JOC The Journal of Organic Chemistry
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Conjugate Addition/[3,3] Sigmatropic Shift Processes for Formation of Medium-Ring Cyclic Amines – Do They Circumvent the Woodward–Hoffmann Rules?

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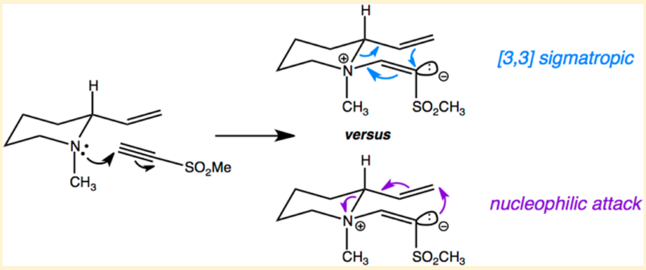
Ⓢ *Supporting Information*

ABSTRACT: Herein we describe our exploration, using density functional theory calculations, of a conjugate addition–rearrangement sequence that leads to medium-ring cyclic amines. On the basis of the results of our calculations, we conclude that the rearrangement step is rate determining. In addition, we analyze the role of a carbanion lone pair in the rearrangement step, concluding that it functions as a substituent on a [3,3] sigmatropic shift, rather than a nucleophile; thus, the Woodward–Hoffmann rules are not circumvented in this reaction via involvement of orthogonal orbitals on an atom involved in the rearrangement.



■ INTRODUCTION

Alkaloid natural products are popular synthetic targets,[1] but formation of medium-sized heterocycles is a synthetic challenge due to transannular and dihedral strain present in the products and transition-state structures preceding them.[2] Recently, a conjugate addition/[3,3] sigmatropic shift sequence was utilized to create medium-ring heterocycles via ring expansion of vinyl piperidines (Scheme 1).[3] The mechanism of this rearrangement was of particular interest to us because it was not clear at the outset whether the carbanion lone pair in the proposed intermediate was a spectator (acting only as a substituent on the aza-hexadiene core while it undergoes a [3,3] sigmatropic shift, Scheme 2, top), an active participant in the rearrangement (functioning as a nucleophile in an allylic substitution, Scheme 2, middle; this scenario would be reminiscent of pseudopericyclic reactions, in which cyclic delocalization is interrupted due to the presence of orthogonal orbitals containing rearranging electrons at one or more sites),[4] or not present during the rearrangement (having been protonated, Scheme 2, bottom). The results of quantum chemical calculations that address this question are described, along with analyses of stereoselectivity and substituent effects for this transformation. The potential for orthogonal orbitals at atoms supporting rearranging electrons to allow the Woodward–Hoffmann rules to be circumvented has been of interest for decades, and the relevance of this concept to the reaction shown in Scheme 1 is revealed herein.[4]

■ METHODS

Density functional theory (DFT) calculations were performed using Gaussian 03[5] and the B3LYP/6-31G(d) functional and basis set, an approach with a long history of success in modeling sigmatropic shifts.[6,7] Structures were first located in the gas phase, and subsequently reoptimized in solvent using UAKS radii with the CPCM solvation model,[8] with dichloromethane (DCM) or chloroform as the solvents (see Supporting Information for results with water). Single point calculations with B3LYP/6-31+G(d,p) were performed on some structures (tests on **4** and **8** with B3LYP/6-311++G(d,p) and M06-2X/6-31+G(d,p) led to only small changes in structure).[9] All structures were characterized as transition-state structures or minima through vibrational analysis. Transition states were connected to their respective minima via intrinsic reaction coordinate (IRC) calculations.[10] All energies reported are Gibbs-free energies at 298 K in DCM unless stated otherwise. Structural drawings were produced with Ball & Stick.[11] For most cases, R^1 (Scheme 1) was modeled as a methyl group for simplicity, although aryl groups were used in our computations on substituent effects (see Figures 7 and 8 and associated text below).

■ RESULTS AND DISCUSSION

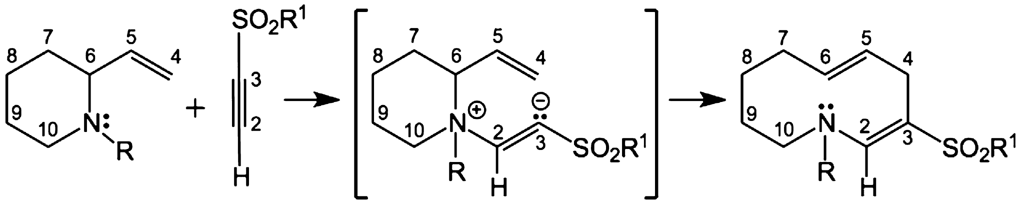
Computed Mechanism and Selectivity. The first step in the reported reaction sequence is the conjugate addition of the α-vinylpiperidine to the alkynyl sulfone (Scheme 1, left).[3] The zwitterion formed by this addition contains a C=C double bond that can, in principle, adopt either an *E* or *Z* geometry (Scheme 3).[9] The predicted barriers for reactions to form both are reasonable (25 kcal/mol for the pro-*E* addition, and 23 kcal/mol for the pro-*Z* addition; Figures 1 and 2). The zwitterions formed in this endergonic step can then rearrange to form heterocycles with 10-membered rings (Scheme 1, right). The major isolated product was reported to contain two

