, No Counterion. Our computational results indicate that the deprotonated anionic 3-hydroxy-1,5-hexadiene (**2a**), 3-thiohydroxy-1,5-hexadiene (**2c**), and 3-formamidyl-1,5-hexadiene (**2d**) Cope substrates undergo concerted rearrangements. In contrast, the deprotonated anionic 3-amino-

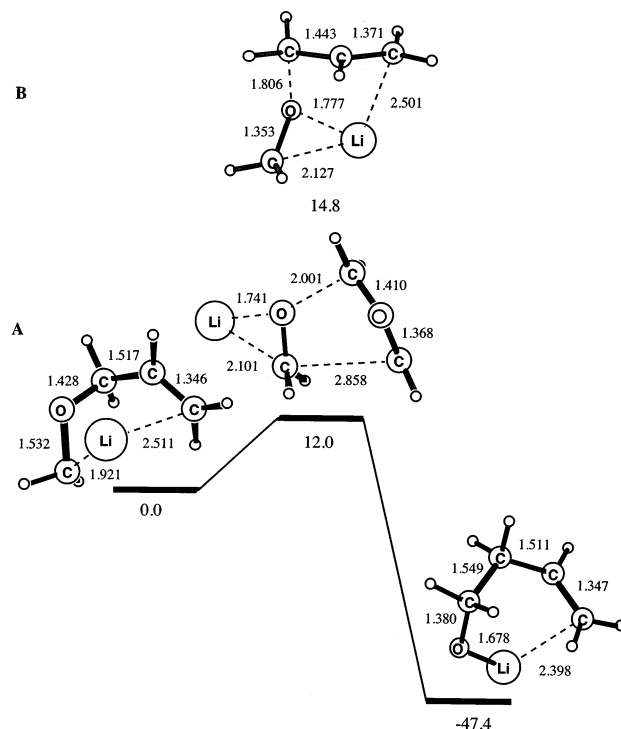


FIGURE 7. Part A shows the ground state, the rearrangement transition state, and the rearranged product of the Wittig rearrangement with a lithium cation coordinated to the substrate. Part B shows the rate-limiting cleavage transition state, which after cleavage and re-combination will result in the rearranged product. The geometries were computed at the B3LYP/6-31+G* level of theory and zero-point energies are included. Selected bond lengths are given in Å.

1,5-hexadiene (**2b**) and 3-methyl-1,5-hexadiene (**2e**) Cope substrates follow nonconcerted cleavage/recombination pathways. The gas-phase Wittig (**1a**), aza-Wittig (**1b**), and carba-Wittig (**1c**) reactions also proceed via cleavage/recombination pathways.

Is there a pattern to the reactivity of these sigmatropic substrates, and can their behavior be predicted? Earlier papers^{7a} showed that rearrangement or cleavage/recombination of the anionic amino- and oxy-Cope reactions can be predicted from comparison of the homolytic and heterolytic bond dissociation energies (BDEs) of the reactants. The transition state of the anionic oxy-Cope rearrangement can be considered as two weakly interacting allyl radicals. Consequently, the energy of the transition state can be estimated by homolytic dissociation of the reactant into the two separated allyl radicals. The cleavage pathway can be described by the heterolytic dissociation of the reactant into acrolein and an allyl anion. The comparison of the homolytic and heterolytic BDEs for the anionic oxy and anionic amino substrates sheds light on why the former rearranges while the latter cleaves and recombines. For the anionic oxy case, the homolytic and heterolytic cleavage energies are comparable, differing by only 1.4 kcal/mol. However, the anionic amino case shows a clear preference, of over 10 kcal/mol, for heterolytic cleavage. This preference manifests itself in the anionic amino-Cope rearrangement following a cleavage/recombination pathway. To ascertain whether this model could be extended to other heteroatomic Cope rearrangements, as well as to other rearrangements such

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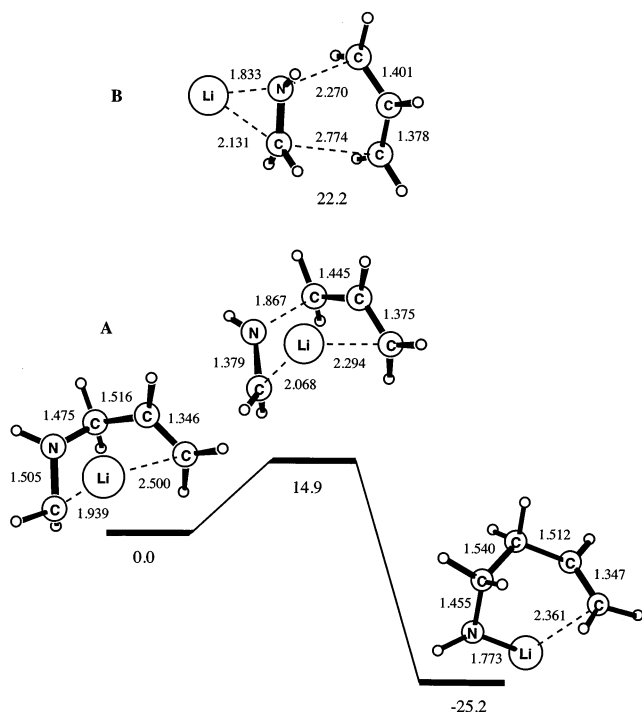


FIGURE 8. Part A shows the ground state, the rate-limiting transition state, and the product of the nonconcerted aza-Wittig cleavage/re-combination reaction with a lithium cation coordinated to the substrate. Part B shows the transition state of the concerted rearrangement pathway. The geometries were computed at the B3LYP/6-31+G* level of theory and zero-point energies are included. Selected bond lengths are given in Å.

