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Intramolecular 4 + 3 Cycloadditions. A Theoretical Analysis of Simple Diastereoselectivity in Reactions of Alkoxyallylic Cations and Furans

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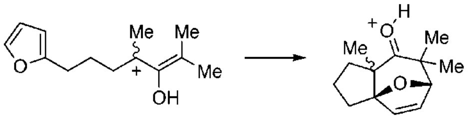
ABSTRACT

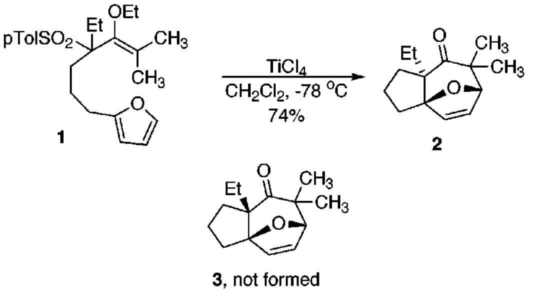


A computational examination (B3LYP/6-31+G*//HF/6-31+G* + ZPVE) of an intramolecular 4 + 3 cycloaddition reaction suggests a stepwise process and the likelihood of reversibility in at least one of the pathways examined.

The intramolecular 4 + 3 cycloaddition of allylic cations and dienes is a powerful reaction for the construction of polycyclic systems containing seven-membered and larger ring systems.[1] The Harmata group has had an interest in this reaction for some time[2] and has been interested in establishing a mechanistic basis for the stereochemical outcomes of intramolecular 4 + 3 cycloaddition reactions. In this paper, we report theoretical results relating to the intramolecular cycloaddition of alkoxyallylic cations with furan dienes.[3]

One of the first examples of an intramolecular 4 + 3 cycloaddition reaction reported by the Harmata group is shown in Scheme 1.[4] This reaction showed complete diastereoselectivity to afford the product **2** exclusively. The cycloaddition of substrates (*E*)-**4** and (*Z*)-**4** also produced **2** without any trace of the other possible diastereomer **3** (Scheme 2).[5]

Scheme 1



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(1) For reviews on 4 + 3 cycloaddition chemistry, see: (a) Rigby, J. H.; Pigge, F. C. [4 + 3] Cycloaddition reactions. *Org. React.* **1997**, *51*, 351−478. (b) Harmata, M. Intramolecular [4 + 3] cycloaddition reactions. *Adv. Cycloaddit.* **1997**, *4*, 41−86. (c) Harmata, M. Heteroatom-stabilized allylic cations in 4 + 3 cycloaddition reactions. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523−535. (d) Harmata, M. Intramolecular cycloaddition reactions of allylic cations. *Tetrahedron* **1997**, *53*, 6235−6280. (d) Cha, J. K.; Oh, J. [4 + 3] cycloaddition reactions of cyclic oxyallyls in natural product synthesis. *Curr. Org. Chem.* **1998**, *2*, 217−232.

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(3) For other theoretical treatments of the 4 + 3 cycloaddition reaction, see: (a) Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641−5644. (b) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523−5532. (c) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176−186.

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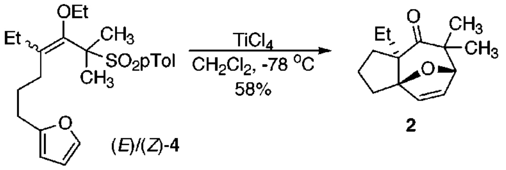
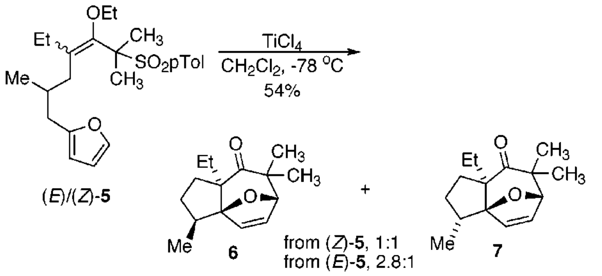
Scheme 2



We wanted to examine whether this result arose from two configurationally intact cations reacting to afford the same product or if they rapidly interconverted and then went on to product. To that end we synthesized three substrates with a stereogenic center in the tether joining the furan and alkoxyallylic sulfone.[6] The "best" result is shown in Scheme 3. In this case, the two isomeric substrates did not give an equal distribution of isomeric cycloadducts, suggesting that the intermediates generated from them did not interconvert faster than the cycloaddition process. This implies that the barriers for these types of transformations must be relatively low, as is also clear from the quick reaction at −78 °C. The evidence does not preclude stereochemical leakage, however.

