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Ab Initio Investigation of the 3-Aza-Cope Reaction

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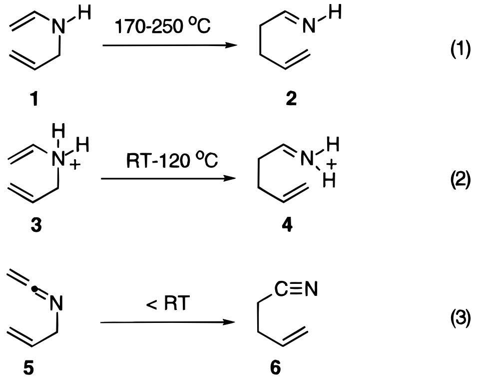
The energies of reaction and activation for three archetypal aliphatic 3-aza-Cope reactions have been investigated by MP4/6-31G*//MP2/6-31G* calculations. The activation energies of these rearrangements (3-aza-1,5-hexadiene (**1** to **2**, eq 1), $\Delta E^{\ddagger} = 34.6$ kcal/mol; 3-azonia-1,5-hexadiene (**3** to **4**, eq 2), $\Delta E^{\ddagger}=21.4$ kcal/mol; 3-aza-1,2,5-hexatriene (**5** to **6**, eq 3), $\Delta E^{\ddagger} = 17.7$ kcal/mol) were found to be consistent with the reported relative facility of substituted versions of these processes. Inclusion of electron correlation in the theoretical model was necessary to reproduce the experimentally observed ordering and relative magnitudes of the activation energies. Comparisons of the transition-structure bond orders for these three reactions show that the *N*-allyl ketenimine rearrangement features the least amount of bond breaking and bond making of any of these processes. Finally, a comparison of the atomic charges on nitrogen (as calculated by the methods of Mulliken, NBO analysis, and CHELPG methods using the MP2 densities) in these three 3-aza-Cope rearrangements provides evidence that charge delocalization in the transition state is an important factor only in the charged 3-aza-Cope reaction. The relative facility of the 3-aza-1,2,5-hexatriene rearrangement is probably due to the favorable reduction of steric congestion in the transition structure which is offered by the heterocumulene structure.

Introduction

In the past few decades several variations of the 3-aza-Cope[1] reaction have been reported.[2] Each one of these variations can be classified as belonging to a subclass of this type of reaction. That is, the basic elements for each of these variations can be found in the rearrangements of either 3-aza-1,5-hexadienes (**1** → **2**, eq 1),[3] 3-azonia-1,5-hexadienes (**3** → **4**, eq 2),[4] or 3-aza-1,2,5-hexatrienes (**5** → **6**, eq 3) (Scheme 1).[5] A review of the literature on these reactions suggests that there exists a general trend toward milder reaction conditions as one progresses from the "neutral" (eq 1) to the "charged" (eq 2) and finally to the ketenimine rearrangement (eq 3). Our interest in the rearrangements of 3-aza-1,2,5-hexatrienes has been driven both by the synthetic potential of this extremely mild transformation and by our desire to more fully understand the relative facility of these three related rearrangements.

Scheme 1



The only quantitative study of the reaction energetics of processes related to these aliphatic sigmatropic reactions is reported in the work of Jolidon and Hansen.[6,7] They determined the $\Delta H^{\ddagger}$ for several examples of the neutral (eq 4) and charged (eq 5) aromatic 3-aza-Cope rearrangements and found that they were generally in the range of 34−40 kcal/mol for the uncatalyzed reactions and 27−30 kcal/mol for the acid-catalyzed variants (Scheme 2).[8]

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(1) There seems to be some ambiguity in the literature, in part exacerbated by publications from this laboratory, as to whether to refer to these transformations as 3-aza-Cope or 3-aza-Claisen reactions. We now agree with Fowler (Wu, P.-L.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 5998−6005) that the term aza-Claisen should be reserved only for those processes in which a *carbon* atom in the allyl−vinyl ether system has been replaced by nitrogen.

(2) For reviews concerned with these and related [3,3]-sigmatropic rearrangements, see: Claisen, (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 5, pp 827−873. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227−232. (e) Rhoads, S. J.; Raulins, N. R. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley and Sons: New York, 1975; Vol. 22, pp 1−252. Hetero-Cope: (f) Blechert, S. *Synthesis* **1989**, *89*, 71−82. Catalysis of Cope and Claisen rearrangements: (g) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247. Chirality transfer in these reactions: (h) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; *Vol.* 3, pp 503−572.

(3) (a) Hill, R. K.; Gilman, N. W. *Tetrahedron Lett.* **1967**, 1421−1423. (b) Kurth, M. J.; Brown, E. G. *Synthesis* **1988**, 362−366.

