Mechanism and Site Selectivity in the Diels–Alder Reaction between Protoanemonin and Butadiene. A Theoretical Study

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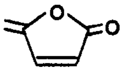
The Diels–Alder reaction between protoanemonin and butadiene has been theoretically studied by means of the semiempirical MNDO and AM1 methods. With use of the results obtained, the experimentally observed site selectivity is discussed regarding the mechanism of the process and the nature of the transition states. It is concluded that this reaction probably proceeds via a diradical intermediate.

Introduction

Protoanemonin (5-methylene-2(5*H*)-furanone, 1), the agent responsible for the blistering property and the antibiotic activity of many plants belonging to the natural order of ranunculaceae,[1] easily dimerizes through a [2+2] cycloaddition to anemonin (2)[2] via a probable biradical mechanism.[2a] In a study of the electrophilic reactions of protoanemonin with a variety of nucleophiles, the site of attack was reported to be governed by the hardness or softness of the nucleophile.[3]



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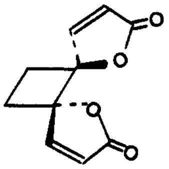

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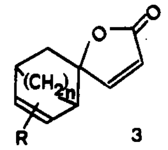

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n = 0,1,2

Protoanemonin also acts as a dienophile in Diels–Alder reactions. Reaction is possible at either of the two double bonds, leading to several possible products. Nevertheless, protoanemonin reacts specifically at the exocyclic double bond with butadiene[4] and several mono- and disubstituted derivatives of butadiene,[5] as well as with cyclic dienes[6] yielding spirolactones of the general structure 3, which have special olefactive properties.[7] We have previously shown that frontier orbital theory[8] fails to predict the site selectivity of these processes. The preferential formation of the exocyclic adduct can be understood if biradical character is invoked for the transition states or if the reaction proceeds as a two-step process. The relative stabilities of such biradical structures have been estimated from a treatment previously proposed.[9]

The possibility of asynchronous transition states[10] or two-step processes[11] for Diels–Alder reactions with unsymmetrical dienophiles has a long history in the literature. Recent studies support these contentions in several cases.[12]

In order to better understand the experimental results, we have undertaken a study of the potential energy surface of the reaction to determine the structure of the transition states and the energy barriers corresponding to the endo- and exocyclic attacks.

Despite numerous theoretical studies,[13] the nature of the transition state(s) in the Diels–Alder reaction remains somewhat controversial. Closed-shell (RHF) calculations tend to favor a synchronous transition state, while multiconfigurational calculations (CI or MCSCF techniques) favor an asynchronous transition state.[13f–h] These results seem borne out by the latest MCSCF ab initio calculations[13h] as well as by the latest (AM1) semiempirical calculations.[13f] Earlier semiempirical calculations using the MINDO/3 and MNDO methods overemphasized the biradical character of the transition states. These results, considered to be artifactual, are explained by the flaws in these methods.[13f]

Method of Calculation

The calculations have been performed with the MNDO[14] and AM1[15] methods implemented in the AMPAC program.[16] Full geometry optimization has been carried out at the RHF level.

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Stationary points of the potential energy hypersurface have been located by minimizing the root-mean-square gradient of the energy and characterized through the calculation of the energy second-derivative (force constant) matrix.[17]

The energies of some structures have also been calculated by both 2 × 2 CI on the RHF closed-shell wave functions and 3 × 3 CI starting with the open-shell singlet wave function calculated with the half-electron method.[18] Some calculations were performed at the RHF-optimized geometries, while others were optimized with CI.

Results and Discussion

Two products are possible from the Diels–Alder reaction of protoanemonin and butadiene in the absence of isotopic labeling. Attack upon the endocyclic double bond of the dienophile leads to one via either an endo or an exo transition state. Attack upon the exocyclic double bond leads to the other, again via two different (endo and exo) transition states. Figure 1 and Table I present the results of the optimized RHF transition states for all four possibilities.

AM1 predicts synchronous or nearly synchronous mechanisms, while the MNDO transition states correspond to very asynchronous approaches. MNDO predicts the formation of the exocyclic adduct to be kinetically preferred, in agreement with experimental evidence. The difference in activation enthalpies, 7.8 kcal/mol, is sufficient to preclude the experimental observation of any of the endocyclic adduct. However, the AM1 calculations seem to fail in the prediction of correct site selectivity (as does frontier orbital theory[7]), since the endocyclic transition state is preferred by 3.1 kcal/mol. This preference is reduced to 1.5 kcal/mol when 2 × 2 CI is performed on the RHF-optimized transition states (see Table I).

