Ab Initio Investigation of Three 3-Aza-Claisen Variations

Michael A. Walters

Department of Chemistry, 6128 Burke Laboratory
Dartmouth College, Hanover, New Hampshire 03755

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We recently became interested in the synthetic potential of the rearrangement of 3-aza-1,2,5-hexatrienes (Scheme 1, **2** → **3**) because this sigmatropic process was known to occur at a much milder temperature than related reactions.[1,2] For example, the neutral[3] (**4** → **5**) and charged[4] (**6** → **7**) 3-aza-Claisen reactions are known to occur at 130−250 and 40−110 °C, respectively. In marked contradistinction to these conditions, the process involving the putative ketenimine intermediate **2** can be effected at room temperature or below with a wide variety of reagents, employing simple *N*-allyl amides **1** as starting materials.[5] In an effort to understand this phenomenon, the differences in energy between the starting materials, products, and transition structures for these three reactions have been calculated at the MP4(SDTQ)/6-31G*//MP2/6-31G* level.[6] These computed values, apparently the first of their kind for this class of reactions, correlate directly with the documented kinetics of these 3-aza-Claisen variants and with the energetics reported for similar [3,3]-sigmatropic processes.[7] This finding suggests that the proposed ketenimine transition structure is a likely intermediate in the conversion of **1** to 4-pentenenitrile (**3**). Additionally, the low energy of activation found for the rearrangement of the 3-aza-1,2,5-hexatriene explains the observed mildness of the transformation relative to similar bond-forming processes. These calculations pave the way for the development of simple models to explain the diastereoselection observed in these reactions and for studies of related rearrangements.

Scheme 1

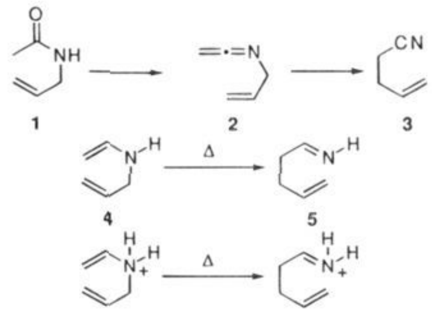

Table 1. MP2/6-31G* Optimized Transition Structure Geometries for the Neutral (1), Charged (2), and Ketenimine (3) 3-Aza-Claisen Reactions

structure	C_1C_2	C_1C_6	C_2X_3	X_3C_4	C_4C_5	C_5C_6
1, X = NH	1.392	2.072	1.363	1.806	1.416	1.393
2, X = NH_2^+	1.370	2.289	1.382	1.994	1.405	1.381
3	1.360	[illegible]	220	1.759	1.425	1.378

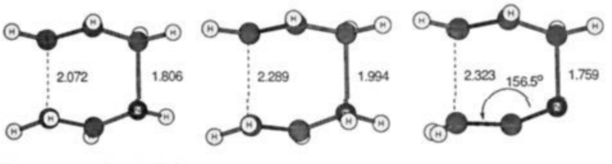

Figure 1. The MP2/6-31G* chair forms of the neutral, charged, and ketenimine 3-aza-Claisen reaction transition structures. Computed distances are in angstroms.

Our theoretical approach was based on reported investigations of the Claisen[8] and Cope[9] rearrangements. Table 1 shows the pertinent geometric data for the chain-like transition structure of each of the archetypal 3-aza rearrangements calculated at the MP2/6-31G* level.[10] Figure 1 shows top views of the optimized transition structures for each of the rearrangements studied.

Table 2 lists the calculated $\Delta H^{\ddagger}$ and ΔH_{rxn} (at 298.15 K) for each reaction process investigated along with the MP4(SDTQ)/6-31G*//MP2/6-31G* values. Studies of the Cope rearrangement suggest that this latter level of theory provides calculated activation energies that are in very good agreement with experiment.[9a] Starting materials and products were optimized to staggered acyclic structures, and transition structures were characterized by their single imaginary vibrational frequency. Inspection of the single negative frequency in each case (animation in SPARTAN 3.0; RHF/6-31G* level and below, and examination of the normal coordinates at the MP2/6-31G* level) revealed a motion of the atoms in the cyclic assembly

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

(2) For reviews concerned with these and related [3,3]-sigmatropic rearrangements, see the following. 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: Blechert, S. *Synthesis* **1989**, *89*, 71−82. Catalysis of Cope and Claisen rearrangements: Lutz, R. P. *Chem. Rev.* **1984**, 205−247. Chirality transfer in these reactions: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, pp 503−572.

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(4) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1961**, *26*, 3576−3577. See also: Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095−5100 and references cited therein.

(5) (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) 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. (e) Nubbemeyer, U. *Synthesis* **1993**, 1120−1128. (f) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1994**, *35*, 3281−3284.