Scheme 3



We still have questions about how these kinds of cycloadditions might be working with respect to simple diastereocontrol. From the very simple perspective of molecular model analysis, there seems to be no overwhelming reason a product like **3** should not be formed.

To elucidate this point further, we performed ab initio computations at the Hartree−Fock (HF) level of theory utilizing a 6-31+G* basis set employing Gaussian98.[7] All fully optimized stationary structures were characterized by harmonic frequency analysis to identify minima (number of imaginary frequencies, NIMAG = 0) and transition structures (NIMAG = 1) and to derive zero-point vibrational energies (ZPVEs). Final relative energies were evaluated at the density functional theory level utilizing Becke's three-parameter gradient-corrected exchange functional[8] in conjunction with the Lee−Yang−Parr nonlocal correlation functional[9] (i.e., B3LYP). Our final energy comparisons therefore refer to the B3LYP/6-31+G*//HF/6-31+G* + ZPVE level, unless noted otherwise. This level seems appropriate for purely qualitative considerations as it offers a reasonable compromise between computational effort and accuracy. For computational feasibility, we used a methyl instead of an ethyl group in the structure of the cation resulting from Lewis acid attack (modeled by protonation of the oxygen) on **1**. The resulting structures are numbered accordingly (**8**−**13**, Figures 1 and 2); all energies are summarized in Table 1; the geometries are available in Supplementary Information. The structures in Figure 1 correspond to the formation of **2** (with the ethyl group changed to a methyl group) in Scheme 3. Likewise, those in Figure 2 correspond to the formation of **3** (with the geometry simplification as for **2**) in Scheme 3.

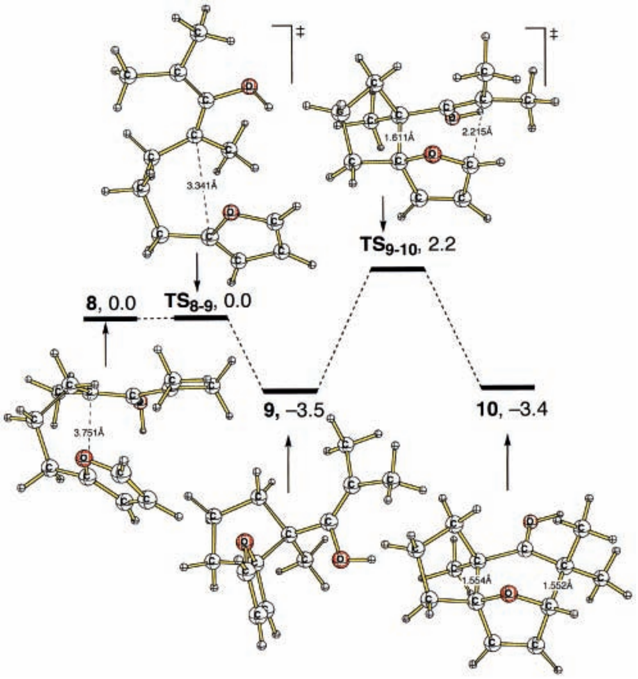


Figure 1. B3LYP/6-31+G*//HF/6-31G* + ZPVE optimized structure and energies of the reaction of **8**.

Each open cation proceeds to a π-complex (**8** and **11**), which upon very slight distortion proceeds through a virtually