TABLE 2. Computed Homolytic and Heterolytic Bond Dissociation Energies^a

reaction	homo	hetero	homo-hetero
[2,3]-Wittig (1a)	2.1	-19.8	21.9
aza-[2,3]-Wittig (1b)	19.5	-15.3	34.8
carba-[2,3]-Wittig (1c)	37.0	-7.6	44.6
1,5-hexadien-3-oxide ^b (2a)	25.5	24.1	1.4
1,5-hexadien-3-amide ^b (2b)	20.0	9.5	10.5
1,5-hexadien-3-thiooxide (2c)	33.4	51.0	-17.6
1,5-hexadien-3-formamide (2d)	29.4	48.9	-19.5
1,5-hexadien-3-methylenide (2e)	14.9	-5.7	20.6

^a The energies are in kcal/mol and were computed at the B3LYP and the UB3LYP/6-31+G* levels. ^b Reference 7a.

as the Wittig and other hetero analogues, the homolytic and heterolytic BDEs for **1a–c** and **2a–e** were computed (Table 2).

While the homolytic BDE for the anionic thiooxy substrate is 33.4 kcal/mol, the heterolytic pathway is a much less favorable 51.0 kcal/mol. Likewise, the homolytic BDE for the anionic formamide is 29.4 kcal/mol, whereas the heterolytic BDE is 48.9 kcal/mol. For both the *thiooxy* and *formamidyl* anionic Copes, a concerted pathway is followed, albeit with a high barrier. The anionic *methyl* Cope shows a large (20.6 kcal/mol) preference for heterolytic cleavage, and accordingly, the substrate follows a cleavage/recombination pathway. Thus, the model holds for a range of anionic Cope substrates.

How general is this “bond dissociation energy model”? Will it also work with the [2,3]-sigmatropic systems? To test this, homolytic and heterolytic BDEs were computed for the Wittig reagents **1a–c** in the gas phase. The

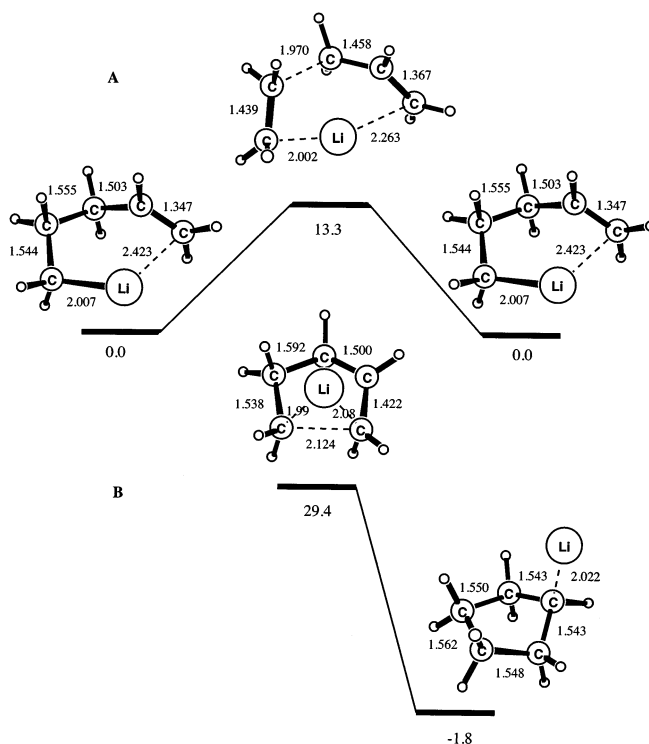


FIGURE 9. Part A shows the cleavage pathway of the nonconcerted carba-Wittig rearrangement with a lithium ion coordinated to the ground state, the rate-limiting transition state, and the rearranged product. Part B shows an associative route with the formation of a five-membered ring slightly lower in energy than the ground state. The geometries were computed at the B3LYP/6-31+G* level of theory and zero-point energies are included. Selected bond lengths are given in Å.

