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Hetero-Cope Rearrangements of Nitrosobutenes. DFT Studies of Thermal and Acid-Catalyzed Reactions

Arash Jabbari and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

houk@chem.ucla.edu

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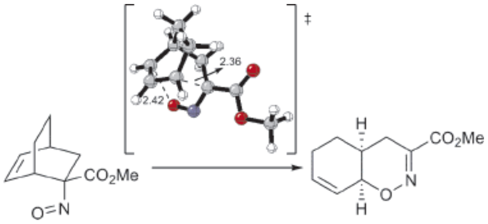
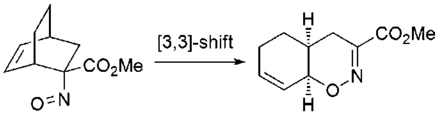
ABSTRACT



Density functional theory studies of the hetero-Cope reactions of 4-nitroso-1-butenes and nitrosobicyclo[2.2.2]hexenes are reported. The reactions proceed via concerted mechanisms. The electron-withdrawing methoxycarbonyl group α- to the nitroso group decreases the activation barrier. Lewis acids such as SbF_5 and $TiCl_4$ accelerate the reactions, as has been found experimentally by Zakarian and Lu.

Recently, Zakarian and Lu reported a new [3,3]-sigmatropic shift, or hetero-Cope rearrangement, of nitrosobicyclo[2.2.2]-hexenes (Scheme 1).[1] Other hetero-Cope rearrangements are known.[2]Most previous theoretical investigations have involved Cope and Claisen rearrangements.[3] Density functional calculations have now been performed with the B3LYP functional to investigate the mechanism of oxaza-Cope rearrangement of **1** and acyclic model systems **3** and **5**. The effect of a CO_2Me substituent and the role of the Lewis acids on the energetics of the reactions were also studied.

Scheme 1. Hetero-Cope Rearrngement of Nitrosobicyclo[2.2.2]hexene



1 **2**

All calculations were performed with Gaussian 03.[4] The hybrid B3LYP functional[5] and the 6-31G(d) basis set[6] for C, H, N, O, F, and Cl were used for the optimization of all of the stationary points in the gas phase. For Ti and Sb, the double-ζ, Hay and Wadt LANL2DZ basis set was used.[7] Frequency calculations were used to characterize stationary points as minima or first-order saddle points. All reactions

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[1] Zakarian, A.; Lu, C. D. *J. Am. Chem. Soc.* **2006**, *128*, 5356.

[2] For leading references and reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Heimgartner, H.; Hansen, H. J.; Schmid, H. In *Iminium Salts in Organic Chemistry*; Bohme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; pp 655. (c) Przheval'skii, N. M.; Grandberg, I. I. *Russ. Chem. Rev.* **1987**, *5*, 477. (d) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (e) Wade, P. A.; Murray, J. K., Jr.; Shah-Patel, S.; Le, H. T. *Chem. Commun.* **2002**, 1090.

[3] (a) Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565. (b) Hrovat, D. A.; Chen, J.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456. (c) Sakai, S. *Int. J. Quantum. Chem.* **2000**, *80*, 1099. (d) Houk, K. N.; Gonzales, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (e) Staroverov, V. N.; Davidson, E. R. *J. Am. Chem. Soc.* **2000**, *122*, 7377.

[4] Frisch, M. J. et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford. CT, 2004. The full reference is listed in Supporting Information.

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and activation enthalpies reported were zero-point (ZPE) corrected with unscaled frequencies.

Four different mechanisms can be envisioned for oxaza-Cope rearrangement of **3**: a concerted pericyclic [3,3]-sigmatropic rearrangement (path A), an associative pathway through a diradical (path B), or a dissociative process involving radical pair (path C) or ion pair formation (path D) (Figure 1).

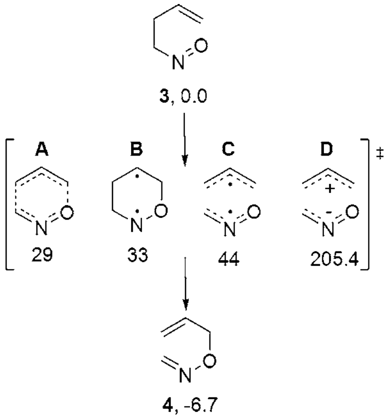

Figure 1. Possible mechanisms of oxaza-Cope rearrangement of 4-nitrosobut-1-ene **3**. Relative enthalpies are in kcal/mol.

The parent [3,3]-sigmatropic shift of 1,5-hexadiene has been studied previously at many levels of theory, including B3LYP/6-31G(d).[8] This level of theory predicts an activation energy of 34 kcal/mol for the chair transition state, in excellent agreement with the experimentally determined barrier of 33.5 ± 0.5 kcal/mol.[9]

The calculated transition structures **TS7** and **TS8** corresponding to concerted pathways for the hetero-Cope rearrangement of **3** are depicted in Figure 2. DFT calculations predicts an activation enthalpy of 29.0 kcal/mol (**TS7**) for the chair oxaza-Cope rearrangement, about 6 kcal/mol lower than that of the all-carbon 1,5-hexadiene. The boat transition structure **TS8** is about 7 kcal/mol higher in energy than **TS7**. The reaction is exothermic by 6.7 kcal/mol. In **TS7**, there is some charge separation; the allyl group has a Muliken charge of +0.19, while the CH_2NO group has a charge of −0.19.