(4) Both quaternary ammonium salts and Lewis-acid-catalyzed reactions fall into this category: (a) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1961**, *20*, 3576−3577. (b) Barta, N. S.; Cook, G. R.; Landis, M. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 7188−7194. (c) Cook, G. R.; Stille, J. R. *Tetrahedron* **1994**, *50*, 4105−4124. A 3-aza-Cope transformation which benefited from being both charge and Lewis-acid catalyzed was recently reported to occur at −60 °C: Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579−588. For a particularly mild example of a presumably proton-catalyzed 3-aza-Cope reaction, see: Welch, J. T.; De Corte, B.; De Kimpe, N. *J. Org. Chem.* **1990**, *55*, 4981−4983.

(5) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1965**, *30*, 2564−2565.

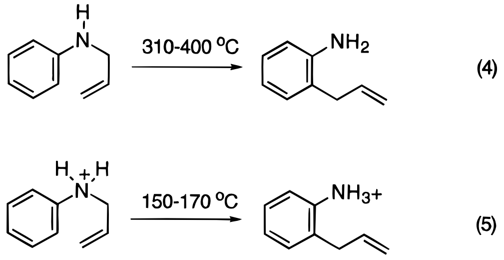
(6) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978−1032.

(7) For applications of this reaction to the synthesis of ergot precursors, see: Danishefsky, S. J.; Phillips, G. B. *Tetrahedron Lett.* **1984**, *25*, 3159−3162. For studies concerning the Lewis-acid-promoted aromatic 3-aza-Cope, see: Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095−5100.

(8) We have been able to reproduce these activation energies quite accurately at the MP2(FC)/6-31G*//HF/6-31G* level (neutral, $\Delta E^{\ddagger} = 42.4$ kcal/mol; charged, $\Delta E^{\ddagger} = 32.7$ kcal/mol). Geometry optimizations at the HF/6-31G* level lead to transition structures in which the amount of C−N bond breaking appears to be exaggerated. We are currently investigating these reactions at correlated levels of theory.

0022-3263/96/1961-0978$12.00/0

Scheme 2



Aliphatic versions of these same reactions occur at lower temperatures, generally between 170 and 250 °C for the neutral rearrangement and rt and 110 °C for the Lewis-acid-catalyzed processes.[1c] We,[9] and others,[10] have found that the ketenimine to nitrile rearrangement occurs conveniently at temperatures less than ambient. The work presented in this paper attempts to match these experimental and empirical observations with theory, examining archetypal examples of each of these reactions for the first time using ab initio techniques.[11] As will be shown, the results of ab initio calculations at the MP2/6-31G*//HF/6-31G* and more sophisticated levels of theory are totally consistent with the experimental observations mentioned above. Additionally, a comparison of the transition-state bond orders for these three reactions shows that the *N*-allyl ketenimine rearrangement features the least amount of bond breaking and bond making of any of these processes. Finally, calculations of the atomic charge on nitrogen in the stationary states along the reaction coordinate of each of these three 3-aza-Cope rearrangements shows that charge delocalization in the transition state is an important factor only in the charged 3-aza-Cope reaction.

Computational Methods

Calculations were performed using SPARTAN[12] and GAUSSIAN 92.[13] The frozen core method was used for all MP2 calculations. Each stationary state was characterized by a frequency calculation, starting materials and products having all positive frequencies, and transition structures all possessing a single negative (imaginary) frequency. No symmetry was assumed for the starting material, transition structures, or products. The normal mode corresponding to the negative frequency was animated in each case to ensure that it corresponded to the expected concerted bond-making/breaking process. All calculations were performed in Cartesian coordinates.

Results and Discussion

Our theoretical study of these three rearrangements was based on similar investigations of the Cope[14,15] and Claisen rearrangements.[16] The energies of starting materials, transition structures, and products for the three known types of aliphatic 3-aza-Cope reactions were calculated using standard semiempirical and ab initio basis sets. Table 1 shows the results of these calculations at increasingly sophisticated levels of theory. Figures 1−3 show the MP2/6-31G* geometries for the neutral (chair, **7**; twist-boat, **8** and **9**), charged (chair, **10**; boat, **11** and **12**), and ketenimine (**13** and **14**) transition structures. While chairlike transition structures were assumed for the neutral and charged rearrangements, geometry optimizations were also performed on the boatlike transition structures for these two reactions up to the MP2/6-31G* level. They were found to be 3.5 (neutral, **9**) and 6.2 (charged, **12**) kcal/mol higher in energy than the corresponding chair transition structures.