AM1 predicts the exo to be favored over the endo transition states for both exo- and endocyclic reactions. This result is consistent with previous[13l,m] and other unpublished results, as well as recent RHF ab initio calculations.[13n] The experimental results available for the reaction of butadiene and protoanemonin do not provide the evidence needed to determine which transition state is favored as only one product (exocyclic) that could have been passed through either of two transition states is formed. An experimental determination with an appropriately isotopically labeled butadiene (such as 1,4-dideuteriobutadiene) would be necessary to determine which of the two possible transition states leading to the observed product is correct.

The comparison of the MNDO and AM1 results with experimental results suggests that there is a connection between site selectivity and the degree of synchronicity of the mechanism. Consequently, we have conducted a detailed (AM1) study of several asynchronous reaction paths for reactions leading to the exocyclic and endocyclic adducts.

In the case of exocyclic attack, a second stationary point with only one negative force constant has been found at the RHF level, whose energy is 4.3 kcal/mol higher than that of the exocyclic transition state presented in Table I. For this structure the lengths of the two partial bonds are $R_1 = 1.766$ Å and $R_2 = 3.096$ Å. In the endocyclic AM1 potential energy surface no asynchronous saddle point could be found at the RHF level.

These results suggest two alternative reaction paths in the RHF/AM1 potential energy surface for the reaction

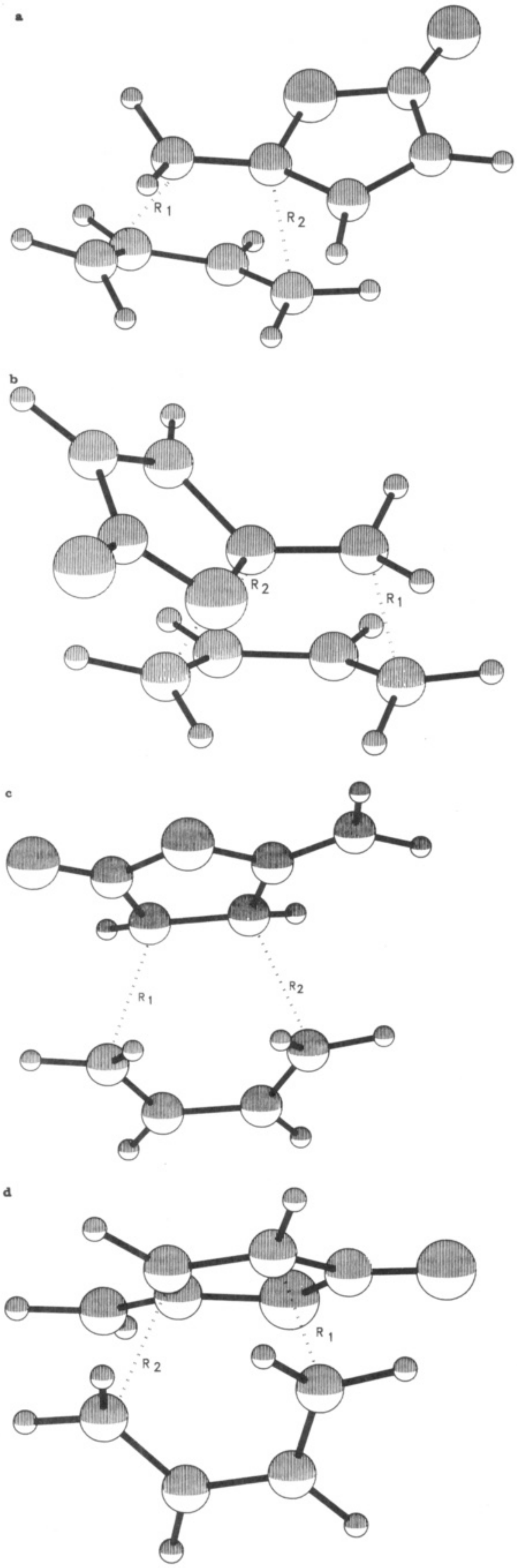

Figure 1. Optimized geometries for the four possible transition states (see Table I for the values of R_1 and R_2): (a) exocyclic attack (endo); (b) exocyclic attack (exo); (c) endocyclic attack (endo); (d) endocyclic attack (exo).

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Table I. Lengths of the Two Forming Bonds at the Transition States and Activation Enthalpies Computed with the AM1 (and MNDO) Methods

type of attack	R_1 (Å)	R_2 (Å)	H (kcal/mol) RHF	H (kcal/mol) CI[a]
exocyclic				
endo[b]	2.040 (1.582)	2.268 (3.005)	27.5 (35.5)	25.5
exo	2.034 (1.581)	2.268 (2.958)	26.6 (35.6)	24.6
endocyclic				
endo	2.150 (1.612)	2.153 (3.237)	25.2 (43.0)	23.9
exo	2.149 (1.622)	2.149 (3.308)	23.5 (43.3)	23.1

[a] 2 × 2 CI at the RHF-optimized geometry. [b] Endo is defined as the structure with the butadiene bent toward the ring oxygen in protoanemonin.