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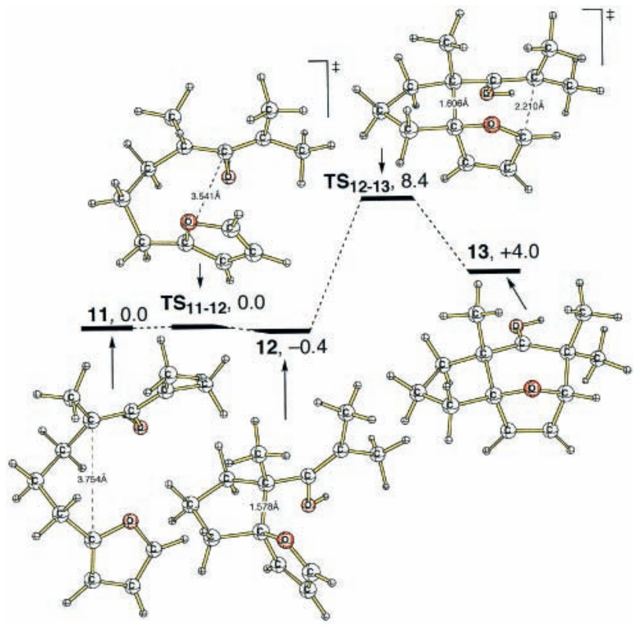

Figure 2. B3LYP/6-31+G*//HF/6-31G* + ZPVE optimized structure and energies of the reaction of **11**.

barrierless transition structure ($\mathbf{TS_{8-9}}$ and $\mathbf{TS_{11-12}}$) to an intermediate σ-complex (**9** and **12**). Intermediate **9** is 1.8 kcal mol^{-1} more stable than **12**; as the barriers are low (vide supra), the formation of this structure is important for the course of the reaction as **12** is far more likely to revert back (barrier < 0.5 for **12** vs 3.5 kcal mol^{-1} for **9**) to the π-complexes and subsequently to the open cation **11**. In the other direction along this part of the potential energy hypersurface, the intermediates proceed to transition structures that represent the final carbon−carbon bond forming event in the cycloaddition process. The barriers to ring closure are significantly different (5.7 and 8.8 kcal mol^{-1} for **9** and **12**, respectively) and agree nicely with the experimental findings.

The product formed in the reaction of **11** is significantly higher in energy (8.8 kcal mol^{-1}, **13**) than intermediate **12**, indicating that the reaction not only is reversible but would lead all the way back to the starting materials. The formation of the product from **8**, however, is approximately thermoneutral, which emphasizes the important role of a discernible σ-complex intermediate. The formation of the final product would hence be dependent on the rate of dealkylation vis-à-vis the rate of reversion to form the σ-complexes **9** and **12**.

The conclusion that one can draw from these data is that the σ-complex **12** can indeed be formed from an open cation but probably reverts to the π-complex or open cation faster than undergoing cycloaddition. The reaction is additionally driven by the 7.3 kcal mol^{-1} greater thermodynamic stability of **10** vs **13**. Hence, fast quenching of **10** would also efficiently move the overall equilibrium in the experimentally observed direction.

Table 1. Absolute Energies (in −au) for all Computed Species; ZPVEs in kcal mol^{-1}

species	HF/6-31+G*	ZPVE [NIMAG]	B3LYP/6-31+G*[a]
8	652.79155	197.8 [0]	656.97977
$\mathbf{TS_{8-9}}$[b]	652.78941	197.7 [1]	656.98061
9	652.80705	199.9 [0]	656.98718
$\mathbf{TS_{9-10}}$	652.77963	200.7 [1]	656.97754
10	652.82214	201.9 [0]	656.99173
11	652.79092	197.8 [0]	656.98031
$\mathbf{TS_{11-12}}$[b]	652.79376	197.8 [1]	656.98431
12	652.80108	200.3 [0]	656.98489
$\mathbf{TS_{12-13}}$	652.77204	200.7 [1]	656.97155
13	652.80895	202.2 [0]	656.98089

[a] Energy single point on the HF/6-31+G* optimized structures. [b] Note that the energies of these transition structures are below those of the preceding minima, in particular when ZPVEs are taken in to account. This is a typical situation when a reaction is barrierless and takes place at an overall very flat potential energy hypersurface.

In conclusion, our computations suggests that the simple diastereoselectivity observed in certain 4 + 3 cycloaddition reactions is the result of a stepwise process which for one stereochemical family of products is reversible. The results suggests that generating an intermediate like **12** and testing the acid stability of the ketone corresponding to **13** (e.g., **3**) should be explored. We intend to pursue these leads to validate these theoretical results. Our progress will be reported in due course.

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Supporting Information Available: Coordinates for all computed species. This material is available free of charge via the Internet at http://pubs.acs.org.

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