Special Issue: 50 Years and Counting: The Woodward-Hoffmann Rules in the 21st Century

Received: May 4, 2015
Published: July 13, 2015

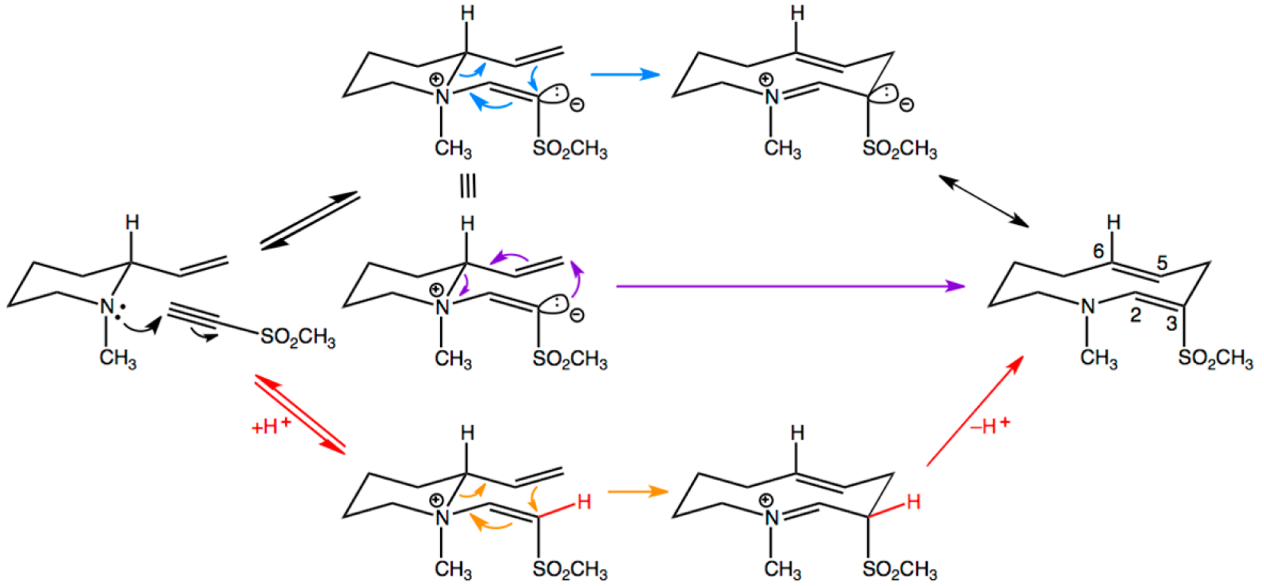
DOI: 10.1021/acs.joc.5b00996
J. Org. Chem. 2015, 80, 11699–11705

Scheme 1. General Reaction Scheme (R = Bn or Me, R^1 = Ar)[a]



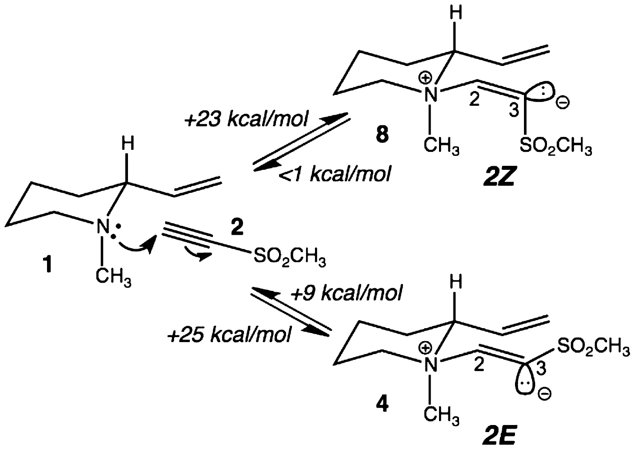
[a]Major product reported to be (2*E*, 5*E*).

Scheme 2. Mechanistic Options[a]



[a]Top (blue): zwitterionic intermediate undergoing sigmatropic shift. Middle (purple): zwitterionic intermediate undergoing carbanion attack/allylic displacement. Bottom: cationic intermediate undergoing sigmatropic shift (orange) after protonation (red) and before deprotonation (red). The pathway to the 2*Z*,5*E* product is shown here as a representative example. Here R^1 (Scheme 1) is shown as CH_3, since this simplification was used in most of the computations (see below).

