Tetrahedron Letters 50 (2009) 1578–1581

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Carbocation rearrangements in aspernomine biosynthesis

Gregory A. Ho, Dustin H. Nouri, Dean J. Tantillo *

Department of Chemistry, University of California, Davis, One Shields Avenue Davis, CA 95616, United States

ARTICLE INFO

Article history:
Received 4 September 2008
Revised 14 January 2009
Accepted 15 January 2009
Available online 23 January 2009

ABSTRACT

Quantum chemical calculations (B3LYP/6-31G(d)) on carbocation rearrangements that are proposed to occur in the biosynthesis of aspernomine are described. Based on these calculations, a pathway involving a concerted but asynchronous [4+2] cycloaddition that avoids the formation of a secondary carbocation is proposed for small model systems.

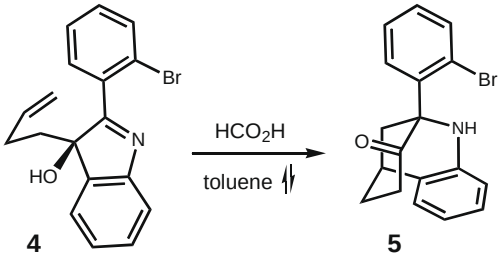
1. Introduction

Aspernomine (**1**, Scheme 1) is a complex indole diterpenoid natural product found in the reproductive organ of the fungus *Aspergillus nomius*.[1,2] It has shown potent anti-insectan properties against the crop pest *Heliothis zea*, anti-fungal properties, and significant cytotoxicity toward three human solid tumor cell lines.[1] Liu, McWhorter, and Hadden proposed that the polycyclic scaffold of aspernomine could be constructed biosynthetically via rearrangement of an oxidized form of another natural product, nominine (**2**).[2,3] Herein, we describe quantum chemical calculations on the mechanism of this rearrangement.

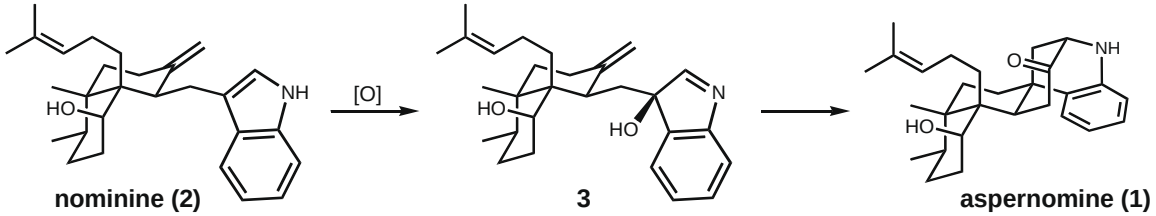
Liu, McWhorter, and Hadden's proposal was based on the observation that compound **4**, which contains a key fragment of nominine, rearranged under acidic conditions to compound **5** (Scheme 2; 65% yield).[2] The mechanism proposed by these authors, which involves cyclization followed by aryl migration, is shown in Scheme 3 for a further truncated structure, **6**, that we utilized in our initial calculations.

2. Methods

All calculations were performed with GAUSSIAN03.[4] Geometries were optimized without symmetry constraints at the B3LYP/6-31G(d) level.[5] All structures were characterized by frequency calculations, and reported energies include zero-point energy corrections scaled by 0.9806.[6] Intrinsic reaction coordinate (IRC)