Table 1 shows that the calculated activation energies of these rearrangements are unacceptably comparable at the semiempirical level and that the experimentally observed relative magnitudes of these activation energies are reproduced only after electron correlation is included in the theoretical model. The use of a diffuse function in the basis set did not appear to be necessary as neither the geometry nor the relative energies calculated for the neutral 3-aza-Cope reaction changed significantly upon optimization and energy determination at the MP2/6-31+G* level of theory.[17] Additionally, single-point energy calculations using the MP2/6-31G* geometries and employing the MP2/6-311G* and UMP/6-31G* basis sets also gave energies that were essentially the same as those calculated using the MP2/6-31G* basis set alone. These results suggest that the MP2/6-31G* level of theory is a reasonable choice for these initial calculations of both the geometries and the energies of these three 3-aza-Cope reactions.[16b] It is noteworthy, however, that the energies of activation calculated at the MP2/6-31G*//HF/6-31G* level are in reasonable agreement with those calculated

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[9] (a) Walters, M. A.; McDonough, C. S.; Brown, P. S., Jr.; Hoem, A. B. *Tetrahedron Lett.* **1991**, *32*, 179−182. (b) Walters, M. A.; Hoem, A. B.; Arcand, H. R.; Hegeman, A. D.; McDonough, C. S. *Tetrahedron Lett.* **1993**, *34*, 1453−1456. (c) Walters, M. A.; Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645−2647.

[10] (a) Bruckner, R.; Huisgen, R. *Tetrahedron Lett.* **1994**, *35*, 3281−3284. (b) Nubbemeyer, U. *Synthesis* **1993**, 1120−1128. (c) Molina, P.; Alajarin, M.; Lopez-Leonardo, C.; Alcantara, J. *Tetrahedron* **1993**, *49*, 5153−5168. (d) Molina, P.; Alajarin, M.; Lopez-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041−4044.

[11] Walters, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11618−11619. While this work was in progress, studies of these reactions at the MNDO level of theory were reported by Gilbert and Cousins. Gilbert, J. C.; Cousins, K. R. *Tetrahedron* **1994**, *50*, 10671−10684.

[12] Hehre, W. J.; Burke, L. D.; Shusterman, A. J. SPARTAN 3.1, Wavefunction, Inc.

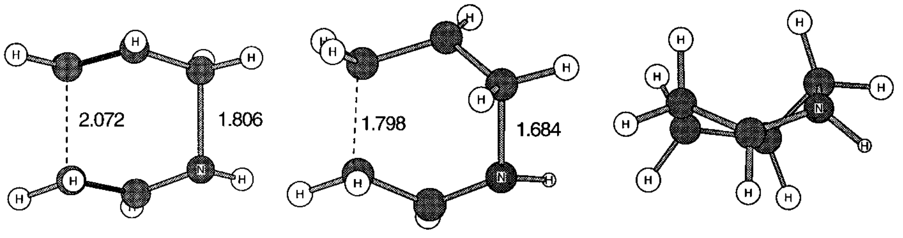
[13] Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. GAUSSIAN 92, Revision A; Gaussian, Inc.: Pittsburgh, PA, 1992.

[14] (a) Kozlowski, P. M.; Dupuis, M.; Davidson, E. R. *J. Am. Chem. Soc.* **1995**, *117*, 774−778. (b) Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072−1076. (c) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 9756−9759. (d) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213−236. (e) Dewar, M. J. S.; Healy, E. F. *Chem. Phys. Lett.* **1987**, *141*, 521−524.

[15] For an excellent discussion of ab initio calculations on a variety of hydrocarbon pericyclic reactions, see: Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682−708.

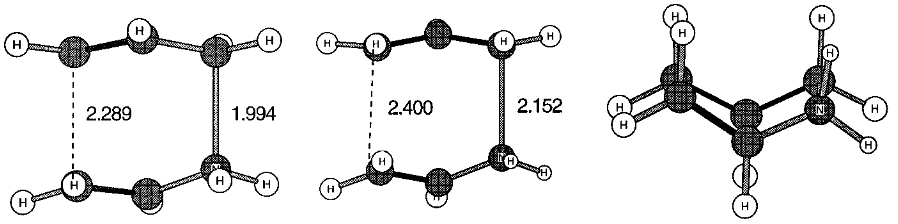
[16] (a) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314−2315. Houk has recently published a significant refinement of the Claisen transition structure using the MCSCF/6-31G* level of theory. (b) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 12047−12048. Whether or not that level of theory would improve upon our results at the MP2(FC)/6-31G* level appears to be a moot point at the present time since no experimental data regarding the kinetics, thermodynamics, or isotope effects in these aliphatic nitrogen-containing rearrangements is currently available.