Scheme 3. Possible Stereochemical Outcomes from Conjugate Addition Using CPCM(DCM)-B3LYP/6-31G(d)



E double bonds. Since the geometry of the newly formed C2═C3 double bond in the intermediate (**4** and **8**) is conserved in the corresponding product due to the geometric constraints associated with the highly organized transition-state structure for [3,3] sigmatropic shift (*vide infra*), it is the conjugate addition step that sets its configuration. The pro-*Z* conjugate addition transition-state structure (**7**‡) is predicted to be 2 kcal/mol lower in energy than the pro-*E* transition-state structure (**3**‡), but both are lower in energy than the sigmatropic shift transition-state structures that follow them (Figures 1 and 2). However, the barrier for reversion of the *Z* intermediate (**8**) to **1** and **2** is neglible. The absence of a significant barrier is likely a result of the antiperiplanar disposition of the anion lone pair and newly formed C−N bond, which makes elimination to reform the reactants facile. Evidence for the reversible addition of KO*t*Bu to alkynyl sulfonamides was recently described.[12] Thus, we arrive at a variation on Curtin−Hammett-type behavior.[13,14] Although formation of the *Z* intermediate (**8**) is favored over formation of the *E* intermediate (**4**), the [3,3] sigmatropic shift of **4** is associated with a lower energy transition-state structure than that of **8**, thereby leading to a kinetic preference for the *E* product.

As described above, the ring-enlarging sigmatropic rearrangements could occur with or without the direct involvement of the carbanion lone pair. In the former scenario, the lone pair would act as a nucleophile and attack the allylic ammonium substructure; such a pathway could be stepwise or concerted (and perhaps best be described as a pseudopericyclic reaction if the latter[4]). The second possibility is that the lone pair acts merely as a substituent during a concerted [3,3] sigmatropic

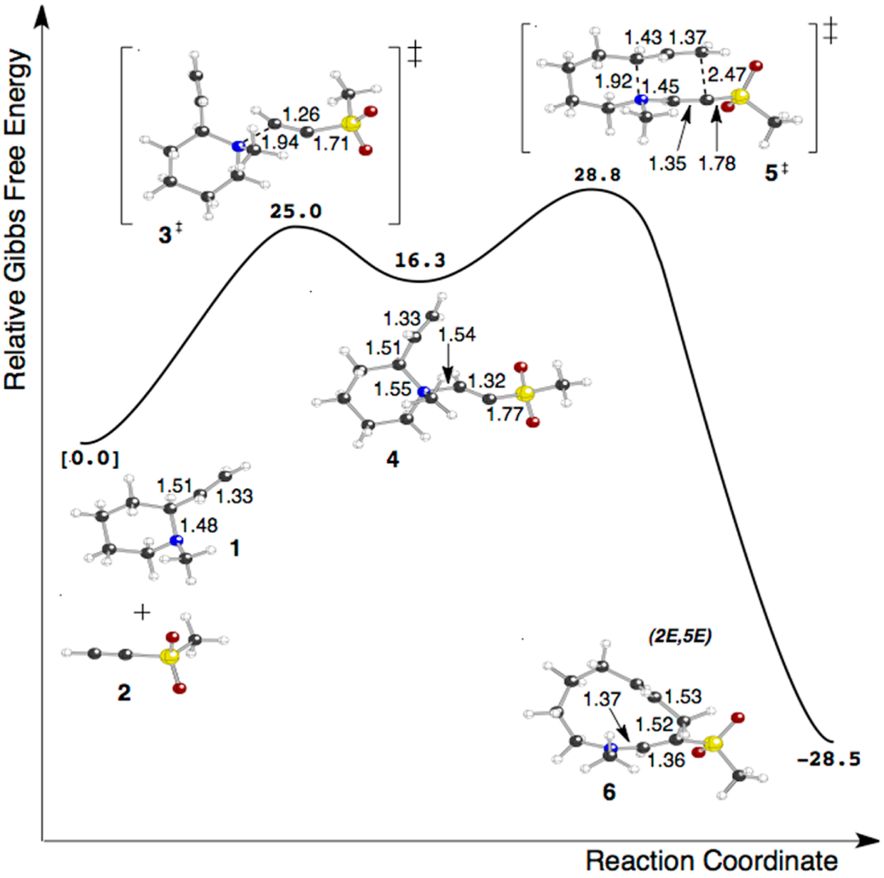


Figure 1. Stationary points involved in the formation of the 2*E*,5*E* product. Relative energies using CPCM(DCM)-B3LYP/6-31G(d) are in kcal/mol, and distances are shown in Å.

rearrangement, only becoming conjugated late on the reaction coordinate. A transition-state structure for the second scenario was found (Figures 1, 3, and 4, right), and the bond breaking and making events in this process are predicted to occur somewhat asynchronously (note the lengths of the partial bonds: the C−N distance is 124% of that in **4**, while the C−C distance is 163% of that in **6**).

