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Transition Structures for MeOH addition to Pentadienyl Cations and Stereochemistry of Intramolecular Ether Cyclization

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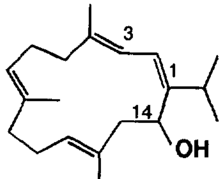
Abstract: Three transition structures for MeOH addition to pentadienyl cations were obtained by *ab initio* quantum mechanical calculations. By applying a force field model of the transition structures with fixed core treatment, we could reproduce the observed stereoselectivity of an intramolecular ether cyclization.

Sarcophytol A (**1**), which has a potent inhibitory activity against tumor promoters, was isolated from the soft coral, *Sarcophyton glaucum.*[1] It attracted much attention because of its biological activities and has been synthesized.[2] We have also reported its total synthesis.[3] During the course of the study we found an interesting stereoselectivity in cyclization reaction of **2** to give dienyl ethers (**3a** and **3b**).



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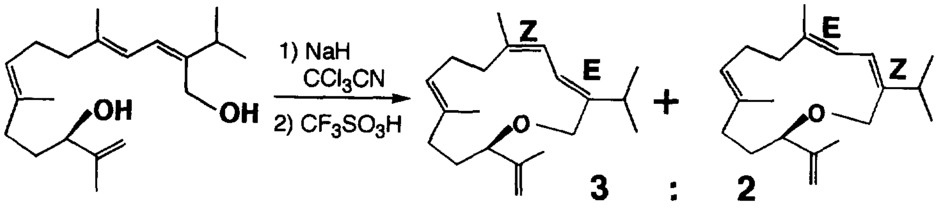


2 **3a** **3b**

The product was a mixture of two ethers in a ratio of 3:2. While the minor product (**3b**) retains the dienyl geometry of its precursor, the major one has the inverted geometry of both the double bonds. From the mechanistic consideration, it is reasonable to assume pentadienyl cations as reaction intermediates,[4] which collapsed by the nucleophilic attack of intramolecular hydroxy group to give cyclic ethers. If it was the case four geometries (EE, EZ, ZE, ZZ) for the pentadienyl cation can be possible and they might give respective cyclic ethers when their termini were attacked by the hydroxyl group intramolecularly. Comparison of the steric energies for the four possible products suggested that the one of the geometrical isomer (EE) can not be formed because of its high strain energy.[5] The ZZ isomer is not severely strained and its steric energy is quite similar to those of EZ and ZE isomers. The idea of the product development control[6] thus can not explain the observed selectivity of the reaction. In order to shed light on the mechanism of the reaction, accurate information on the geometries of the transition state of the cyclization step should be necessary. It is known that *ab initio* quantum mechanical calculation should give quantitative information about the geometry and energetics of the transition state. This method, however, can not be applied directly to large size molecules such as **1**, hence we used force field based transition state modeling.[7]

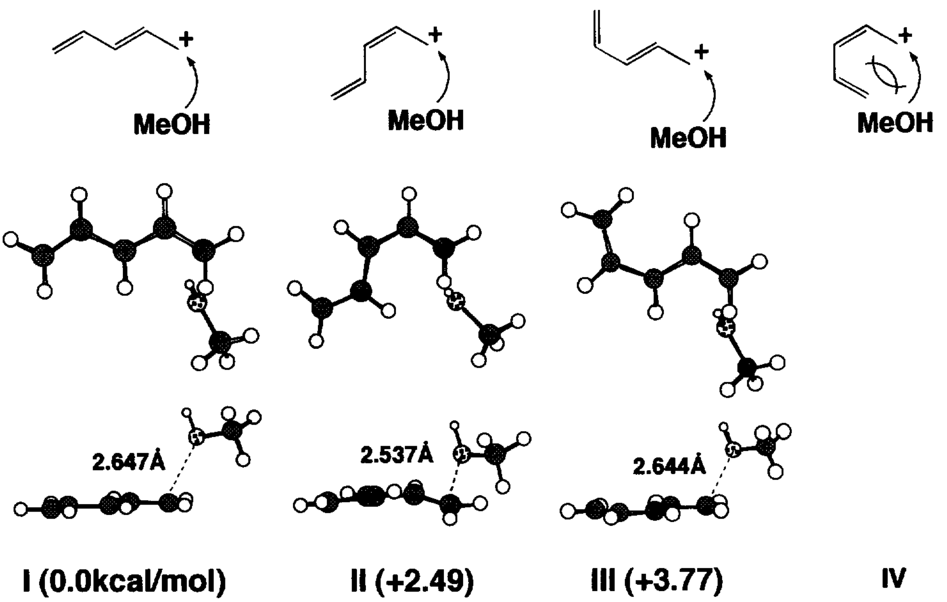


Figure 1. Schematic representation of four attacking modes for MeOH addition to pentadienylcation and three transition structures (**I**, **II**, and **III**) optimized at 3-21G basis set. The energies are MP2/6-31G*//RHF/3-21G.