[17] A similar observation was recently reported by Houk in his computational work concerning the anionic chorismate to prephenate rearrangement. (a) Wiest, O.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 7582−7584. Although this basis set was developed primarily for use with anionic systems (see, for example: (b) Chandrasekhar, J.; Andrade, J. G.; von Rague Schleyer, P. *J. Am. Chem. Soc.* **1981**, *103*, 5609−5614. (c) Spitznagel, G. W.; Clark, T.; Chandrasekhar, J.; von Rague Schleyer, P. *J. Comput. Chem.* **1982**, *3*, 363−371. (d) van Eikema Hommes, N. J. R.; von Rague Schleyer, P. *Tetrahedron* **1994**, *50*, 5903−5916. (e) Mikami, K.; Uchida, T.; Hirano, T.; Wu, Y.-D.; Houk, K. N. *Tetrahedron* **1994**, *50*, 5917−5926) it has also been suggested as an appropriate method for molecules bearing lone pairs: (f) Wiberg, K. B.; Marquez, M.; Castejon, H. *J. Org. Chem.* **1994**, *59*, 6817−6822.



7 **8** **9**

Figure 1. Chair **7** and twist-boat (**8** and **9**) transition structures for the neutral 3-aza-Cope rearrangement (MP2/6-31G* geometry; distances in angstroms).



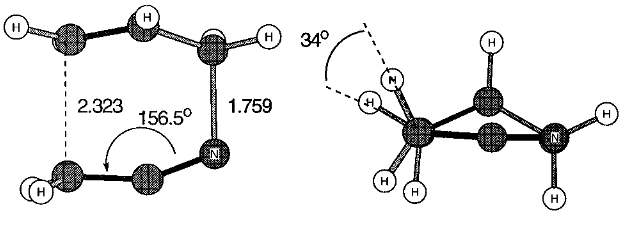
10 **11** **12**

Figure 2. Chair **10** and boat (**11** and **12**) transition structures for the charged 3-aza-Cope rearrangement (MP2/6-31G* geometry; distances in angstroms).

Table 1. Calculated Energy of Activation and Reaction for the Neutral, Charged, and *N*-Allyl Ketenimine 3-Aza-Cope Reactions (kcal/mol)

	neutral		charged		Ketenimine	
	ΔE_{act}	ΔE_{rxn}	ΔE_{act}	ΔE_{rxn}	ΔE_{act}	ΔE_{rxn}
PM3[a]	35.3	−8.8	33.5	−6.54	32.8	−24.0
STO-3G	53.4	−10.5	43.6	−10.0	34.3	−52.6
3−21G*	51.6	−1.21	23.6	−10.0	28.0	−35.4
6-31G*	56.8	−9.1	24.5	−14.9	38.0	−34.3
MP2/6-31G*//6-31G*	31.5	−9.7	18.8	−11.7	13.5	−37.0
MP2/6-31G*	30.7	−10.2	18.8	−10.2	14.8	−39.0
MP2/6-31+G*	30.6	−8.8				
MP2/6-311G*//MP2/6-31G*	28.9	−9.6	18.2	−10.3	13.6	−38.7
$\Delta S^{\ddagger\,b}$	−7.7		−7.8		−7.6	
MP2/6-31G* + ZPE + E (thermal)[c,d]	28.9	−9.7	16.2	−10.5	13.3	−36.9
MP4(SDTQ)/6-31G*//MP2/6-31G*	34.6	−10.6	21.4	−9.8	17.7	−36.8
MP4(SDTQ)/6-31G*//MP2/6-31G* with MP2/6-31G* correction	32.8	−10.1	18.7	−10.1	16.2	−34.7
Boat transition structures; MP2/6-31G*	34.2		25.0			

[a] This method calculates ΔH. [b] cal/(mol K). [c] $\Delta H^{\ddagger}$ at 298.15 K. [d] ΔH_{rxn} at 298.15 K.



13 **14**

Figure 3. Half-chair (**13** and **14**) transition structure for the *N*-allyl ketenimine 3-aza-Cope rearrangement (MP2/6-31G* geometry; distances in angstroms).

at the MP2/6-31G* level, suggestive of a relatively flat potential energy surface for these reactions. While this observation might simplify future *energy* calculations on larger, related systems,[8] the calculated transition structure geometries at these two levels of theory are actually quite different (*vide infra*) and would probably require further refinement.[18]

The value of $\Delta E^{\ddagger} = 34.6$ kcal/mol calculated for the neutral rearrangement at the MP4(SDTQ) level[19] is consistent with the empirical observation that this type of reaction usually occurs at slightly higher temperatures than do the analogous Claisen ($\Delta H^{\ddagger} = 30.6$)[20] and Cope ($\Delta H^{\ddagger} = 33.5$)[21] reactions.[2g] By inference then, the activation energies for the charged 3-aza-Cope ($\Delta E^{\ddagger}$=21.4) and ketenimine 3-aza-Cope ($\Delta E^{\ddagger} = 17.7$) calculated at this same level of theory are probably reasonable estimates of the actual values for these unsubstituted systems.

