Origins of *Endo* Selectivity in Diels–Alder Reactions of Cyclic Allene Dienophiles

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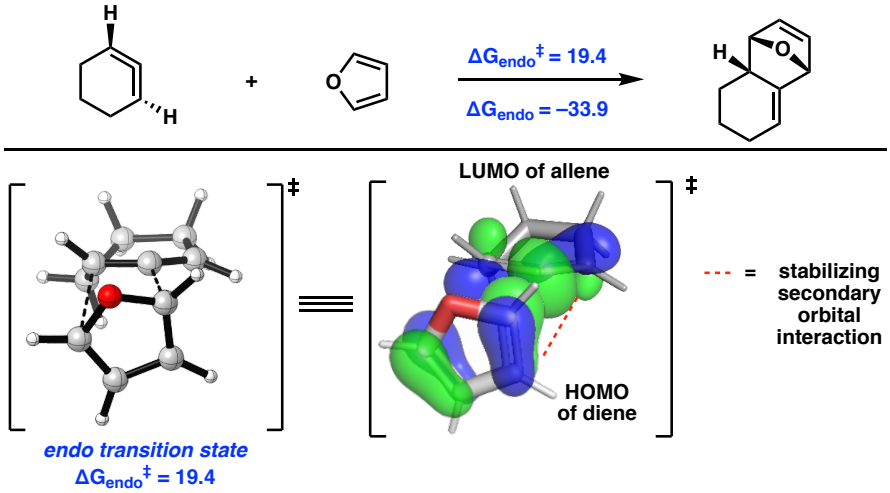
Abstract:



Strained cyclic allenes, first discovered in 1966 by Wittig,[1] have recently emerged as valuable synthetic building blocks.[2] Previous experimental investigations, and computations reported herein, demonstrate that the Diels–Alder reactions of furans and pyrroles to 1,2-cyclohexadiene and heterocyclic analogs are *endo* selective. This unprecedented stereoselectivity gives the adduct with the allylic saturated carbon of the cyclic allene *endo* to the diene carbons. We analyze the molecular orbital structure of cyclic allenes and show how secondary orbital and electrostatic effects influence *endo* selectivity. These mechanistic studies are expected to prompt the further use of long-avoided strained cyclic allenes in chemical synthesis.

References:

[1] G. Wittig, P. Fritze, *Angew. Chem., Int. Ed. Engl*. **1966**, *5*, 846.
[2] For recent examples of synthetic methodologies involving cyclic allene chemistry, see: (a) M. V. Westphal, L. Hudson, J. W. Mason, J. A. Pradeilles, F. J. Zécri, K. Briner, S. L. Schreiber, *J. Am. Chem. Soc.* **2020**, *142*, 7776–7782; (b) S. Drinkuth, S. Groetsch, E.-M. Peters, K. Peters, M. Christl, *Eur. J. Org. Chem.* **2001**, *14*, 2665–2670; (c) J. S. Barber, M. M. Yamano, M. Ramirez, E. R. Darzi, R. R. Knapp, F. Liu, K. N., Houk, N. K. Garg, *Nat. Chem.* **2018**, *10,* 953–960; (d) M. M. Yamano, R. R. Knapp, A. Ngamnithiporn, M. Ramirez, K. N. Houk, B. M. Stoltz, N. K. Garg, *Angew. Chem., Int. Ed.* **2019**, *58*, 5653–5657; (e) J. S. Barber, E. D. Styduhar, H. V. Pham, T. C. McMahon, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 2512–2515; (f) M. M. Yamano, A. V. Kelleghan, Q. Shao, M. Giroud, B. J. Simmons, B. Li, S. Chen, K. N. Houk, N. K. Garg, *Nature*, **2020**, *586*, 242–247; (g) M. S. McVeigh, A. V. Kelleghan, M. M. Yamano, R. R. Knapp, N. K. Garg, *Org. Lett.* **2020**, *22*, 4500–4504; (h) J. Chari, F. Ippoliti, N. K. Garg, *J. Org. Chem.* **2019**, *84*, 3652–3655; (i) E. Guitián, D. Peña, D. Perez, I. Quintana,

Eur. J. Org. Chem. **2009**, 5519–5524; (j) V. A. Lofstrand, F. G. West, *Chem. Eur. J.* **2016**, *22*, 10763–10767; (k) B. Wang, M. G-. Constantin, S. Singh, Y. Zhou, R. L. Davis, F. G. West, *Org. Biomol. Chem.* **2021**, *19*, 399–405; (l) Y. A. Almehmadi, F. G. West, *Org. Lett.* **2020**, *22*, 6091−6095; (m) M. Schreck, M. Christl, *Angew. Chem., Int. Ed.* **2017**, *56*, 10070–10086; (n) M. Christl, H. Fischer, M. Arnone, B. Engels, *Chem. Eur. J.* **2009**, *15*, 11266–11272; (o) V. A. Lofstrand, K. C. McIntosh, Y. A. Almehmadi, F. G. West, *Org. Lett.* **2019**, *21*, 6231−6234; (p) B. Engels, J. C. Schöneboom, A. F. Münster, S. Groetsch, M. Christl, *J. Am. Chem. Soc.* **2002**, *124*, 287–297