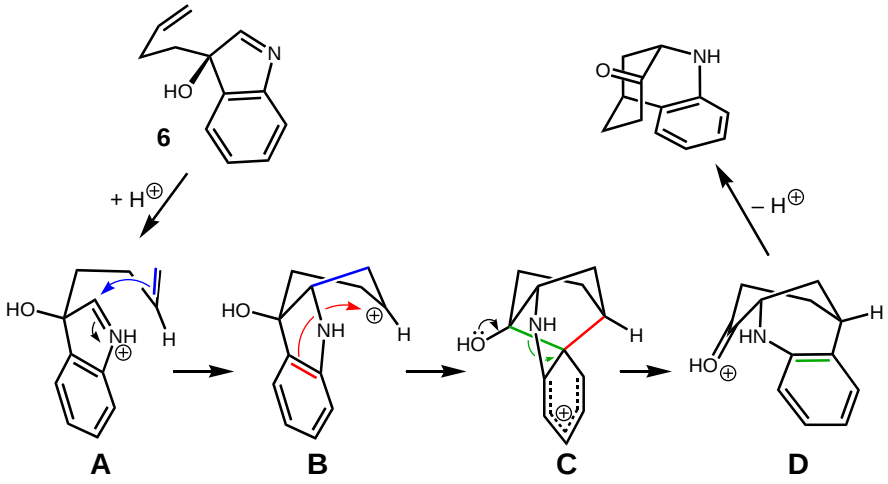
Scheme 2.



Scheme 1.

* Corresponding author.
E-mail address: tantillo@chem.ucdavis.edu (D.J. Tantillo).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.098



Scheme 3.

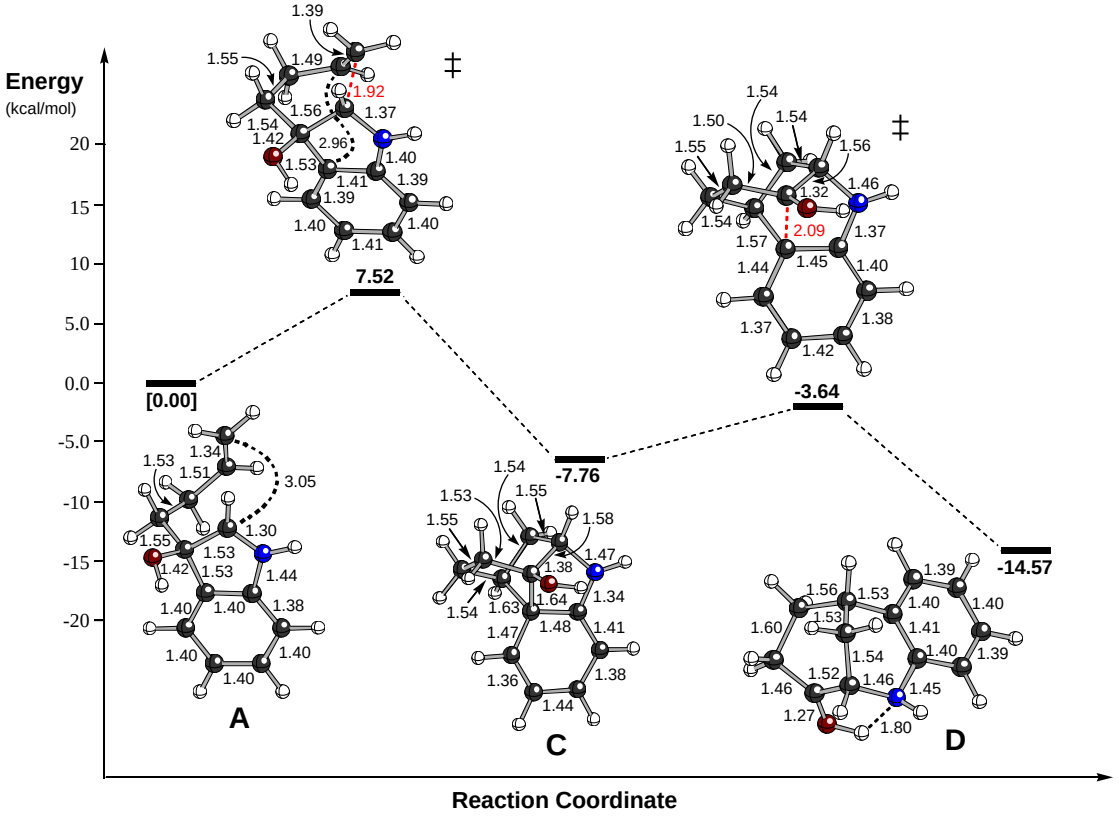


Figure 1. Computed (B3LYP/6-31G(d)) geometries (selected distances in Å) and relative energies (kcal/mol) of structures involved in the conversion of A to D.