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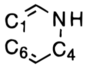
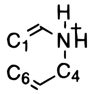
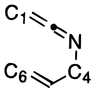
[18] Optimization of the geometry at the MP2/6-31G* level of theory appears to be sufficient, but further refinement of the transition structures geometries of these reactions beyond that level might be accomplished through the use of either CASSCF,[16a] MRMP2,[14a] or DFT methods. (DFT = density functional theory. Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864−871. Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133−1138. For leading references to this approach, see: Weber, J.; Hyber, H.; Weber, H. P. *Chimia* **1993**, *47*, 57−59.)

[19] Borden has reported the energy of activation for the Cope rearrangement at the MP4(SDTQ)/6-31G*//CASSCF/6-31G* level to be 33.8 kcal/mol. See ref 14b, footnote 33.

[20] Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299−5306.

[21] Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155−3159. The solution phase value is 25.4 kcal/mol. Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984−6986.

Table 2. Interatomic C_1-C_6 and N_3-C_4 Distances for the Transition Structures for the Neutral, Charged, and *N*-Allyl Ketenimine 3-Aza-Cope Reactions at Selected Levels of Theory[a]

						
level	C_1-C_6	$N-C_4$	C_1-C_6	$N-C_4$	C_1-C_6	$N-C_4$
PM3	1.829	1.580	1.849	1.800	1.933	1.641
STO-3G	1.876	1.687	1.952	1.895	2.097	1.697
RHF/3-21G*	2.071	1.920	2.355	2.223	2.320	1.925
RHF/6-31G*	2.157	1.968	2.627	2.427	2.348	1.957
MP2/6-31G*	2.072	1.806	2.289	1.994	2.323	1.759

[a] Distances are in angstroms.

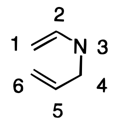
Each of the rearrangements has a $\Delta S^{\ddagger} \sim -7.7$ cal/(mol K), which is consistent with a pericyclic reaction and identical with the value which has been determined experimentally for the Claisen reaction.[20]

Table 2 shows the important bonding/nonbonding interatomic distances in each of the three transition structures as a function of the level of theory employed in the calculation. Significantly, the results indicate that there exist considerable differences between the transition structure geometries calculated at these various levels of theory, suggesting that calculations aimed at predicting the *geometry* of more complicated systems will have to be carried out at a level of theory that includes electron correlation.

Comparison of the bonded ($N-C_4$) and nonbonded (C_1-C_6) distances at the HF/3-21G*, HF/6-31G*, and MP2/6-31G* levels reveals a few important trends. The HF/6-31G* geometry consistently has the largest values for these two parameters. If these transition structures are compared at the HF/3-21G* and MP2/6-31G* levels, the difference in geometry is largely reflected in a shortening of the bond which is being broken in the reaction. For example, the largest change in calculated C_1-C_6 (bond-making) distance between these two levels of theory is seen for the charged rearrangement and even in that case is only 0.066 Å. In contrast to this, the $N-C_4$ bond (bond-breaking) length is always shorter at the MP2/6-31G* level than at the 3-21G* level, the change in length ranging from a contraction of 0.229 Å in the charged case to 0.114 Å for the neutral rearrangement. Therefore, the inclusion of electron correlation always makes the transition structures for these 3-aza-Cope reactions more reactant-like. This same trend is not found in pericyclic reactions of hydrocarbons, where the difference between 3-21G and MP2/6-31G* transition structure geometries is reported to be only on the order of several hundreths of an angstrom,[15] but is observed in the case of the Claisen reaction where the MP2/6-31G* value for the C–O bond distance is reported to be 0.12 Å shorter than that calculated at the HF/6-31G* level.[22]

A more thorough description of the transition structure geometries of these reactions can be found in Table 3, which lists heavy-atom interatomic distances as the three rearrangements move from starting materials to product at the MP2/6-31G* level. Values for the interatomic distances between the π-carbons involved in the bond-forming process varied from 2.072 to 2.289 Å, comparable to the range of 1.95–2.28 Å reported by Houk for similar bond-forming interactions in a wide variety of hydrocarbon pericyclic reactions.[15] On the other hand, the calculated range of lengths for the C–N bonds being broken in the transition structure varied from 1.759 to 1.994 Å.