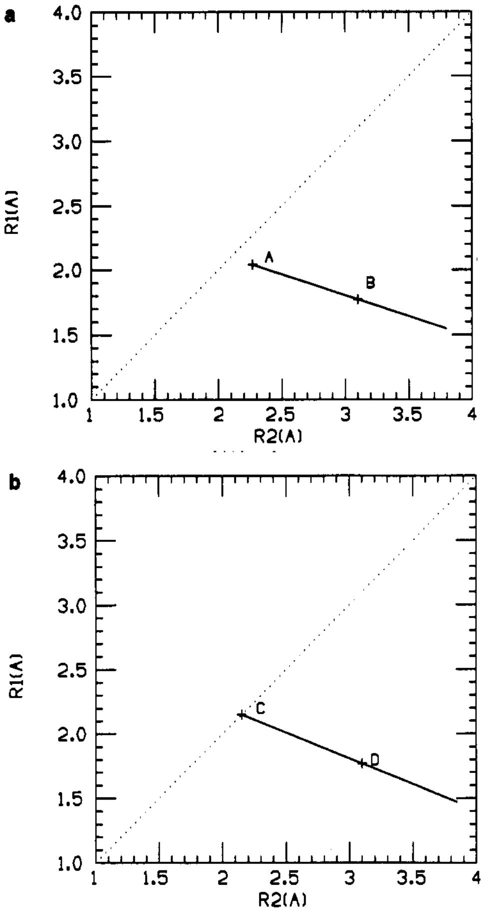


Figure 2. Reduced surfaces for the CI calculations for the exocyclic (a) and endocyclic (b) reaction paths. See text for details and discussion.

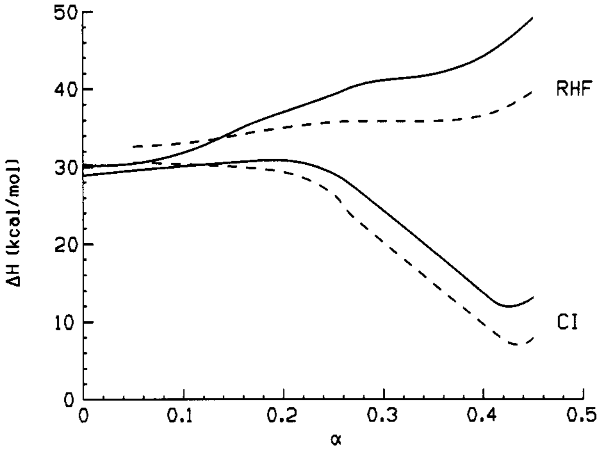


Figure 3. Variation of the RHF and CI energies with the degree of asynchronicity, α (see text for definition).

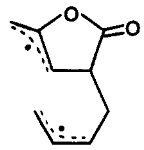
leading to the exocyclic adduct, with the nearly synchronous one favored, while only a synchronous process exists for the endocyclic reaction. The introduction of configuration interaction should modify the shape of these potential energy surfaces, since asynchronous structures should have a significant biradical contribution which is not properly described at the RHF level. To investigate this effect, we have carried out CI calculations for several points of the bidimensional potential energy surfaces. These reduced surfaces are obtained by taking R_1 and R_2 as independent variables and by optimizing the rest of the geometrical parameters for each pair of values of R_1 and R_2. The points chosen in each case are schematically shown in Figure 2, where the stationary points have also been indicated.

For the exocyclic reaction (Figure 2a) we have considered the points situated along the straight line connecting the nearly synchronous transition state (R_1 = 2.04 Å and R_2 = 2.27 Å) and the asynchronous saddle point (R_1 = 1.77 Å and R_2 = 3.10 Å). In the endocyclic reaction (Figure 2b) we have considered the straight line linking the transition state (R_1 = 2.15 Å and R_2 = 2.15 Å) and an asynchronous structure with the values or R_1 and R_2 identical with those corresponding to the asynchronous saddle point of the exocyclic reaction (R_1 = 1.77 Å and R_2 = 3.10 Å). Along these straight lines we define the degree of asynchronicity as $\alpha = (R_2 - R_1)/(R_2 + R_1)$. Figure 3 presents the variation of the RHF and CI energies with respect to the degree of asynchronicity for the reactions.