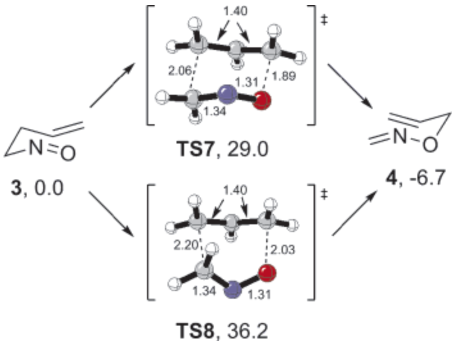

Figure 2. Concerted oxaza-Cope rearrangement of **3** via chairlike (**TS7**) and boatlike (**TS8**) transition structures. Bond lengths are in Å. Relative enthalpies are in kcal/mol.

Further calculations on paths B through D show that the formation of 1,4-diyl (path B), a radical pair (path C), or ion pair intermediate (path D) requires 33, 44, and 205.4 kcal/mol energy, respectively. The last is very high due to charge separation energetics in the gas phase. The energetics of pathways A−D predict that the concerted process is highly favored over other mechanisms (Figure 1).

In order to study the role of the electron-withdrawing group on energetics of the oxaza-Cope rearrangement, similar calculations were performed on methoxycarbonyl derivative **5**. The computed relative enthalpies of reactant, transition state, and product are shown in Figure 3. Compared to the parent oxaza-Cope rearrangement of **3** to **4**, the barrier for rearrangement of **5** to **6** is lower by 2 kcal/mol. The charge transfer from the allyl fragment to MeO_2CCHNO has become 0.29*e* in **TS9**. The methoxycarbonyl group on carbon adjacent to nitrogen makes the transition state more dissociative in **TS9** as compared to **TS7**. The forming and breaking bonds lengthen by 0.07−0.08 Å. The formation of **6** again is exothermic by 9.8 kcal/mol.

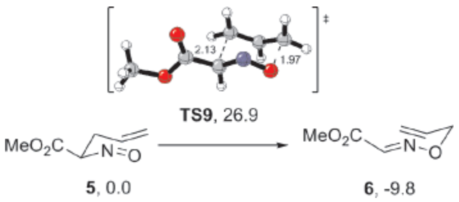

Figure 3. Oxaza-Cope rearrangement of **5** and its corresponding transition structure **TS9** and product **6**. Bond lengths are in Å. Relative enthalpies are in kcal/mol.

While the chair transition state is favored for acyclic hexadienes, the polycyclic geometry allows only boat transition states.[10] The calculated structure of the bicyclic system **1** studied by Zakarian and Lu and the corresponding transition state **TS10** are depicted in Figure 4. The activation enthalpy for this process is 19.5 kcal/mol.

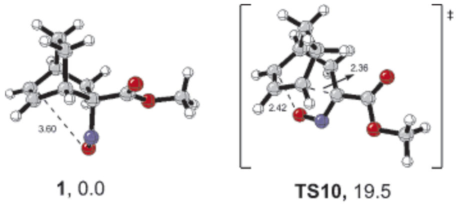

Figure 4. Bicyclic nitroso compound **1** and corresponding transition structure **TS10**. Bond lengths are in Å. Relative enthalpies are in kcal/mol.

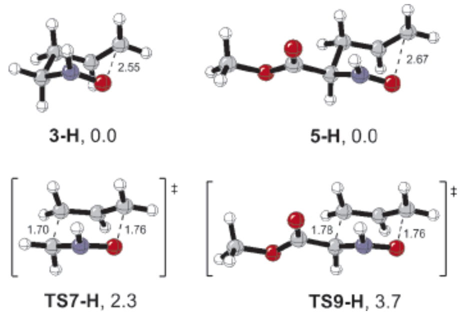

Figure 5. Computed protonated reactants **3-H** and **5-H** and corresponding transition structures **TS7-H** and **TS9-H**. Bond lengths are in Å. Relative enthalpies are in kcal/mol.

Bond-forming and -breaking bond lengths in **TS10** are close to each other (2.42 and 2.36 Å, respectively) and are much longer than in **TS7** or **TS9**. The formation of the corresponding oxazine **2** is exothermic by 17.6 kcal/mol.

Lewis acids were used by Zakarian and Lu[1] to catalyze the hetero-Cope rearrangements. Rate acceleration is attributed principally to charge separation in the transition state and stabilization of the charge by the Lewis acid.[11]

Calculations were performed to explore the role of the Lewis acids such as $TiCl_4$ and SbF_5 in facilitating the isomerization of **1** to **2**. As a first step, the isomerization of systems **3** and **5** with a proton as Lewis acid was studied. The proton can be coordinated to the nitroso group via O or N. Thermodynamically, the protonation of the nitrogen in both **3** and methoxycarbonyl derivative **5** is favored over protonation of oxygen by 12.5 and 16.8 kcal/mol, respectively. The activation barrier for oxaza-Cope rearrangements substantially decreases to 2.3 and 3.7 kcal/mol, respectively, from 29 kcal/mol for the uncatalyzed reaction. The chairlike protonated reactants **3-H** and **5-H** and corresponding transition structures **TS7-H** and **TS9-H** are shown in Figure 5. In comparison to the unprotonated transition structures **TS7** and **TS9**, the transition structures for protonated species have shorter forming and breaking bonds, and the transition structures are more synchronous and much less dissociative.