(6) Calculation at lower levels of theory (PM3, STO-3G, RHF/3-21G*, and RHF/6-31G*) do not arrive at the same relative ordering of the activation energies for these three rearrangements. Programs used were SPARTAN 3.0 (Hehre, W. J.; Burke, L. D.; Shusterman, A. J. Wavefunction, Inc.: Irvine, CA) and Gaussian 92, Revision A (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, Inc.: Pittsburgh, PA, 1992).

(7) For a review of the *ab initio* calculations as applied to the transition structures of hydrocarbon pericyclic reactions, see: Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682−708.

(8) 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.

(9) (a) Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072−1076. (b) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213−236.

(10) The energy of the corresponding boat-like transition structures for both the neutral and charged 3-aza-Claisen rearrangements was also calculated at the MP2/6-31G* level. These transition structures (characterized by their single negative frequency) were calculated to be ~5 kcal/mol higher in energy than their chair-like counterparts (neutral, $\Delta\Delta H^{\ddagger} = 4.4$ kcal/mol; charged, $\Delta\Delta H^{\ddagger} = 5.4$ kcal/mol).

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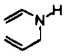
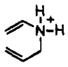
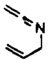
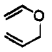
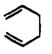
Table 2. Calculated Kinetic and Thermodynamic Parameters for the Neutral, Charged, and Ketenimine 3-Aza-Claisen Reactions (kcal/mol)

starting material	$\Delta H^{\ddagger}$ [a]	ΔH_{rxn} [a]	ΔE_{act} [b]	ΔE_{rxn} [b]
	28.9[c]	−9.7	34.6 (32.8)[d]	−10.6 (−10.1)
	16.2[c]	−10.5	21.4 (18.7)	−9.8 (−10.1)
	13.4	−36.9	17.6 (16.2)	−36.8 (−34.7)
	22.9,[e] exp. 30.6[g]			
	exp 33.5[g]		33.8[h]	

[a] MP2/6-31G*; $\Delta H^{\ddagger}$, and ΔH_{rxn} = Δ(ZPE+Thermal+MP2) at 298.15 K. [b] MP4(SDTQ)/6-31G*//MP2/6-31G*. [c] $\Delta H^{\ddagger}$ = 34−40 kcal/mol for the aromatic 3-aza-Claisen reaction and 27−30 kcal/mol for the related acid-catalyzed rearrangement.[12] [d] Values in parentheses refer to MP4(SDTQ) values corrected employing the ΔZPE+ΔThermal values obtained at the MP2/6-31G* level. [e] MP2/6-31G*//RHF/3-21G corrected using vibrational frequencies from RHF/3-21G scaled by 0.89 at T = 455 K. Ref 8. [g] Gas phase experimental value, ref 13. The solution phase value is 25.4 (Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983). [g] Solution phase experimental value, ref 14. [h] MP4(SDTQ)/6-31G*//CASSCF/6-31G*. See ref 9a, footnote 33.

which corresponded to lengthening of the N_3-C_4 bond (bond breaking) with simultaneous shortening of the C_1-C_6 distance (bond making).

These transition structure geometries and energy calculations characterize the rearrangement of the parent 3-aza-1,2,5-hexatriene as a very exothermic reaction process with a transition structure that resembles starting materials more so than in the other 3-aza-Claisen variations. For example, the C−N bond in the *N*-allyl ketenimine transition structure has only stretched 19% of its length from the reactant, while the charged and the neutral are 30% and 23% stretched, respectively. This early transition state, along with distortions from the ideal chair-like transition structure, may account for the relatively low diastereoselectivity observed for some cases of this reaction.[5d,e,11] The low activation energy calculated for this rearrangement is probably due, in large part, to a decrease in steric repulsion in the transition structure (relative to the other two reactions) as a result in the absence of substituents on C_2 and N in the ketenimine. Moreover, the ketenimine does not have to distort to any appreciable extent to be accommodated into the cyclic transition structure. The $C_1-C_2-N_3$ bond angle only has to bend 17.9° from the starting material value of 175.4°, in the process making the C_1-N_3 distance only 0.10 Å longer than the allyl moiety.

In conclusion, theoretical calculations at the MP2/6-31G* level are necessary and sufficient to produce activation energies which correlate well with the observed facility of these three 3-aza-Claisen reactions. These findings should provide impetus for kinetic studies on this class of rearrangements, investigations which are surprisingly absent from the chemical literature. Further studies on more highly substituted *N*-allyl ketenimines are currently being undertaken at both the experimental and theoretical levels.

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Supplementary Material Available: Optimized Cartesian coordinates and thermochemical information for the starting materials, transition structures (chair and boat-like), and products of each of these rearrangements at the MP2/6-31G* level and energies for each of these stationary states at the MP4(SDTQ)/6-31G*//MP2/6-31G* level (8 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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(12) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978.
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