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Computational and ^{13}C Investigations of the Diazadienes and Oxazadienes Formed via the Rearrangement of Methylenecyclopropyl Hydrazones and Oximes

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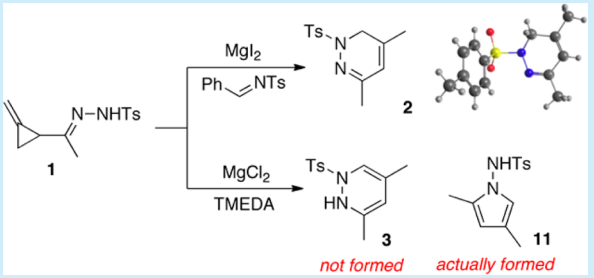
Supporting Information

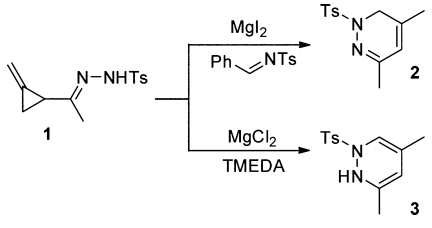
ABSTRACT: Computational and further experimental investigations of the previously reported diazadienes, obtained via the rearrangement of methylenecyclopropyl hydrazone **1** are reported. Calculations at the CCSD(T)/cc-pVTZ//B3LYP/6-31G(d) level of theory indicate that the initially reported product **3** would, if formed, undergo rapid electrocyclic ring opening and, hence, would be unstable under the reaction conditions. Based on this computational prediction, further analysis of the ^{13}C NMR spectrum, previously attributed to **3**, led to the revision of structure **3** to that of its *N*-tosylaminopyrrole constitutional isomer **11**. Similarly, structure **8**, formed in the rearrangement of oxime **6**, was revised to that of *N*-hydroxypyrrole **12**.



Owing to their strained cyclopropane rings and alkene functionality, methylenecyclopropanes (MCPs) and their analogues represent versatile synthetic building blocks for a wide range of Lewis and Brønsted acid catalyzed, as well as transition-metal-mediated transformations.[1] One of the synthetically beneficial properties of these strained carbocycles is the ability of a common MCP building block to undergo reactions by different pathways, depending on the reaction conditions used.[2] This type of reaction path control enables access to a range of different products from a common precursor.

In 2007, two of us (M.E.S. and M.L.) reported the utilization of this type of product control in the rearrangement of activated MCP hydrazones, catalyzed by different Lewis acids under different reaction conditions (Scheme 1).[3] In the presence of MgI_2, rearrangement of **1** was found to furnish the cyclic azadiene **2** in good yield, while reaction of **1** at high temperature with $MgCl_2$/TMEDA was reported to yield the constitutional isomer **3**.

Scheme 1. Divergent Rearrangements of MCP Hydrazone 1



More recently, as part of a study of reactions that might involve heavy-atom tunneling,[4] three of us (B.C., D.A.H., and W.T.B.) investigated computationally the electrocyclic ring opening reactions of heterocyclic analogs of 1,3-cyclohexadiene, in which a weak bond between two heteroatoms cleaves. Such reactions would be expected to have low barriers and to involve only minimal amounts of motion of the two heteroatoms, conditions that should be conducive to tunneling.

In the course of this study, we carried out calculations on the electrocyclic ring opening reactions of hydrazone **4** and hydrazine **5**, in which the tosyl and two methyl groups of **2** and **3** are replaced by hydrogens (Figure 1). We also performed calculations on the analogous reactions of oxime **9** and alkoxyamine **10** (Figure 2).

Geometries were optimized and vibrational analyses and tunneling calculations were performed with the B3LYP functional[5] and the 6-31G* basis set.[6] Single-point energies were obtained at the CCSD(T) level of theory,[7] using the cc-pVTZ basis set.[8] Small curvature tunneling calculations were carried out using POLYRATE.[9] All of the other calculations were performed with Gaussian 09.[10]

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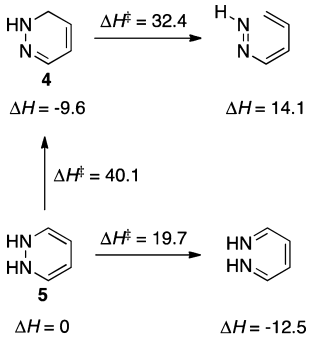


Figure 1. CCSD(T)/cc-pVTZ//B3LYP/6-31G(d) relative enthalpies and enthalpies of activation, both in kcal/mol.