The calculations indicate that $TiCl_4$ coordinates to both nitrogen and carbonyl oxygen of the methoxycarbonyl group. The coordination of the nitroso compound with $TiCl_4$ is exothermic by 4.1 kcal/mol. The activation barrier for rearrangement of **1-TiCl₄** to the corresponding product **2-TiCl₄** is 12.3 kcal/mol, which is 7.2 kcal/mol lower in energy than the uncatalyzed reaction. The isomerization reaction forming the corresponding coordinated product **2-TiCl₄** is exothermic by 20.6 kcal/mol. The reaction profile for the oxaza-Cope rearrangement in the presence of $TiCl_4$ is shown in Figure 6. Similar calculations were performed to investigate the role of the SbF_5 on the hetero-Cope rearrangement of **1**. SbF_5 prefers to coordinate only to nitrogen. Coordination of SbF_5 to nitroso compound **1** is exothermic by 19.7 kcal/mol. The activation barrier for the oxaza-Cope rearrangement is 10.7 kcal/mol, and formation of coordinated product **2-SbF₅** is exothermic (17.5 kcal/ mol). The reaction profile for interconversion of **1** in the presence of SbF_5 is shown in Figure 6. As expected, with the addition of Lewis acids, the charge separation on O═N(LA)CCO$_2$-Me moieties increases, reflecting the increasing polarity of the transition states. **TS10** for the thermal reaction of the

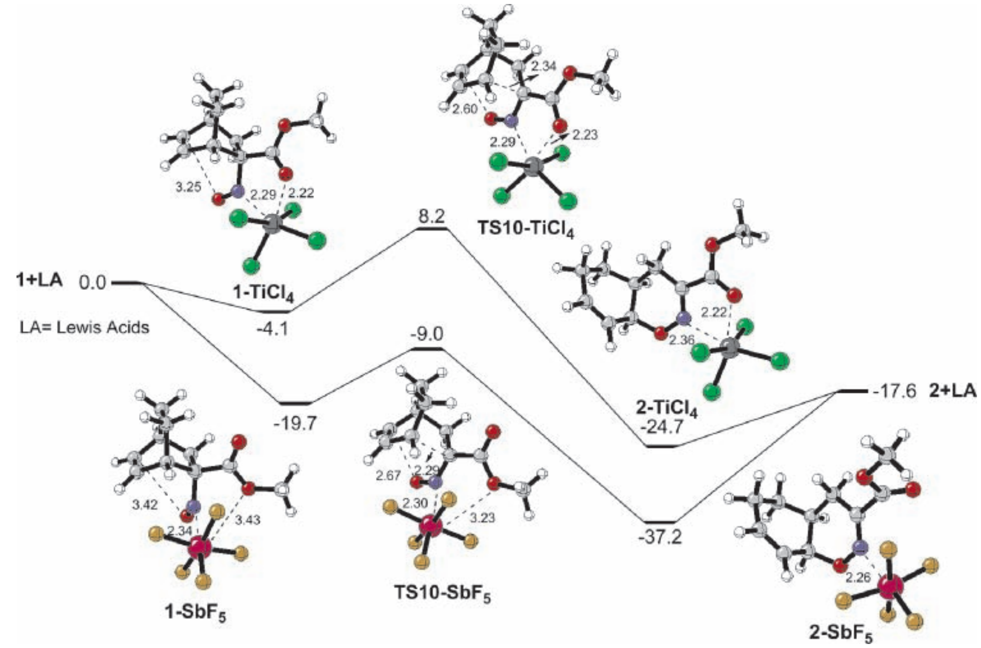

Figure 6. Energy profile for oxaza-Cope rearrangement of cyclic system **1** in presence of $TiCl_4$ and SbF_5. Relatives energies are in kcal/mol. Bond lengths are in Å.

bicyclic system has a charge separation of 0.3*e*, and this increases to 0.5*e* in the catalyzed transition states **TS10-SbF$_5$** and **TS10-TiCl$_4$**.

In conclusion, theoretical calculations indicate that oxaza-Cope rearrangements of acyclic systems **3** and **5** proceed via concerted chair transition states. The α-methoxycarbonyl group lowers the activation barrier. Isomerization of the cyclic system **1** occurs through a boatlike transition structure. Lewis acids such as SbF$_5$ and TiCl$_4$ preferentially coordinate to nitrogen of the nitroso group (and the carbonyl of the methoxycarbonyl in the case of TiCl$_4$) and substantially decrease the activation barrier of the reaction.

Supporting Information Available: Cartesian coordinates and enthalpies of optimized structures of ground states and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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