Let us first consider the RHF profiles. In the case of the exocyclic reaction, the energy regularly increases with α in the vicinity of the nearly synchronous transition state. However, an asynchronous reaction path is situated in a very shallow valley at α = 0.3. Conversely, the energy monotonously increases with the degree of asynchronicity in the endocyclic profile. The transition states for the endocyclic reactions are lower in energy. However, the situation is reversed in the asynchronous region of the potential energy surfaces.

The introduction of configuration interaction drastically changes the shapes of these energy profiles. In both cases, the asynchronous region becomes lower in energy than the synchronous, presumably due to the better description of biradical structures at the CI level. Thus, introduction of CI seems to reverse the erroneous site selectivity predicted by the RHF AM1 calculations.

Optimization of the transition state (using 3 × 3 CI on the open-shell excited singlet wave functions) for formation of a biradical from protoanemonin and *s-trans*-butadiene leads to an activation energy of 19.6 kcal/mol for this process. This reaction path implies a two-step reaction involving a biradical intermediate, 4, which could close to product in a faster second step. Such a reaction profile seems reasonable as the biradical is comprised of two stabilized radicals. The radical site on the five-membered ring in 4 is particularly stabilized as it is a heteroaromatic system with six π-electrons in the ring (two from the ox-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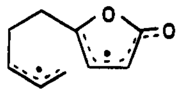
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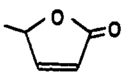
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ygen lone pair and one each from the four ring carbons). To illustrrate this point, we have calculated the bond dissociation energy of the annular C–H bond in the 5-methyl-2(5*H*)-furanone (β-angelica lactone, **6**). This value of 78.0 kcal/mol is significantly less than the corresponding calculated value (89.7 kcal/mol) for the benzylic hydrogens in toluene and lower than any of the similarly calculated bond dissociation energies of the benzylic C–H's of any of the possible α and/or para cyano- or hydroxy-substituted toluenes.[19] The result also agrees with the experimental observation that protoanemonin can dimerize to form a [2+2] adduct, presumably via an analogous biradical intermediate.

Some difference of opinion has been expressed in the literature about the use of CI with AM1 and MNDO calculations. Dewar has suggested that CI artifactually lowers the energy of biradicals by about 15 kcal/mol.[10f] However, many calculations using MNDO or AM1 and CI on the rearrangement of semibullvalenes,[20] bond thermolysis of azoalkanes,[21] radical recombinations of carbon- and nitrogen-centered radicals,[22] and recombination of benzyl radicals[23] have been remarkably successful both qualitatively and quantitatively. A study of bond dissociations of small molecules using MNDO/CI gave reaction profiles similar to MP4 and MCSCF ab initio calculations, even when CI up to 136 × 136 was used.[24]

Dewar has also noted that, without CI, AM1 RHF calculations cannot account for the rate-enhancing effects of substituents on the dienophile, such as cyano.[10f]

The results presented here suggest that the experimentally observed site selectivity in the Diels–Alder reaction between protoanemonin and butadiene can be better understood by invoking either a highly asynchronous or two-step mechanism. The ability of protoanemonin to form a cyclic, aromatic radical (as part of a biradical) upon attack by butadiene at the exocyclic methylene group is probably the determining factor in the observed selectivity.

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Registry No. Protoanemonin, 108-28-1; butadiene, 106-99-0.

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Formation of a Chiral 1-Fluoro-2,2-diphenylcyclopropyl Radical in the Barton Decarboxylation Reaction[†,1]

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The chiral 1-fluoro-2,2-diphenylcyclopropyl radical (**8**), generated in the Barton decarboxylation reaction, was used as a probe to evaluate a variety of halogen and hydrogen atom donating reagents as radical traps.

The thermal decomposition of *N*-hydroxypyridine-2-thione esters to produce radicals which can react with a variety of halogen-donating reagents resulting in an halogenative decarboxylation reaction or with H-atom donating sources to give rise to products of decarboxylation has been given the appellation, Barton decarboxylation reaction.[2] In an ancillary study the need arose to prepare chiral 1-bromo-1-fluoro-2,2-diphenylcyclopropane (**1**), and the Barton decarboxylation reaction was selected to carry out the conversion of the available[3] chiral 1-fluoro-2,2-diphenylcyclopropanecarboxylic acid (**2**) to the desired **1**.

There exists a large body of evidence[4] that shows, barring large steric interactions,[5] that the cyclopropyl radical is a rapidly inverting (10^{11}–10^{12} s^{-1} at 71 °C) bent σ radical[6] incapable of maintaining its configuration. However, electronegative substituents in the α-position, such as fluorine or alkoxy, are known to slow down the inversion frequency to the extent that if a very good radical trap is

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[†] This article is dedicated to Professor Derek H. R. Barton in recognition of his many important contributions to organic chemistry.

[‡] Visiting Professors from the Department of Chemistry, A. Mickiewicz University, Poznan, Poland.

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