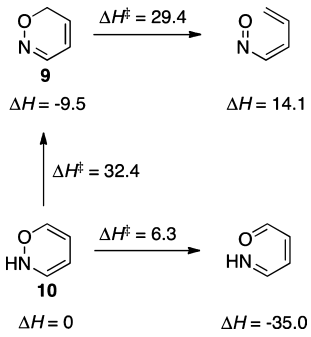


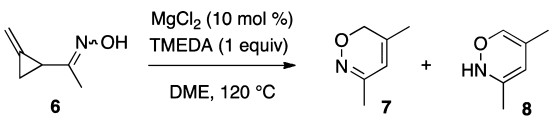
Figure 2. CCSD(T)/cc-pVTZ//B3LYP/6-31G(d) relative enthalpies and enthalpies of activation, both in kcal/mol.

Our computational results for **4** and **5** are summarized in Figure 1. Hydrazone **4** is calculated to be thermodynamically stable to both electrocyclic ring opening and to the 1,5-hydrogen shift that would convert it to **5**. Hydrazine **5** could rearrange to **4** by the latter pathway, but the barrier to this reaction is calculated to be 20.4 kcal/mol higher than the barrier to electrocyclic ring opening of **5**.

The low calculated barrier to electrocyclic ring opening of **5** should make this reaction very fast at 120 °C, the temperature of the reaction from which **3** was purportedly isolated. The calculated rate constant for electrocyclic ring opening at this temperature is $k = 6.3 \times 10^2$ s^{-1}, giving **5** a lifetime on the order of 10^{-3} s at 120 °C. Thus, our calculations rule out the possibility that a derivative of **3**, such as **5**, could have been isolated from a reaction conducted at this temperature.

In a reaction, analogous to the rearrangement in Scheme 1, treatment of MCP-oxime **6** with $MgCl_2$/TMEDA was reported to give rise to oxime **7** and hydroxylamine **8** (Scheme 2).[3] In

Scheme 2. Rearrangement of MCP Oxime 6



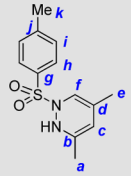
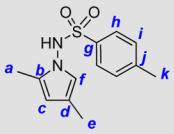
order to assess the thermodynamic and kinetic stabilities of **7** and **8**, we performed calculations on the unsubstituted compounds **9** and **10**. The results of our calculations are summarized in Figure 2.

Oxime **9** is calculated to be thermodynamically stable to both electrocyclic ring opening and to rearrangement to **10**. In contrast to **9**, **10** can undergo two thermodynamically favorable reactions. However, the barrier to electrocyclic ring opening of **10** is much lower than the barrier to the 1,5-hydrogen shift that would convert **10** to **9**.

The very low barrier to electrocyclic ring opening of **10** and the small amount of heavy-atom motion that is required in this reaction suggested that tunneling could make this reaction very fast, even at cryogenic temperatures. In fact, below 30 K the temperature-independent rate constant for ring opening by tunneling from the lowest vibrational level of **10** was computed to be 4.4×10^4 s^{-1}. The calculated half-time of ca. 10^{-5} s for the disappearance of **10** at cryogenic temperatures rules out the possibility of isolation of **8** via rearrangement of **6** at 120 °C (Scheme 2).