calculations were used to further characterize the nature of transition state structures (see Supplementary data for details).[7] Structural drawings were produced using Ball & Stick.[8]

3. Results and discussion

To determine if the mechanism shown in Scheme 3 is energetically feasible, we calculated the structures and energies of all of the intermediates involved and the transition state structures connecting them. We began with a simplified model system based on **6**, as shown in Scheme 3. The geometries and relative energies of species involved in the **A**-to-**D** rearrangement are shown in Figure 1. Interestingly, we found a transition state structure that connects **A** and **C** directly. In other words, if **A** adopts the conformation shown, secondary carbocation **B** is bypassed in a concerted, but very asynchronous, [4+2] cycloaddition, in which the two new C–C single bonds are formed to greatly different extents in the transition state structure (see Fig. 1).[9] Starting from a different conformation, a carbocation of type **B** was located (Fig. 2), but this species is 17 kcal/mol higher in energy than **A** and therefore

approximately 10 kcal/mol higher in energy than the **A**-to-**C** transition state structure. Fragmentation of **C** to produce **D** has a low barrier. Overall, the two-step rearrangement of **A** to **D** is exothermic by approximately 15 kcal/mol and has a calculated barrier of less than 10 kcal/mol, making this rearrangement extremely facile.[10]

The **A**-to-**C**-to-**D** mechanism is energetically feasible, but we wondered whether adding more of the structural elements present in aspernomine would change this situation. Along these lines, we reexamined the rearrangement mechanism using models with either a cyclohexane or cis-decalin fused to **6** (Chart 1). Both chair and boat conformations for each added ring were examined. Computed energies for all intermediates located and transition state structures connecting them are listed in Table 1 (geometries of all structures can be found in the Supplementary data). Chair conformations were favored for both rings.[11] For these larger model systems, concerted **A**-to-**C** reactions were not found. This is likely a result of the fact that appending the additional rings leads to versions of **B** that bear tertiary rather than secondary carbocation centers, which also leads to low barriers for pathways through intermediates **B**.

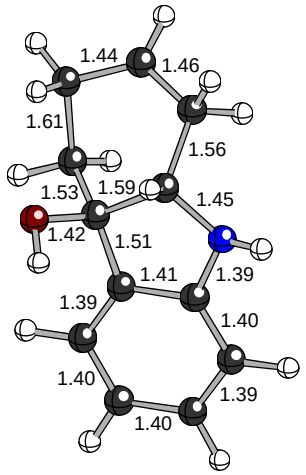


Figure 2. Computed (B3LYP/6-31G(d)) geometry (selected distances in Å) of B.

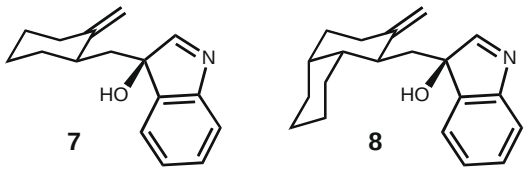


Chart 1.

Thus, we conclude that the mechanism originally proposed by Liu, McWhorter, and Hadden for formation of aspernomine is quite feasible on energetic grounds, but the reaction of **4** that prompted this mechanistic proposal may well involve a concerted, but very asynchronous, [4+2] reaction.

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.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.098.