We were unable to locate a transition-state structure for attack by the carbanion,[15] but a constrained calculation with the H−C2−N-C6 dihedral angle fixed to 180° led to a structure (Figure 4, left) that is approximately 9 kcal/mol higher in energy than the transition-state structure for the sigmatropic shift. When the constraint was removed and the structure reoptimized (with either restricted or unrestricted B3LYP), the sigmatropic shift transition-state structure was found. Attempts to find transition-state structures for a dissociative stepwise process were also unsuccessful without introducing geometric constraints.[16] Taken together, these results indicate that the rearrangement is most likely concerted and the carbanion lone pair is not directly involved in bond formation.

Other conformations of the [3,3] sigmatropic shift transition-state structure are also possible. Addition of the *α*-vinyl piperidine to the alkyne can result in adduct structures with a *cis* or *trans* relationship for the vinyl moieties that participate in the sigmatropic rearrangement. However, the vinyl moieties need to be near enough to one another so that their *π*-systems can react, thereby excluding conformations where both groups are axial. Taking this into consideration, along with *E*/*Z* possibilities for the vinyl anion, one arrives at six possible transition-state geometries for the rearrangement (Figure 5). Only chair-like geometries are shown here, since test calculations indicated that boat-like transition-state structures are significantly higher in energy (up to ∼20 kcal/mol higher; see Supporting Information). All three transition-state structures involving *Z* vinyl anion substructures are approximately 10 kcal/mol higher in energy than their *E* isomers, due in large part to steric clashes (A^{1,3} strain) involving the sulfonyl group and also likely due to a reduction of lone $\text{pair}_{\mathrm{C}} \leftrightarrow \sigma^*_{\mathrm{CN}}$ hyperconjugation as the reaction progresses. Of the three transition-state structures involving *E* vinyl anion substructures, **TS2** and **TS6** lead to a 2*E*,5*E* geometry after rearrangements, which corresponds to the reported major product, and **TS4** leads to a 2*E*,5*Z* geometry, corresponding to the minor observed product. **TS2** is predicted to be the lowest energy transition-state structure (it is the only *trans*-decalin-like structure of the three) and **TS4** the second lowest; **TS6** appears to be higher in energy due to strain between the *N*-alkyl group and the adjacent C−H bond, which are related by a dihedral angle of only 6° in **TS6**. **TS2** and **TS4** are predicted to be 1.6 kcal/mol different in energy, consistent with the 95:5 product ratio determined by NMR integration[3] and assuming a kinetically controlled reaction where the relative energies of the [3,3] shift transition-state structures determine the product distributions.

The reaction was also reported to occur in protic solvents like methanol.[3] This observation begs the question of protonation state during the sigmatropic rearrangement, i.e., could the intermediate zwitterion be protonated by solvent