Based on the results of these calculations, we revisited the structural assignment of compounds **2**, **3**, **7**, and **8**. Further analysis of the spectroscopic data for **2**, which involved comparison between both expected and predicted ^{1}H and ^{13}C NMR, confirmed the initially reported structure.[3] Further confirmation of this assignment was obtained by single crystal X-ray analysis.[11] However, upon re-examination of **3**, slight discrepancies were evident between the observed and predicted ^{13}C NMR spectra (Table 1). While the majority of the

Table 1. Experimental[a] versus Predicted[b] ^{13}C NMR Chemical Shifts (ppm) for 3 and 11

observed[a]	predicted[b]	predicted[b]
		
	*originally assigned, **3***	*revised structure, **11***
10.9	17.8 (e)	12.0 (e)
12.2	19.7 (a)	12.9 (a)
21.9	21.8 (k)	21.5 (k)
107.4	110.0 (c)	105.3 (c)
117.4	115.3 (f)	118.5 (d)
118.0	127.0 (d)	119.9 (f)
128.7	129.4 (h)	127.7 (h)
130.1	129.7 (i)	130.0 (i)
130.5	130.8 (g)	134.0 (g)
134.7	141.3 (j)	135.0 (b)
145.2	143.7 (b)	143.9 (j)

[a]In $CDCl_3$ at 600 MHz. [b]^{13}C NMR predictions obtained using ACD Laboratories Prediction + DB Version 12.5.[12]

experimentally observed values closely matched the predicted ^{13}C shifts, small but significant differences between the predicted and observed ^{13}C shifts for methyl groups ***a*** and ***e*** were found (Table 1).

Using the experimentally observed ^{13}C shifts, we then reconsidered other related constitutional isomers of **3** and found that the 2,4-dimethyl pyrrole isomer **11** provides a better fit to the ^{13}C NMR data. We note that, following our initial publication in this area, a subsequent report by Shi and co-workers proposed similar analogues of **11** to be formed via an

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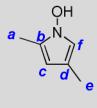
analogous rearrangement of methylene substituted MCP hydrazones.[13] In these examples, the related methyl-substituted analogues showed chemical shifts (12 ppm) that are close to what we also predict and observe for **11**.

Similarly, while re-examinination of the ^{1}H and ^{13}C NMR data for **7** was found to be consistent with the initially proposed structure,[3] comparison of the experimentally observed ^{13}C chemical shifts for **8** with the predicted values revealed even larger differences than those between the observed and predicted chemical shifts for the methyl groups in **3**. Especially large deviations were found between the observed and predicted ^{13}C chemical shifts for sp^2 hybridized carbons ***b***, ***d***, and ***f***, leading us to revise the structure, originally assigned to **8**, to that of the *N*-hydroxypyrrole derivative **12** (Table 2).

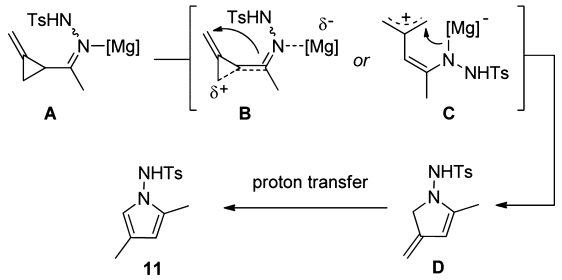
Table 2. Experimental[a] versus Predicted[b] ^{13}C NMR Chemical Shifts (ppm) for 8 and 12

observed[a]	predicted[b]	predicted[b]
		
	*originally assigned, **8***	*revised structure, **12***
10.6	16.1 (e)	11.4 (a)
12.4	16.4 (a)	11.8 (e)
102.3	106.6 (c)	102.3 (c)
112.6	121.3 (d)	112.1 (f)
113.7	132.5 (f)	116.0 (d)
125.3	143.3 (b)	124.8 (b)

[a]In $CDCl_3$ at 600 MHz at −40 °C. [b]^{13}C NMR predictions obtained using ACD Laboratories Prediction + DB Version 12.5.[12]

Mechanistic studies, using deuterium-labeled MCP hydrazone **1**, indicated that, under the $MgCl_2$/TMEDA conditions,[3] rearrangement occurs without scrambling of the two methylene groups. With the structures of **3** and **8** being revised to **11** and **12**, a mechanism, which takes into account these experimental findings, is proposed and shown in Scheme 3 ([Mg] = Mg^{2+} complex).

