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Influence of Ground-State Conformations on the Intramolecular Amidofuran Diels–Alder Reaction

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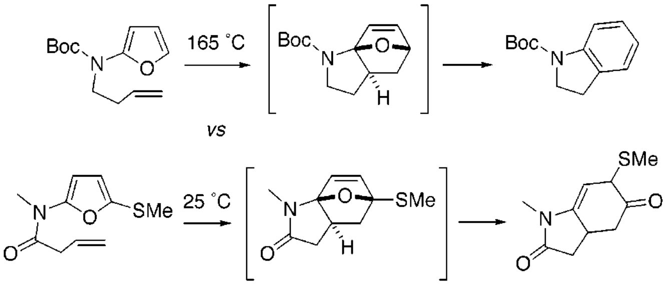
ABSTRACT



Various factors that influence the rate of the intramolecular Diels–Alder reaction of amidofurans were investigated with density functional theory calculations using the Becke3LYP/6-31G* model. Conformational effects imposed by the placement of a carbonyl group within the tether, combined with a rotational bias about the C(2)–N bond, account for the observed rate differences in the thermal chemistry of these amidofurans.

The intramolecular Diels−Alder reaction of 2-amidofurans has proven to be a powerful tool for the rapid construction of polycyclic nitrogen containing scaffolds,[1] and successful strategies for the syntheses of several natural products have incorporated this disconnection.[2] In the course of investigating the general nature of this reaction, significant rate differences were noticed when comparing seemingly similar systems. A computational investigation was therefore initiated to help define the nature of structural features thought to accelerate the progress of the amidofuran intramolecular Diels−Alder cycloaddition.

In an early example of the amidofuran Diels−Alder reaction, we noted that the thermal cyclization of **1** required heating at 165 °C for several hours in order to produce dihydroindole **3** (Scheme 1).[1a] The oxabicycle **2** that was first formed reorganized under the reaction conditions via a sequential ring-opening/aromatization pathway. In sharp contrast, the conversion of thiomethylfuran **4** into enamido-ketone **6** proceeded at room temperature.[3] Again, the suspected intermediate oxabicycle **5** could not be isolated.

The primary structural differences between the two starting furans are the location of the amide carbonyl and the presence of a thiomethyl group in **4**. Because thio substituents are known to have little effect on the facility of Diels−Alder reactions,[4] the increase in the reactivity of **4** vis-à-vis **1** was presumed to originate in the placement of the carbonyl center within the dienophilic tether. A second rate effect was noted when a cyclic constraint was added to the furanyl system. For example, the cyclization−rearrangement cascade for

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[1] (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304−5305. (b) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986−3997. (c) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986−3997.

[2] (a) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595−3607. (b) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233−3235. (c) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2000**, *66*, 1716−1724.

[3] Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M.; Padwa, A. Manuscript in preparation.

[4] (a) Kotsuki, H.; Mori, Y.; Ohtsuka, N. H.; Ochi, M.; Matsuoka, K. *Heterocycles* **1987**, *26*, 2347−2350. (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233.

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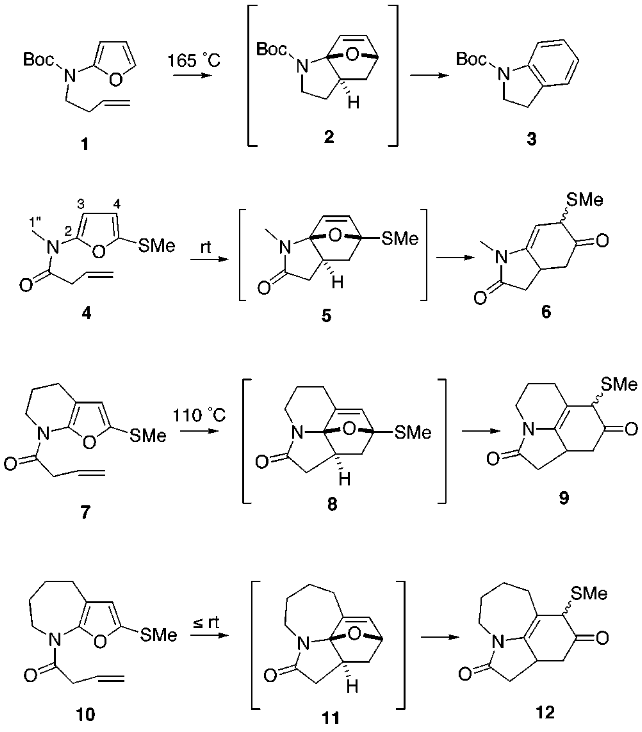
Scheme 1. Intramolecular Diels−Alder Reactions