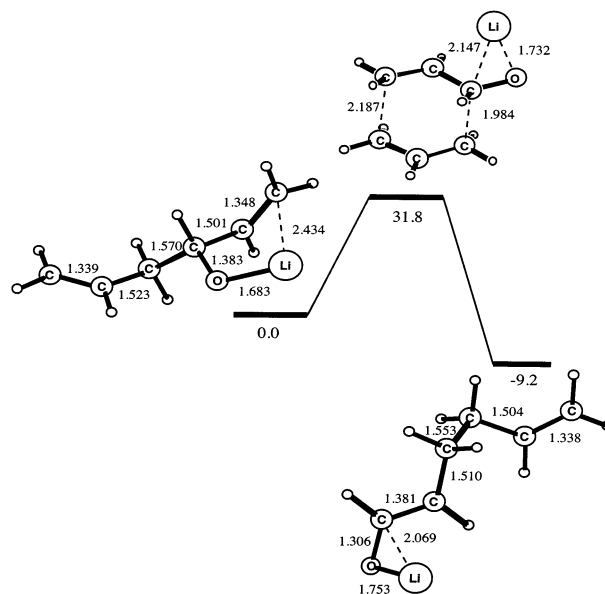


FIGURE 10. The ground state, the transition state, and the product of the anionic oxy-Cope rearrangement with a lithium cation coordinated to the oxygen anion. The geometries were computed at the B3LYP/6-31+G* level of theory and zero-point energies are included. Selected bond lengths are given in Å.

heterolytic BDEs are lower than the homolytic BDEs for all three [2,3]-rearrangements (see Table 2). For the parent Wittig rearrangement, the homolytic BDE energy

of the substrate is 2.1 kcal/mol, versus a corresponding heterolytic BDE energy of only -19.8 kcal/mol; therefore, the BDE model predicts a cleavage pathway. This result is consistent with our gas-phase calculation of the reaction coordinate (Table 1, Figure 3A).

For the aza-Wittig substrate, the BDE model predicts gas-phase cleavage, also consistent with the calculation of the reaction coordinate (Table 1, Figure 3B). Last, the model also predicts that the carba-Wittig substrate will react via a cleavage pathway. Again, the gas-phase calculation of the reaction coordinate is in agreement with the model's prediction (Table 1, Figure 3C). The bond dissociation energy model is therefore of general value, predicting the gas-phase pathways for both Cope and Wittig rearrangements.

Related to the homolytic/heterolytic BDE model is proton affinity. We further postulate that the proton affinity of the anionic reactants of these [2,3]- and [3,3]-sigmatropic rearrangements should be related to the energetically preferred mechanistic pathway. Intuitively, heterolytic cleavage should be favored as the anionic reactant becomes less stable. Generally, the less stable an anion, the greater its proton affinity. To test this relationship, we calculated the gas-phase proton affinities for the substrates of interest (Table 1).

For the Cope rearrangements, the *anionic methyl and amino* substrates are the most basic reactants, with proton affinities of 402 and 382 kcal/mol. Since these anionic substrates are not very stable, heterolytic cleavage will be preferred. The anionic oxy, thiooxy, and formamidyl substrates are much more stable, with predicted proton affinities of 361, 341, and 350 kcal/mol. This stability translates to a concerted rearrangement pathway. The Wittig substrates are all very basic, with proton affinities of 405, 410, and 411 kcal/mol for the parent, aza, and carba reactants (Table 1). These high proton affinities translate to unstable ions which should be prone to cleavage.

Comparison of the computed gas-phase acidities with known pK_a values¹³ of similar substances reveals a good correlation. For example, the quite acidic BuSH with a pK_a value of 10–11 and CH_3CONH_2 with a pK_a value of 15 compare well with the computed gas-phase acidities of the anionic thiooxy-Cope and the formamidyl-Cope substrates ($\Delta H = 341$ and 350 kcal/mol, respectively). The somewhat more basic anionic oxy-Cope substrate with a computed gas-phase acidity of $\Delta H = 361$ kcal/mol compares with the pK_a value of *i*-PrOH (16.5 kcal/mol),

while the anionic amino and methyl-Cope substrates are extremely basic with computed gas-phase acidities of $\Delta H = 382$ and 402 kcal/mol, respectively. Again, these values correspond to the pK_a values of the much more basic compounds NH_3 ($pK_a = 38$ kcal/mol) and $\text{CH}_3\text{CH}_2\text{CH}_3$ ($pK_a = 50$ kcal/mol). Consequently, substituent acidities are related to the cleavage vs rearrangement propensities of these rearrangements.

Rearrangements in the Gas Phase, with Lithium Counterion. The addition of a lithium counterion would be expected to stabilize the negatively charged moiety of these anionic substrates and therefore favor rearrangement pathways. Indeed, the parent Wittig substrate with a lithium counterion prefers rearrangement to cleavage (Table 1), consistent with the solution-phase experimental results. For the lithiated aza-Wittig, a cleavage path is still favored, which is consistent with the solution-phase results of Coldham et al.^{5c}

Conclusions

The results suggest that [2,3]- and [3,3]-pericyclic rearrangements are promoted by heteroatoms such as sulfur and oxygen, which are not highly basic and are therefore relatively stable. Heteroatoms such as nitrogen and carbon are considerably more basic than sulfur and oxygen, both in the gas phase and in solution, and therefore they promote cleavage/recombination. This heteroatom basicity argument is closely related to and consistent with the heterolytic/homolytic BDE model set forth by us previously. A lithium cation stabilizes the negative charge on the heteroatom and promotes rearrangement.

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Supporting Information Available: Geometry-optimized structures and energies of the stationary points. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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