Table 3. Interatomic Distances for the Charged, and *N*-Allyl Ketenimine 3-Aza-Cope Reactions at the MP2/6-31G* level[a]



	C_1-C_2	C_2-N	$N-C_4$	C_4-C_5	C_5-C_6	C_1-C_6
			3-Aza-1,5-hexadiene			
SM	1.343	1.398	1.463	1.498	1.338	
TS	1.392	1.363	1.806	1.416	1.392	2.072
PR	1.503	1.284		1.339	1.500	1.538
			3-Azonia-1,5-hexadiene			
SM	1.330	1.472	1.531	1.492	1.340	
TS	1.370	1.381	1.994	1.405	1.381	2.289
PR	1.470	1.293		1.338	1.500	1.599
			3-Aza-1,2,5-hexadiene			
SM	1.321	1.235	1.477	1.498	1.338	
TS	1.360	1.220	1.759	1.425	1.378	2.323
PR	1.466	1.181		1.338	1.500	1.540

[a] SM = starting material; TS = transition structure; PR = product. Distances are in angstroms.

In order to compare these three 3-aza-Cope reactions to each other, the relative extent of bonding which they each featured in their transition structures was quantified. Since different types of C–N bonds are being broken in each of these processes, it is appropriate to discuss the extent of bond breaking (BB) and bond making (BM) in the transition structures for these reactions in terms of bond order. The bond orders for these transition-structure bonds were calculated using the modified Pauling[23] bond order equation[24] suggested by Gajewski.[25] This modified bond order equation was recently employed by Houk to compare the influence of calculation type on extent of bond making and bond breaking in the Cope rearrangement.[26] The bond orders calculated in this fashion (neutral $n_p(BB) = 0.56$, $n_p(BM) = 0.41$; charged $n_p(BB) = 0.46$, $n_p(BM) = 0.30$; ketenimine $n_p(BB) = 0.62$, $n_p(BM) = 0.27$) are graphed in a bond order diagram (Figure 4) along with the bond orders obtained for the Claisen reaction ($n_p(BB) = 0.51$, $n_p(BM) = 0.33$) calculated at the same level of theory and at the CASSCF/6-31G* level ($n_p(BB) = 0.31$, $n_p(BM) = 0.18$).[16b] These values characterized the 3-aza-1,2,5-hexatriene rearrangement as having the least amount of both transition-structure bond making and bond breaking of any of these heteroatom substituted Cope reactions at

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(22) Compare the results reported in refs 16a and 16b.

(23) Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542–553.

(24) $n_p = n_o \exp[(R_o - R)/0.6]$, where n_p is the modified Pauling bond order, n_o is the bond order of the fully formed bond of length R_o, and R is the length of the bond of bond order n_p. The 0.6 proportionality constant has been suggested to be more appropriate to use than the 0.3 value in cases where the bond in question is less than order 1.[26] Whether or not this value is appropriate for use with C–N bonds is not yet known. The transition structure bond orders for the three 3-aza-Cope rearrangements employing the 0.3 proportionality constant are: neutral, $n_p(BB) = 0.32$, $n_p(BM) = 0.16$; charged, ($n_p(BB) = 0.21$, $n_p(BM) = 0.09$); ketenimine, $n_p(BB) = 0.39$, $n_p(BM) = 0.07$. The values calculated for $n_p(BM)$ seem abnormally low using this constant. For a study examining the bond order–bond length relationship, see: Paolini, J. P. *J. Comput. Chem.* **1990**, *11*, 1160–1163.

(25) Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAI Press, Inc.: Greenwich, CT, 1990; Vol. 2, pp 65–92.

(26) Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565–8572.

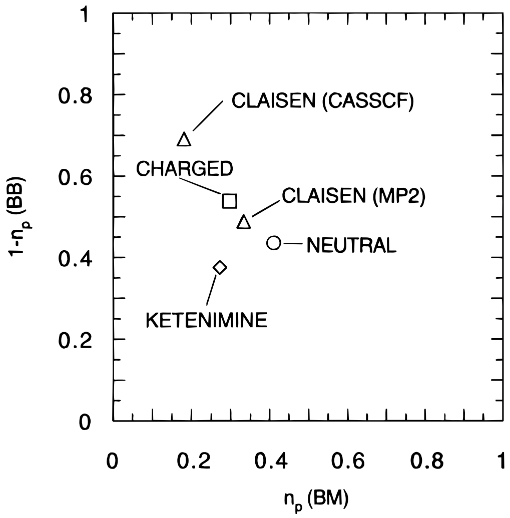

Figure 4. Diagram comparing the transition-structure bond orders for the neutral, charged, and ketenimine 3-aza-Cope reactions using MP2/6-31G* geometries and the Claisen rearrangement using both the MP2/6-31G* and CASSCF/6-31G* geometries. The modified Pauling bond order equation using a 0.6 proportionality constant was employed to calculate the bond orders.

