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Vinylogous Mannich Reactions: Some Theoretical Studies on the Origins of Diastereoselectivity

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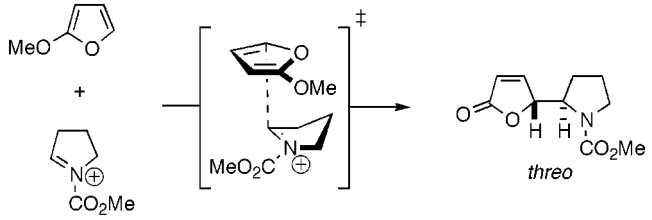
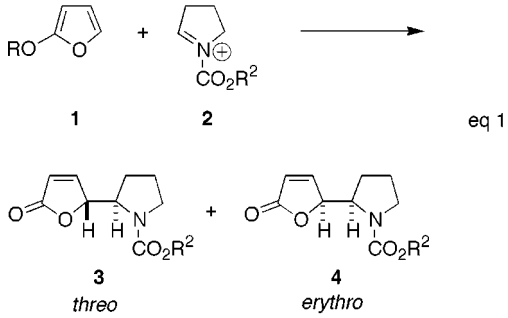
ABSTRACT



Ab initio calculations at the RHF/3-21G* level were used to investigate the limiting transition states in the addition of 2-methoxyfuran to a pyrrolinium ion. Four stationary points were found on the potential energy surface with relative energies of *threo* Diels–Alder, 0.0 kcal/mol; *erythro* open, 0.9 kcal/mol; *erythro* Diels–Alder, 1.3 kcal/mol; and *threo* open, 1.8 kcal/mol.

The vinylogous Mannich reaction, which is exemplified by the addition of 2-trimethylsilyloxyfuran (**1**, R = TMS) to the cyclic *N*-alkoxycarbonyl pyrrolinium ion **2** (R^2 = Bn) to provide a mixture (8.5:1) of diastereomeric adducts **3** (*threo*) and **4** (*erythro*) (eq 1),[1] has received considerable



attention in recent years.[2,3] We recently reported the results of experiments designed to probe some of the substituent effects that guide the stereochemical outcome of these *threo*-selective vinylogous Mannich reactions.[4] On the basis of transition state geometries proposed for various nucleophilic additions to carbonyl groups,[5] a set of four limiting transition states, shown in Figure 1 as Newman projections about the incipient carbon−carbon bond, may be envisioned. Within these four transition states, the reaction partners could

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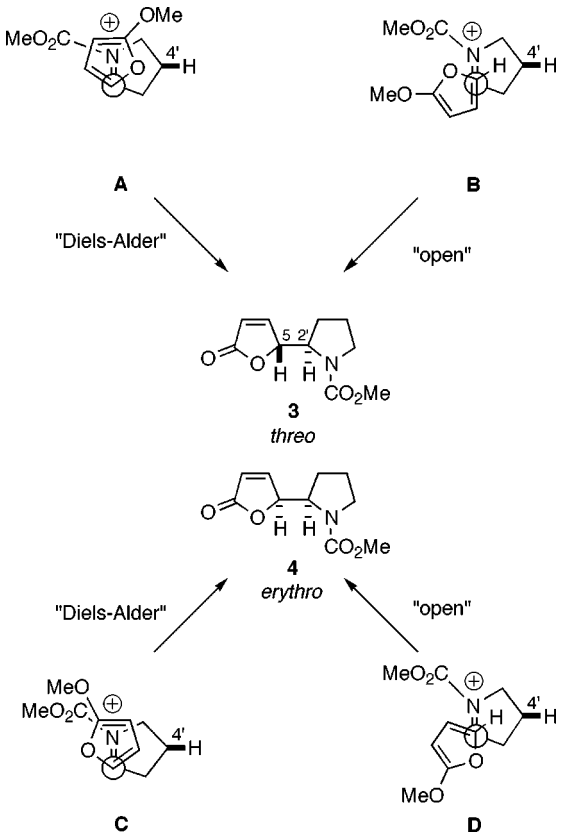

Figure 1. Proposed limiting transition states for the addition of **1** to **2** to give **3** and **4**.

approach each other in "Diels–Alder" like (**A** and **C**) or "open" (**B** and **D**) orientations. Although transition state conformation **A** appeared more consistent with the observed substituent effects, there were no data that compellingly supported **A** as being favored relative to transition states **B**–**D**.