furan **7** required heating at 110 °C to produce **9**.[5] In stark contrast, amidofuran **10** could not be isolated under the conditions of its formation, as it rapidly furnished amidoketone **12** at or below room temperature.[3] Neither **8** nor **11** was observed. That none of the intermediate oxabicycles could be observed in the course of these reactions suggests that the cycloaddition step is rate determining.

Dramatic effects originating from the placement of a carbonyl group on the tether have previously been noted: In one example involving an intramolecular dipolar cycloaddition, a severe steric interaction was found in the transition state while no such interaction was identifiable in either the starting material or product ground states.[6] Introduction of a carbonyl group on the tethered dipolarophile relieved the source of the strain. Similarly, the effects of amide- and ester-linked tethers on the diastereoselectivity of intramolecular Diels−Alder reactions have been attributed to relative transition state stabilities.[7] Jung and Gervay, however, reported data for intramolecular Diels−Alder reactions which suggest that substitution on the tether results in an increase in the population of reactive rotomers.[8] Thus, the rate enhancement was suggested to originate from a restricted rotation that enforces a more reactive conformer in the lowest energy ground state.

Because there was no clear precedent regarding whether the origin of the rate differences resided in either ground-state conformational effects or in relative strain within the transition states, we explored the conformational space of furans **1**, **4**, **7**, and **10**. Low-energy conformers obtained using Monte Carlo conformational searching (MCMM) as implimented by MacroModel7.0[9] with either MM2* or MMFF parameters contained high-energy steric interactions due to inadequate parametrization for these systems.[10] For example, MM2* parameters predicted a C(3)−C(2)−N−C(1") dehedral angle of 6.6° in **4** (Scheme 1). As a result, the C(3) proton is only 2.40 Å from the proximal C(1") proton.[11] A similar dihedral angle places the C(4) proton 2.46 Å from the nearest thiomethyl proton. Because the low-energy conformations generated by the MCMM protocol were unsuitable for our purposes, optimization of the ground-state conformations was then performed using density functional methods. Using the Becke3LYP functional[12] and the 3-21G* basis set with Gaussian 98,[13] ground-state conformations were explored by optimizing structures with, for example, various *gauche* and *anti* conformations about rotatable bonds. The low-energy conformations were then reoptimized using the 6-31G* basis set. Transition states for each of the Diels−Alder reactions were also located using the 6-31G* basis set (Figure 1).[14] Each transition state was modeled with an *exo*-oriented tether on the basis of the known stereochemical preference for these reactions.[1a,2b,3,5]

The calculated relative energies of activation are qualitatively consistent with experimental trends for compounds **1**, **4**, **7**, and **10**, though the difference in activation energies calculated for **1** and **7** (0.3 kcal/mol) appears somewhat small

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[5] Ginn, J. D.; Lynch, S. M.; Padwa, A. *Tetrahedron Lett.* **2000**, *41*, 9387−9391.

[6] Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001−2010.

[7] For examples, see: (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590−593. (b) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593−595. (c) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, 3313−3316. (d) Turner, C. I.; Williamson, R. M.; Paddon-Row, M. N. *J. Org. Chem.* **2001**, *66* 3963−3969. (e) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938−1940.