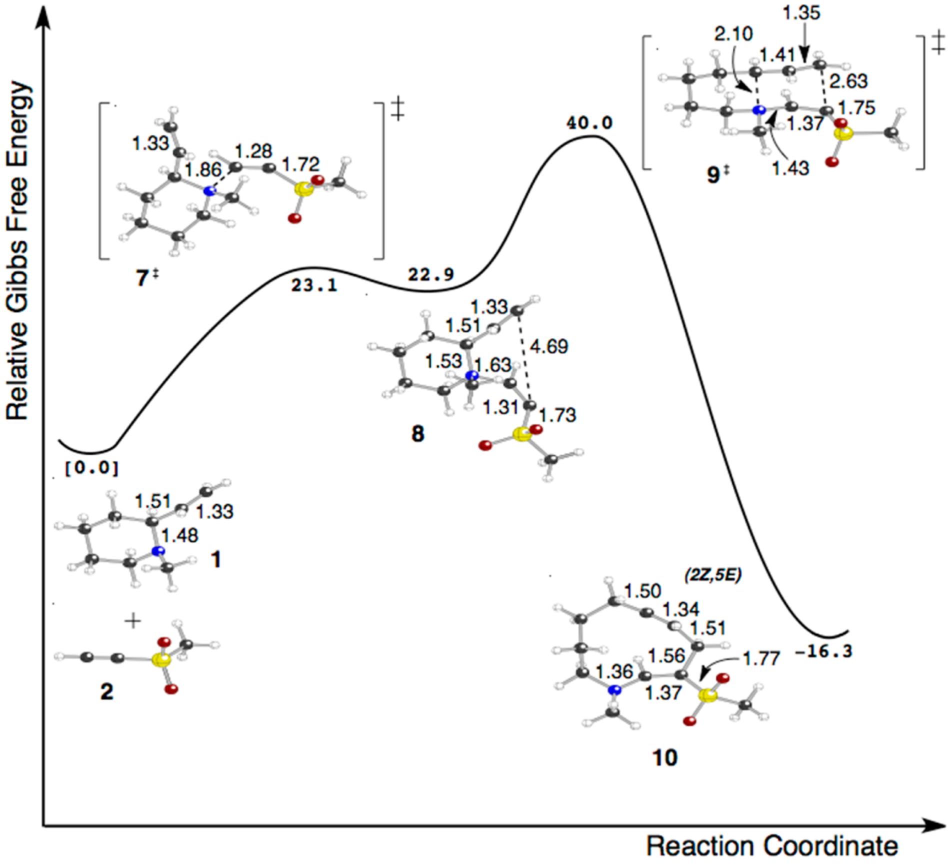


Figure 2. Stationary points in the formation of the (2*Z*,5*E*)-product. Relative energies with CPCM(DCM)-B3LYP/6-31G(d) are in kcal/mol, and distances are shown in Å.

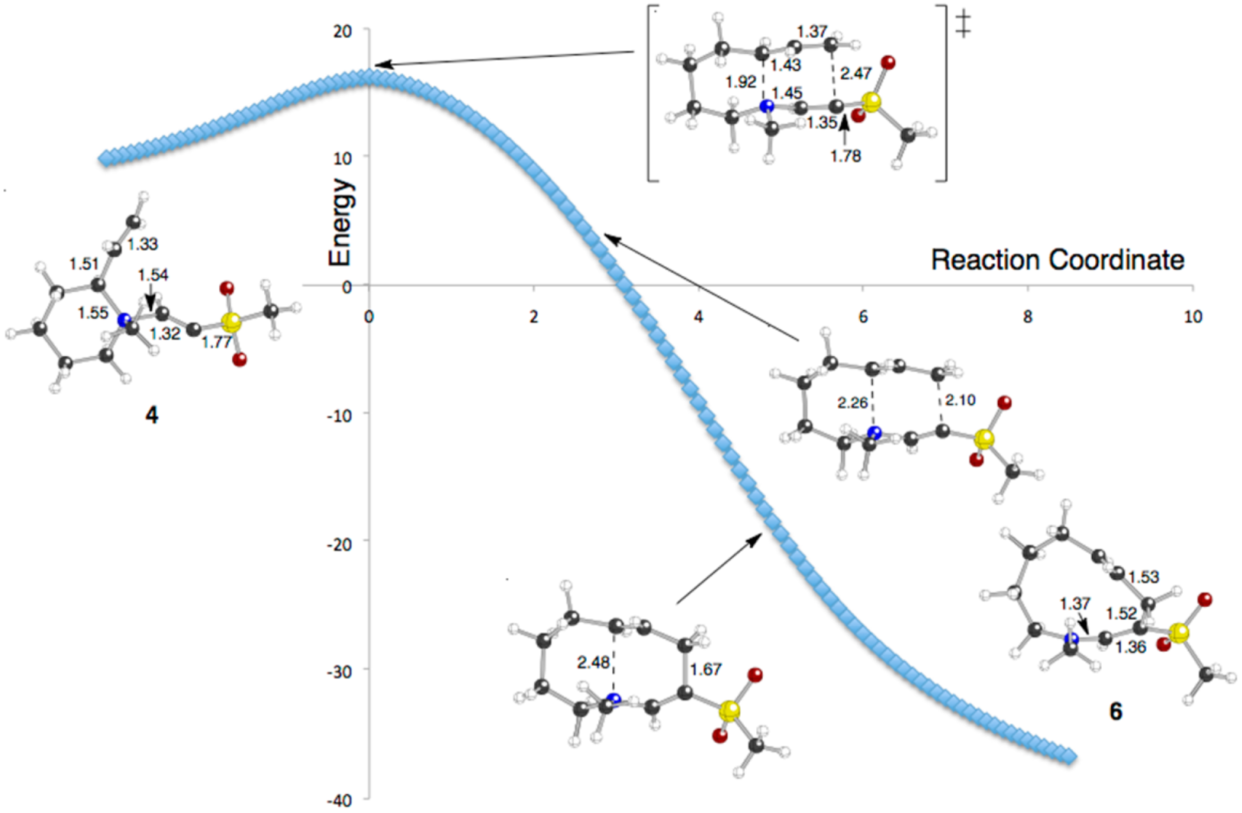


Figure 3. IRC calculation (B3LYP/6-31G(d)) for the formation of the 2*E*,5*E* heterocycle in the gas phase.