To probe the basis for the observed stereochemical preferences in these additions, a theoretical investigation of the energetics for the transition state geometries **A**–**D** was conducted. A model system that retained the essential features of an alkoxycarbonyl group on the nitrogen and a 2-alkoxy or silyloxy group on the furan and that was simple enough to study at reasonable levels of theory was needed for the computational studies. The addition of 2-methoxyfuran (**1**, R = Me) to the pyrrolinium ion **2** (R^2 = Me) leading to products **3** and **4** (R^2 = Me) was expected to meet these conditions.

Initial attempts to find stationary points on the potential energy surface of the reaction were carried out using semiempirical AM1 calculations.[6,7] Although saddle points corresponding to each of the four transition states in Figure 1 were located, the differences in relative energies between the competing pathways were small and hence could not account for the experimentally observed *erythro*/*threo* stereoselectivities. For example, both "open" transition states **B** and **D** were calculated to have a relative energy of 0.0 kcal/mol while the calculated energies of both "Diels–Alder" transition states were only 0.4 kcal/mol higher. Another deficiency in these calculations was that the cyclic iminium ion was predicted to be a planar structure rather than an envelope conformation as would be anticipated on the basis of experimental data.[8]

Owing to the aforementioned shortcomings of the AM1 method, ab initio calculations were pursued at the RHF/3-21G* level. Using the transition state geometries calculated by AM1 as a starting point, the saddle points corresponding to the four proposed transition states were again located (Figure 2). The relative energies calculated for these four stationary points suggested that the "Diels–Alder" array **A** had the lowest energy, with the "open" orientation **D** lying

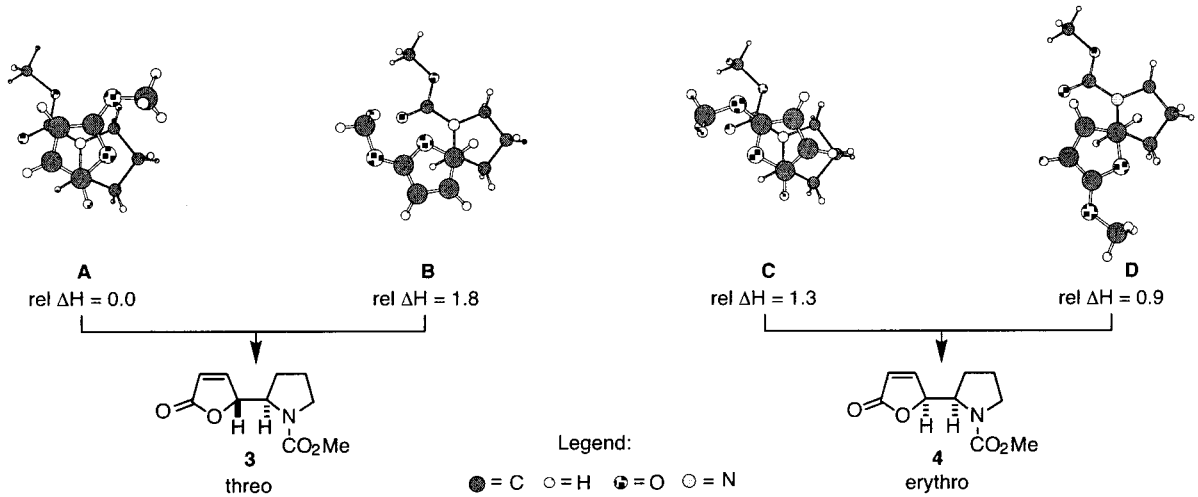

Figure 2. Ball and stick drawings of the saddle point structures corresponding to the proposed transition states. Relative energies are shown in kcal/mol.