[8] (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232. See also (b) Sternbach, D. D.; Rossana, D. M.; Onan, D. D. *Tetrahedron Lett.* **1985**, *26*, 591−594. (c) See also: Giessner-Prettre, C.; Hükel, S.; Maddaluno, J.; Jung, M. E. *J. Org. Chem.* **1997**, *62*, 1439−1448.

[9] (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467. (b) See also http://www.schrodinger.com.

[10] For MMFF parameters, see: (a) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730−748. (b) For a comparison of parameters, see: Gundertofte, K.; Liljerfors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429−449.

[11] The van der Waals radius of a C−H hydrogen is 1.2 Å (Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384−7391), implying an *r*(H···H) contact distance of 2.4 Å.

[12] For Becke's three parameter exchange functional, see: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. For the LYP correlation functional, see: (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

[13] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. J.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

[14] Transition state structures were characterized by one imaginary vibrational frequency (Nimag = 1) corresponding to the bonding event. No zero-point energy corrections were applied to any of the calculated structures.

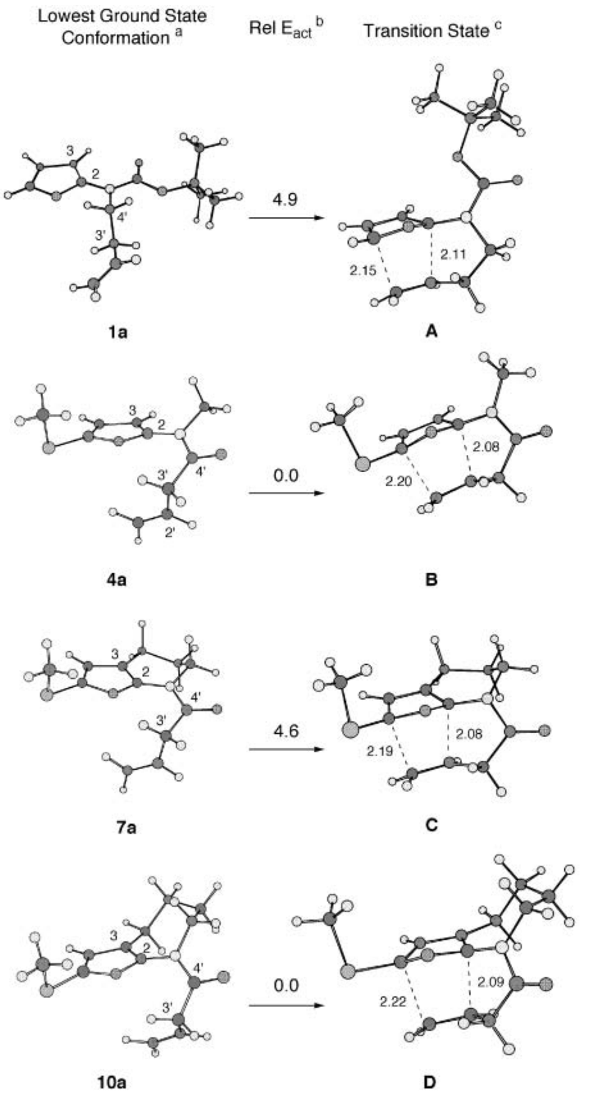

Figure 1. (a) Becke3LYP/6-31G* optimized ground-state conformations **1a**, **4a**, **7a**, and **10a**. (b) Calculated relative energies of activation for the cycloaddition in kcal/mol. (c) Corresponding transition state structures **A**−**D** with transitional bond lengths in angstroms.

on the basis of experimental observation (Figure 1, vide infra). Because none of the optimized transition states appear to suffer from obvious strain that would account for the differences in activation energy, the ground-state conformations were examined for conformational features that could form the basis for the observed differences. Two such features were easily identified.