Scheme 3. Proposed Reaction Mechanism



The Lewis acid−base complex **A** could develop partial positive charge on C3 of the cyclopropane ring, as represented by structure **B**; or **A** could undergo ring opening to form zwitterion **C**. In **B**, the process could proceed via a more concerted-type process (Cloke-type rearrangement[14]), while, in **C**, rapid nucleophilic attack (relative to bond rotation) at C1 by nitrogen would afford the five-membered ring in **D**. Proton transfer would then give **11**.

In summary, based upon our computational results and ^{13}C NMR analyses, we revise the originally assigned structure of the second product of the rearrangement of **1** in Scheme 1, from **3** to **11** (Table 1), and the originally assigned structure of the second product of the rearrangement of **6** in Scheme 2, from **8** to **12** (Table 2). These revisions illustrate that calculated energies can play an important role in assessing the viability of possible structures that are provisionally assigned to the products of organic reactions.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, CIF file for compound **2**, calculated rate constants and geometries, and absolute energies of calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117−3179. (b) Yu, L.; Guo, R. *Org. Prep. Proced. Int.* **2011**, *43*, 209−259. (c) Shi, M.; Lu, J.-M.; Wei, Y.; Shao, L.-X. *Acc. Chem. Res.* **2012**, *45*, 641−652. (d) Zhang, J.; Xiao, Y. Cyclization of Cyclopropane- or Cyclopropane-Containing Compounds. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: New York, 2010; Vol. *2*, pp 733−812.

(2) For select examples, see: (a) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175−1178. (b) Yao, L.-F.; Shi, M. *Org. Lett.* **2007**, *9*, 5187−5190. (c) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem.—Eur. J.* **2006**, *12*, 510−517. (d) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419−4422. (e) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028−4029. (f) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521−5524.

(3) Scott, M. E.; Bethuel, Y.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 1482−1483.

(4) (a) Zuev, P. S.; Sheridan, R. S.; Albu, T. V.; Truhlar, D. G.; Hrovat, D. A.; Borden, W. T. *Science* **2003**, *299*, 867−870. (b) Datta, A.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2008**, *130*, 6684−6685. (c) Zhang, X.; Datta, A.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2009**, *131*, 16002−16003. (d) Gonzalez-James, O. M.; Zhang, X.; Datta, A.; Hrovat, D. A.; Borden, W. T.; Singleton, D. A. *J. Am. Chem. Soc.* **2010**, *132*, 12548−12549. (e) Zhang, X.; Hrovat, D. A.; Borden, W. T. *Org. Lett.* **2010**, *12*, 2798−2801. (f) Zhang, X.; Hrovat, D. A.; Datta, A.; Borden, W. T. *Org. Biomol. Chem.* **2011**, *9*, 3142−3145. (g) Kozuch, S.; Zhang, X.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2013**, *135*, 17274−17277.

(5) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(6) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.
(7) (a) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910−1918. (b) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. H. *Chem. Phys. Lett.* **1989**, *157*, 479−483.
(8) (a) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1023. (b) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796−6806.
(9) Zheng, J.; Zhang, S.; Lynch, B. J.; Corchado, J. C.; Chuang, Y.-Y.; Fast, P. L.; Hu, W.-P.; Liu, Y.-P. Lynch, G. C.; Nguyen, K. A.; Jackels, C. F.; Ramos, A. F.; Ellingson, B. A.; Melissas, V. S.; Villa, J.; Rossi, I.; Coitino, E. L.; Pu, J.; Albu, T. V.; Steckler, R.; Garrett, B. C.; Isaacson, A. D.; Truhlar, D. G. *POLYRATE*, version 2008; University of Minnesota: Minneapolis, MN, 2008.
(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.;Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.
(11) Crystallographic data for **2** has been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1013087. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx.
(12) *ACD/C+H NMR Predictors and DB*, ACD/Labs Release 12.00, Product Version 12.5, Build 28856, November 11, 2008; Advanced Chemistry Development, Inc.; 2011.
(13) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 5983−5986.
(14) (a) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174−1187. (b) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835−838.