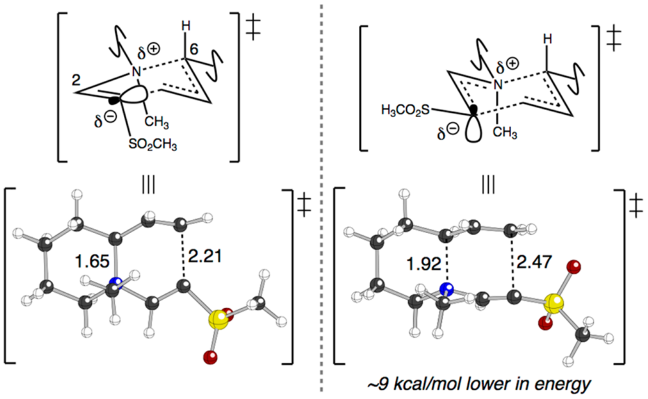


Figure 4. Constrained model of a transition-state structure for nucleophilic addition of the carbanion lone pair onto the alkene (left) and the concerted [3,3] shift transition-state structure (right). Note that the front-facing C−H bond of the CH_2 group and the top sulfonyl oxygen are aligned such that a C−H···O interaction is possible.

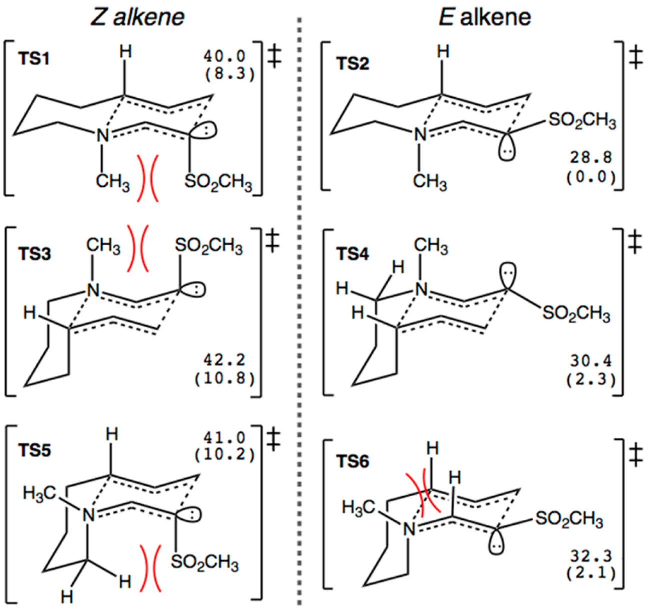


Figure 5. Possible transition-state structure geometries for [3,3] sigmatropic rearrangement. Computed (CPCM(DCM)-B3LYP/6-31G(d)) rearrangement barriers (vs **1** + **2**) are shown in kcal/mol (normal text). Energies in parentheses are for structures where the vinyl anion was protonated before rearrangement and are relative to that of the lowest energy transition-state structure.

before undergoing ring expansion? While this is a difficult question to answer (in part because energies of protonation are difficult to compute accurately),[17] we find that the barriers for the rearrangement of protonated species (i.e., cationic rather than zwitterionic adducts) are low (Figure 5; consistent with previously reported barriers for cationic aza-Cope rearrangements).[1] In addition, the order of energies for **TS1**-**6** does not change greatly upon protonation, with the 2*E*,5*E* product still computed to be kinetically preferred (with a slightly smaller preference than for the zwitterionic system).

Morpholines Rather than Piperidines. α-Vinyl morpholines were also shown to be competent substrates for addition/rearrangement.[3] A 9:1 mixture of 2*E*,5*E* and 2*E*,5*Z* products was reported, corresponding to comparable, but slightly lower, selectivity for morpholine than piperidine substrates. We predict a 1.3 kcal/mol difference in energy between the corresponding **TS2** and **TS4** structures (Figure 6; in DCM), consistent with the experimental observation (although, given the expected accuracy of such calculations, the quantitative nature of the agreement is likely coincidental).[18]

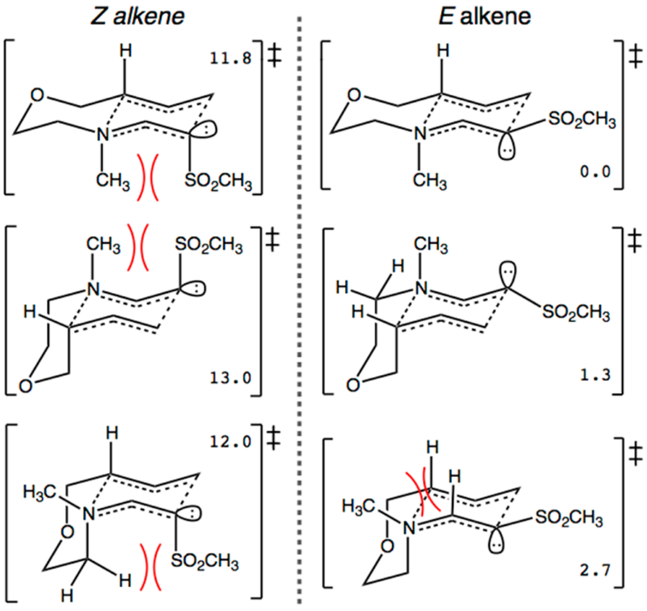


Figure 6. Possible transition-state structure geometries for [3,3] sigmatropic rearrangement of morpholine adducts.