References and notes

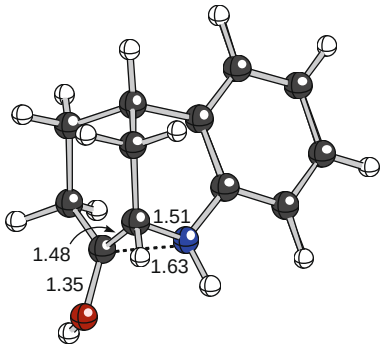
1. Staub, G. M.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Am. Chem. Soc.* **1992**, *114*, 1015–1017.
2. Liu, Y.; McWhorter, W. W.; Hadden, C. E. *Org. Lett.* **2003**, *5*, 333–335.
3. Gloer, J. B.; Rinderknecht, B. T.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530.
4. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. GAUSSIAN03, Revision B.04, Gaussian, Pittsburgh PA, 2003.
5. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377; (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789; (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.
6. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
7. (a) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527; (b) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368.
8. Müller, N.; Falk, A. *Ball and Stick V.3.7.6*, Molecular Graphics Application for MacOS Computers, Johannes Kepler University, Linz, 2000.
9. For a recent review on concerted but asynchronous carbocation rearrangements, see: (a) Tantillo, D. J. *J. Phys. Org. Chem.* **2008**, *21*, 561–570; (b) A similar transition structure for an *inter*molecular analog (replacing the CH_2CH_2 bridge with two H's) was also located; the computed barrier (not including entropy) for this [4+2] reaction is 10.72 kcal/mol and it is exothermic by 14.87 kcal/mol. See Supplementary data for details.
10. Two different conformations of the hydroxyl group were actually explored. Please see the Supplementary data for results with the alternative conformer. The biggest consequence of changing the hydroxyl conformation is felt for structure **D**. For one hydroxyl orientation (see Fig. 1), an intramolecular O–H···N hydrogen bond is observed, but for the alternate hydroxyl orientation

Table 1
Computed (B3LYP/6-31G(d)) energies (kcal/mol; relative to the lowest energy conformer of **7**-H$^+$ or **8**-H$^+$) of intermediates and transition state structures involved in the rearrangements of *N*-protonated **7** and 8

Model	A	$TS_{A\text{-to-}B}$	B	$TS_{B\text{-to-}C}$	C	$TS_{C\text{-to-}D}$	D
7-H$^+$ (Chair)	[0.00]	3.44	−1.89	−1.33	−6.37	−1.86	−8.53
7-H$^+$ (Boat)	4.29	7.66	2.07	3.70	−0.54	3.62	−5.79
8-H$^+$ (Chair/chair)	[0.00]	1.86	−4.54	−3.55	−7.90	−3.30	−9.79
8-H$^+$ (Chair/boat)[a]	3.78	10.24	4.99	3.78	0.97	5.63	−0.71
8-H$^+$ (Boat/chair)[b]	5.78	8.78	3.01	4.77	1.12	6.89	−1.38
8-H$^+$ (Boat/boat)	8.35	10.59	4.03	6.03	2.51	8.10	−1.40

[a] The 'chair/boat' conformer has a chair conformation for the ring closest to the heterocycle.
[b] The 'boat/chair' conformer has a boat conformation for the ring closest to the heterocycle.

(see below), an interaction between the nitrogen lone pair and the π^*_{C-O} of the protonated carbonyl is observed. The latter sort of interaction has been observed for various other molecules, including natural products; see, for example: (a) McCrindle, R.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 61–62; (b) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987–12002; (c) Gautier, A.; Pitrat, D.; Hasserodt, J. *Bioorg. Med. Chem.* **2006**, *14*, 3835–3847; (d) Waibel, M.; Hasserodt, J. *J. Org. Chem.* **2008**, *73*, 6119–6126.



11. The relative energies of **A** and $\mathbf{TS_{A\text{-}to\text{-}B}}$ for **8**-H^+ (chair/chair) were recalculated (CPCM(UAKS)-B3LYP/6-31G(d)//B3LYP/6-31G(d)) in $CHCl_3$ (a solvent with a dielectric constant similar to that of a typical enzyme active site) and water. The computed **A**-to-**B** barriers in these solvents are 3.85 and 4.53 kcal/mol, respectively, consistent with the transition state $\mathbf{TS_{A\text{-}to\text{-}B}}$ being less polar than **A**, but also suggesting that the barrier for this reaction is likely to be low in a variety of environments.