There should be four possible modes for MeOH addition to the pentadienyl cation (Figure 1). Among these, three transition structures corresponding to **I**, **II**, and **III** were obtained by *ab initio* quantum mechanical calculations[8] at the level of 3-21G geometry optimization.[9] No transition

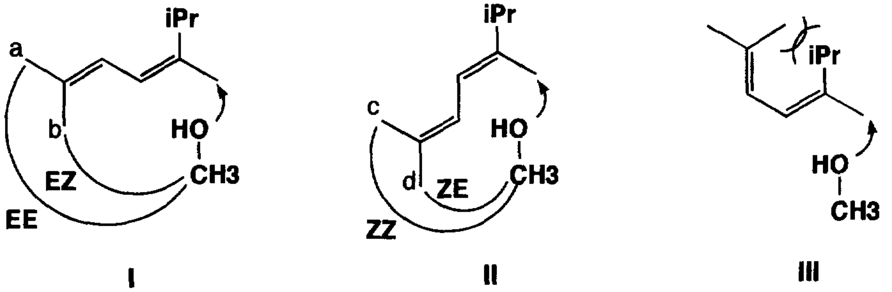
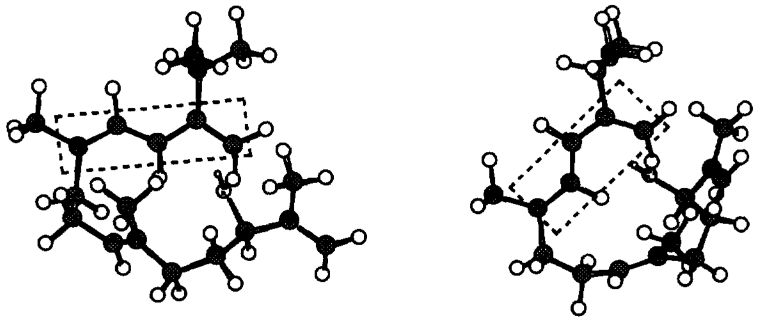


Figure 2. Cyclization modes of open chain precursors (**2**) to give 13-membered ring.

structure having the geometry (**IV**) could be obtained probably because of its severe steric repulsion between the two termini of the pentadienyl part. Before applying these structures to a force-field transition state modeling, simple consideration with a molecular model excluded the structure (**III**) because of its severe steric repulsion between the substituents on the pentadienyl part (Figure 2). It also disclosed that the formation of EE and ZZ products should be unfavorable because the distances between the carbon of MeOH and terminus (a) of **I** and that (c) of **II** are both so distant as to construct the 13-membered rings.

Force field modeling of the transition state of the cyclization reaction was then carried out using the two possible transition structures (**I** and **II**) as the reacting cores. We applied fixed core treatment:[10] the geometries of the reacting cores were kept rigid and the remaining part of the molecule were optimized by MM2 force field. All the plausible structures of the carbon chain were



TS 1(EZ) **TS 1(ZE)**

Figure 3. The most stable transition structures leading to EZ- and ZE-isomers, respectively.

constructed by our MMRS program.[11] The lowest energy transition structures leading to EZ and ZE products are shown in Figure 3. Several other structures leading to the two products are also obtained. The steric energies of these structures are listed in Table 1. Boltzman weighting distribution of these structures are estimated by these steric energies. By summing those

Table 1. Boltzman weighting distribution of transition structures.

	EZ-isomer		ZE-isomer	
	SE(kcal/mol)	Prob.	SE(kcal/mol)	Prob.
TS 1	19.62	43.8 %	20.77	6.4 %
TS 2	19.78	33.5	20.93	4.9
TS 3	21.21	3.0	21.22	3.0
TS 4	21.38	2.3	21.67	1.4
TS 5	21.79	1.1	22.14	0.6
Sum		83.7 %		16.3 %

probability, we can predict the ratio of the two products. The value (84:16) is satisfactory when compared to the observed.

From these calculations, it was found that the force field modeling of the transition states can reasonably explain not only the correct stereochemistry of the macrocyclization but also selective formation of the two geometrical isomers. Hence, this approach can be an effective tool to predict correct stereochemistry of a macrocyclization.

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