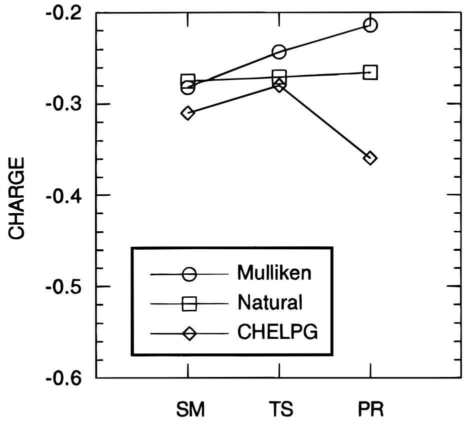

Figure 5. Atomic charge on nitrogen in the neutral 3-aza-Cope reaction (SM = starting material, TS = transition structure, PR = product; hydrogen charges summed into nitrogen).

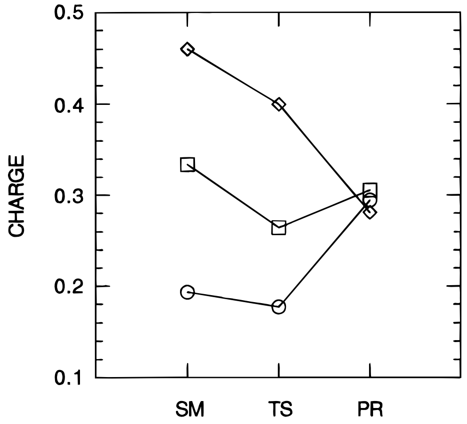

Figure 6. Atomic charge on nitrogen in the charged 3-aza-Cope reaction (SM = starting material, TS = transition structure, PR = product; hydrogen charges summed into nitrogen. See Figure 5 for the legend).

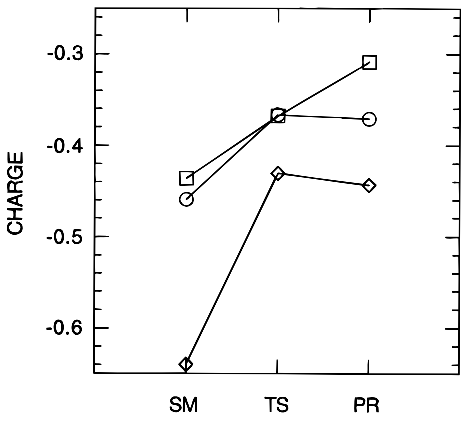

Figure 7. Atomic charge on nitrogen in the ketenimine 3-aza-Cope reaction (SM = starting material, TS = transition structure, PR = product; hydrogen charges summed into nitrogen. See Figure 5 for the legend).

the MP2/6-31G* level. This early transition state in the 3-aza-1,2,5-hexatriene case is consistent with the Hammond postulate[27,28] given the marked exothermicity of this reaction (calculated $\Delta H_{\mathrm{rxn}} = -37$ kcal/mol) relative to the other two 3-aza-Cope reactions ($\Delta H_{\mathrm{rxn}} = -10$) and the Claisen reaction ($\Delta H_{\mathrm{rxn}} \sim -17$ kcal/mol).[16a]

Since electronic effects have been used to rationalize the observed acceleration of the charged 3-aza-Cope reaction relative to the neutral case,[2g] the flow of charge in the three reaction processes was examined by the method of Mulliken,[29] the natural bond orbital (NBO) method of Weinhold et al.,[30] and the CHELPG method of Breneman and Wiberg.[31,32] (Compilations of these charges are included in the Supporting Information.) These methods were chosen because they are each readily accessible in the GAUSSIAN 92 package[13] and because they represent methods based both on molecular orbitals (Mulliken, NBO) and on electrostatic potentials (CHELPG).[33] Additionally, the NBO-derived charges have been found to correlate well with substituent electronegativity in cumulenes and heterocumulenes,[34] and the CHELPG method has been used to analyze atomic charges in the transition structure of the chorismate–prephenate rearrangement, an enzyme-catalyzed [3,3]-sigmatropic reaction.[17a]

Figures 5–7 show the calculated atomic charges on nitrogen (with hydrogen atom charges summed into nitrogen) as each rearrangement proceeds from starting material to transition structure and, finally, to product. All of the methods for computing atomic charge show that

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[27] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

[28] The relatively low levels of diastereoselection which have reported in the rearrangement of substituted 3-aza-1,2,5-hexatrienes may be a consequence of this early transition state.[9c,10b,d]

[29] Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833–1840; 1841–1846; 2338–2342; 2343–2346.

[30] Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO Version 3.1.

[31] Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361–373.