0.9 kcal/mol higher in energy. The energy of the "Diels–Alder" transition state **C** was calculated to be 1.3 kcal/mol higher than that for **A**, and the energy of the "open" transition state **B** was 1.8 kcal/mol above that of **A**. The energetic difference between the two lower transition states **A** and **D** corresponds to an 8:1 ratio of *threo*:*erythro* products at −78 °C, a value that is consistent with the experimentally observed 8.5:1 product distribution observed with closely related reactants.[1]

The calculations at the RHF/3-21G* level not only gave energies that were consistent with experiment but they also predicted that the cyclic iminium ion would adopt the expected shallow envelope conformation.[8] Namely, in transition states **A**–**D**, C(4′) was displaced approximately 19–23° out of the N(1′)–C(2′)–C(3′) plane (Figure 3). In the transition state for the addition, the furan approached the iminium ion from "inside" the fold, thereby giving rise to the product directly in a staggered conformation. The alternate mode of addition from the side opposite the fold initially forms the adduct in an eclipsed conformation, but initial efforts to locate a saddle point corresponding to this "outside" addition mode were unsuccessful. The importance of staggered vs eclipsed conformations in transition states has been noted by Houk,[9] and Woerpel has recently invoked this inside attack to rationalize the stereochemical course of nucleophilic additions to five-membered ring oxocarbenium ions.[10] The angle between N(1′)–C(2′)–C(5) corresponds to the trajectory of the approaching nucleophilic center in the methoxyfuran to the plane of the iminium ion. In accord with expectations,[11] these angles were found to be 105° for **A** and **B**, 108° for **C**, and 111° for **D**.

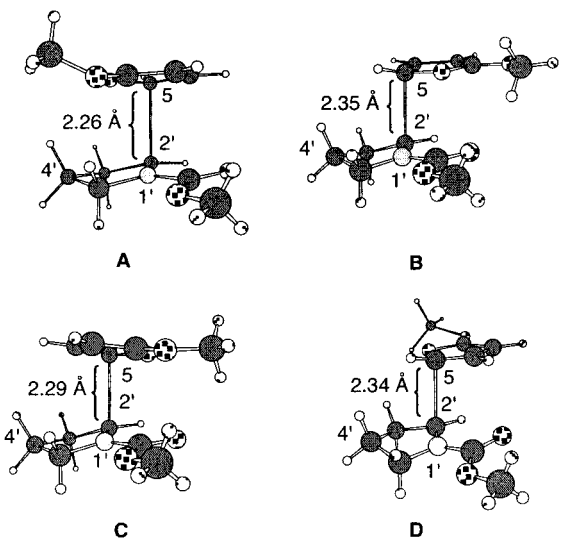

Figure 3. Side view of the calculated geometries for **A**–**D**.

The present study validates the use of calculations at the RHF/3-21G* level to replicate experiment for vinylogous Mannich reactions of simple substrates. Ideally, one would like to identify the interactions responsible for favoring the calculated transition state **A** over **B**–**D**. However, because examination of the possible steric interactions in transition states **A**–**D** does not reveal any that seem dominant, it remains uncertain whether transition state **A** is favored by cumulative steric interactions or by stabilizing stereoelectronic factors as proposed by Jefford and Mulzer.[5a,b] To address this intriguing question, it is now necessary to apply this method to the vinylogous Mannich reactions of more highly substituted reactants wherein substituents might have a more pronounced effect upon the stereochemical outcome.

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Supporting Information Available: Coordinates for each of the calculated transition state geometries in Protein Data Base format. This material is available free of charge via the Internet at http://pubs.acs.org.

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