The first feature involves the role that the carbonyl group plays on the ground-state conformations when placed within the tether. In conformer **1a**, the adjacent methylene carbons C(3′) and C(4′) adopt an *anti*-conformation, and the olefin is thus projected away from the furan. Comparison of **1a** to transition state **A** reveals that a *gauche*-conformation about these two atoms is required for the reaction to proceed. Placement of a carbonyl group within the tether, however, changes the preferred conformation. In conformer **7a**, for example, the C(2′)−C(3′) bond has a nearly synclinal/perpendicular relationship to the amide carbonyl (O−C(4′)−C(3′)−C(2′) = −100.8°),[15] effectively placing the olefin in closer proximity with the furan; thus, the minimum energy conformers are closer to the reactive conformers.

Although the energy differences associated with one simple bond rotation cannot account for the large differences in activation energies, another conformational feature places **4a** closer to a reactive conformation than **1a**. The C(3)−C(2)−N−C(4′) dihedral angle in **1a** was calculated to be 172.5° while the same dihedral angle in **4a** was 131.7°. Thus, the rotation about the C(2)−N bond appears to be biased toward a reactive conformer in **4a**. The C(3)−C(2)−N−C(4′) dihedral angle in transition state **A** was calculated to be 123.4° while the same torsional angle was approximately 130° in the other transition states. Conformer **4b**, which is similar to the low-energy conformation of **1a,** was calculated to be less than 0.1 kcal/mol higher in energy than **4a** (Figure 2).

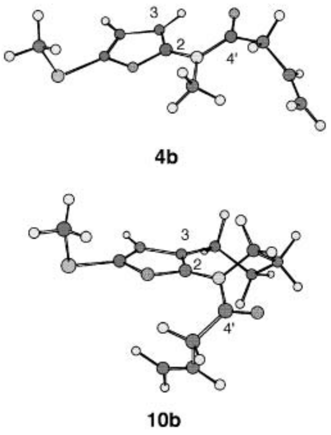

Figure 2. Second low-energy conformers of **4b** and **10b**.

Preferred ring conformations dictate the C(3)−C(2)−N−C(4′) dihedral angle in **7a** and **10a**. The six-membered ring annealed to the furan in **7a** adopts a half-chair conformation in which the C(3)−(C2)−N−C(4′) dihedral angle is 156.0°. The seven-membered ring annealed to the furan in **10a** adopts a low-energy conformation that imparts a 119.7° angle, but a simple ring flip provides a conformation (**10b**) in which the angle increases to 132.7° (Figure 2). The rapid interconversion of **10a** and **10b** (a calculated 2.2 kcal/mol energy difference) allows **10** to adopt a reactive conformation more readily than **1** or **7**. The differences in reactivity among furans **1**, **4**, **7**, and **10**, therefore, appear to correlate with a bias in the rotation about the C(2)−N bond.

The small difference in calculated activation energies between the conversion of **1** to **2** and **7** to **8** caused us to reexamine the reaction conditions required to effect the cycloaddition of **1**. It was discovered that the Diels−Alder

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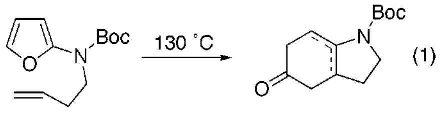
[15] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 617.

reaction proceeded at 130 °C to produce a mixture of enamino ketones **12a**,**b** as a mixture (3:2) of regioisomers in 64% yield (eq 1). Furthermore, **12a**,**b** could be isolated (less than 10%) from the reaction mixture when **1** was heated to 110 °C, although decomposition pathways appear to be much more rapid than cycloaddition at these temperatures.



1 **12a,b** (1)

In summary, conformational effects that have a dramatic impact on the relative reaction rates were identified in the low-energy ground-state conformations of furans **1**, **4**, **7**, and **10**. Specifically, the placement of a carbonyl in the tether caused the molecules to adopt conformations that were much closer to the reactive conformations than molecules that lacked this tether-carbonyl. A bias in the rotation about the C(2)−N bond was also found to correlate with the rates at which these molecules undergo intramolecular Diels−Alder cycloadditions. More detailed results of this study will be published in due course.

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