[32] For a comparsion of the different methods employed to calculate atomic charges and their relative merits, see: Wiberg, K. B.; Rablen, P. R. *J. Comput. Chem.* **1993**, *14*, 1504–1518.

[33] In all cases atomic charges were calculated using the MP2 density. Wiberg, K. B.; Hadad, C. M.; LePage, T. J.; Breneman, C. M.; Frisch, M. J. *J. Phys. Chem.* **1992**, *96*, 671–679.

[34] For a detailed discussion of the relative efficacy of a number of methods of charge calculation as applied to these compounds, see: McAllister, M. A.; Tidwell, T. T. *J. Org. Chem.* **1994**, *59*, 4506–4515 and reference therein.

in both uncharged cases (Figures 5 (neutral) and 7 (ketenimine)) the atomic charge on nitrogen increases from starting material to transition structure. This is in contrast to what is observed in the 3-azonia-1,5-hexadiene rearrangement (Figure 6), where the charge on nitrogen can be clearly seen to decrease in going from the starting material to the transition structure regardless of the method employed to calculate the charge. These results are consistent with the concept of charge dispersal (i.e., charge moving away from the most electronegative atom) in the transition state as being a contributing factor in the acceleration of the charged 3-aza-Cope reaction relative to the neutral case.[2g] However, since this analysis also predicts a similar inhibition for the 3-aza-1,2,5-hexatriene rearrangement, the relative acceleration of the this case must be explained in terms of steric rather than electronic effects.

The low activation energy calculated for the ketenimine rearrangement is probably due in large part to a decrease in steric repulsion in the transition structure as a result of the absence of substituents on C_2 and N in the ketenimine, effectively allowing this system to adopt the proper transition-structure orientation at a much lower energy cost than in the other two rearrangements. Additionally, the fact that the ketenimine does not have to distort to any appreciable extent to be accommodated into the cyclic transition structure is also energetically favorable. The $C_1-C_2-N_3$ bond angle only has to bend 17.9° from the calculated starting material value of 175.4° to reach the transition state,[35] in the process making the C_1-N_3 distance only 0.10 Å longer than that of the counterpoised allyl moiety.

Conclusions

In this work a reasonable correlation between experimentally observed and calculated activation energies for the neutral, charged, and *N*-allyl ketenimine 3-aza-Cope reactions has been found to exist at the MP2/6-31G*//HF/6-31G* level of theory. Additionally, fully optimized transition-structure geometries for these three 3-aza-Cope variants have been located at the MP2/6-31G* level. Calculations at the MP4(SDTQ)/6-31G*//MP2/6-31G* level lead to the estimation that the energies of activation for these archetypal processes is on the order of 35 kcal/mol for the 3-aza-1,5-hexadiene rearrangement, 21 kcal/mol for the 3-azonia-1,5-hexadiene reaction, and 18 kcal/mol for the 3-aza-1,2,5-hexatriene rearrangement. This ordering of activation energies appears to be consistent with the empirical observation that the ketenimine reaction occurs at much milder temperatures than do the other two analogous transformations. The decrease in charge on nitrogen in the transition state for the charged rearrangement most likely explains some of its acceleration relative to the neutral case. Additionally, the charged rearrangement features a more open transition structure than does either the neutral or ketenimine cases, the bond-breaking distance in the transition structure being almost 0.2 Å longer in the charged process. This should lead to a diminution of the steric interactions in this transition structure relative to the neutral case, and hence a lowering of the activation energy. Similar factors appear to explain the acceleration exhibited by the *N*-allyl ketenimine reaction relative to the other two cases, as it appears that the facility of this reaction cannot be explained on electronic grounds.

In an effort to substantiate the findings reported herein, we plan to examine the aromatic 3-aza-Cope reactions at the MP2/6-31G* level. We also plan to gather further experimental details concerning the stereochemical biases involved in the rearrangement of 3-aza-1,2,5-hexatrienes by examining the reaction of more highly functionalized *N*-allyl ketenimines. This should lead to a further understanding of both the unique features of the half-chair transition state involved in this transformation and, perhaps, to a better definition of the transition state geometry.

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Supporting Information Available: Cartesian coordinates and energies (MP4(SDTQ)/6-31G*//MP2(FC)/6-31G*) for the starting materials, transition structures (chair and boat), and products presented in this paper; MP2/6-31+G* coordinates and energies for the neutral 3-aza-Cope rearrangement; Mulliken, NBO, and CHELPG charges for the starting materials, transition structures (chair), and products presented in this paper (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[35] The calculated starting material value of ~175° is comparable to the C=C=N angle found in the X-ray structures of some aryl-substituted ketenimines. Naqvi, R. R.; Wheatley, P. J. *J. Chem. Soc. A* **1970**, 2053−2058.