Substituent Effects. An analysis of substituent effects on the addition/rearrangement process was also performed by Weston et al. (using an isoprene rather than vinyl group on the piperidine ring, necessitating an elevated reaction temperature, and substituents at the *para* position of the sulfone aryl group).[3] A slope of the Hammett plot for the systems examined was +1.18, indicating that the reaction is faster with electron-withdrawing substituents, consistent with a buildup of negative charge at a position in direct communication with the substituent in the rate-determining step. This observation was taken as evidence that the rate-determining step is the initial conjugate addition, while our calculations suggest that the [3,3] sigmatropic rearrangement is rate-determining. In an attempt to provide an explanation for this apparent discrepancy between experiment and theory, we calculated barriers for both conjugate addition and rearrangement for a variety of systems: (Br, Cl, F, CH_3 and OCH_3 at the *para* position of the aryl group on the sulfonyl).[19] As shown in Figure 7, the predicted barrier for conjugate addition is indeed lower with electron-withdrawing substituents. As shown in Figure 8, however, the predicted barrier for rearrangement—overall barrier from separated reactants—is also lower with electron-withdrawing substituents. Consequently, the experimentally observed substituent effect is also consistent with the rearrangement step being rate-determining, as predicted on the basis of our computed energetics. Since our calculations indicate that the carbanion lone pair is present at the transition-state structure for rearrangement (rather than acting as a nucleophile), the rearrangement transition-state structures should also benefit from appended electron-withdrawing groups (note that the hyperconjugation discussed above should also be sensitive to aryl substituents). In fact, the barriers computed using the rearrangement transition-state structures are predicted to be, in

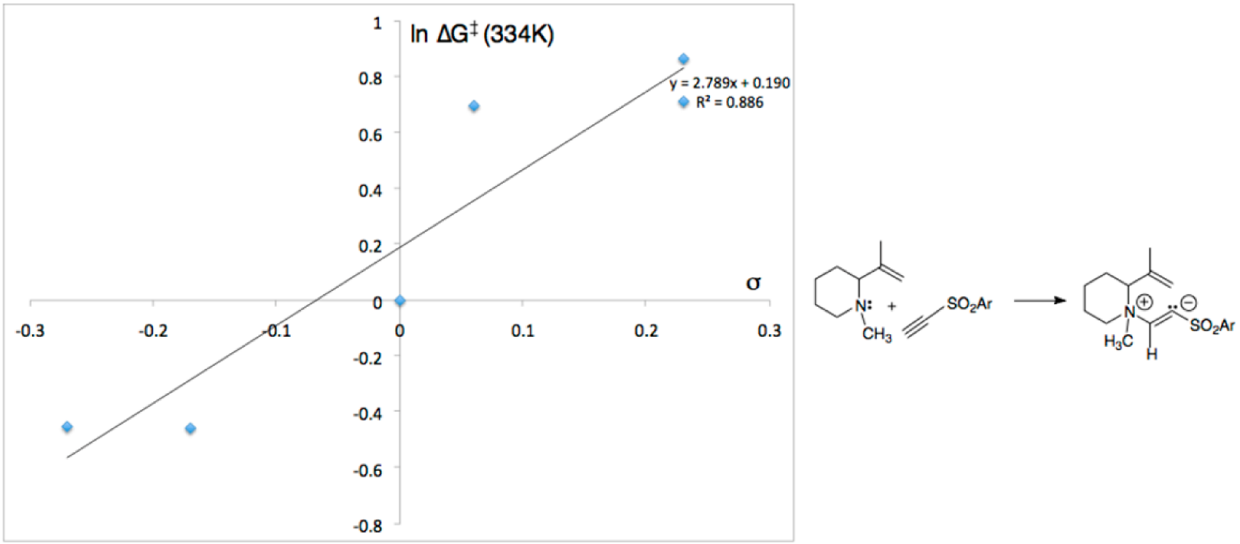


Figure 7. Plot of ln $\Delta G^\ddagger$ (334 K) versus σ for conjugate addition (relative to separate reactants; results for other conformations can be found in the Supporting Information).[19] Electron-donating groups are on the left of the *x*-axis, while electron-withdrawing groups are on the right. Calculations were performed with CPC(chloroform)-B3LYP/6-31G(d), temp = 334 K.

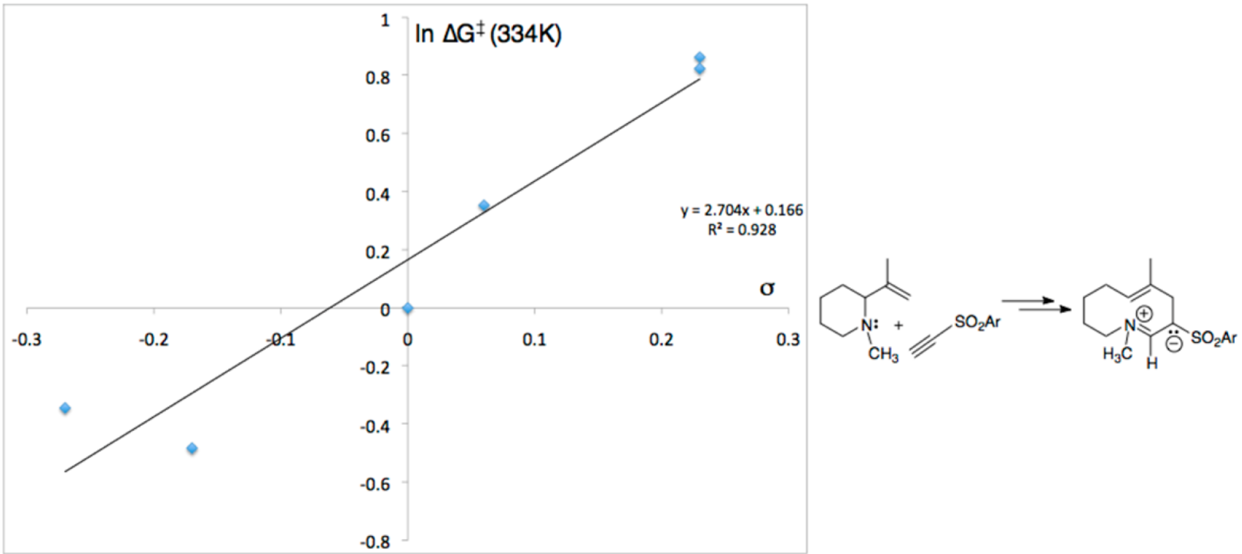


Figure 8. Plot of ln $\Delta G^\ddagger$ (334 K) versus σ for overall barriers from separate reactants to [3,3] sigmatropic shift transition-state structure (results for other conformations can be found in the Supporting Information).[19] Electron-donating groups are on the left of the *x*-axis, while electron-withdrawing groups are on the right. Calculations were performed with CPC(chloroform)-B3LYP/6-31G(d), temp = 334 K.

general, more sensitive to the nature of the substituents than those for conjugate addition (see Supporting Information for isomers, where the difference in slopes is more apparent), consistent with the fact that the vinyl carbanion is fully formed in the former but not in the latter.

■ CONCLUSIONS

The conjugate addition−rearrangement reaction of piperidines and alkynyl sulfones was explored using DFT calculations. On the basis of our results, we conclude that the [3,3] sigmatropic rearrangement is rate-determining. Transannular strain in the rate-determining transition-state structures controls product selectivity. The carbanion formed upon addition of a piperidine to an alkynyl sulfone behaves as a relatively innocuous substituent in the rearrangement reaction rather than an active participant, i.e., as a nucleophile. Thus, the rearrangement is a classic [3,3] sigmatropic shift despite the presence of a potentially reactive orthogonal orbital on one of the atoms involved in the rearrangement.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Coordinates and energies for all computed structures and additional computational data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00996.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the University of California–Davis, the donors of the American Chemical Society Petroleum Research Fund, the National Science Foundation CAREER program, and the National Science Foundation's Partnership for Advanced Computational Infrastructure (Pittsburgh Supercomputer Center) for support of this research.

■ DEDICATION

Dedicated to Roald Hoffmann, a mensch among mere men of mechanisms.

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(14) While *E*/*Z* isomerization of the intermediates could occur, attempts to find transition-state structures were unsuccessful. In polar solvents like water and methanol, a transition-state structure was found, but it was higher in energy than the transition-state structures for the conjugate addition steps; see Supporting Information for details. The barrier for *E*/*Z* isomerization in a closely related system was computed, with similar methods to those employed here, to be 8 kcal/mol. Pinto, L.V. F.; Gloria, P. M. C.; Gomes, M. J. S.; Rzepa, H. S.; Prabhakar, S.; Lobo, A. M. *Tetrahedron Lett.* **2009**, *50*, 3446–3449. See also: Knorr, R.; Ruhdorfer, J.; Böhrer, P. *Organometallics* **2015**, *34*, 1038–1045.

(15) Scans in which the C3–C4 bond was decreased led to the transition-state structure for concerted [3,3] shift.

(16) A scan in which the N–C6 bond was increased led to the transition-state structure for concerted [3,3] shift.

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