Diastereoselective Decarboxylation of Cyclopentene Dicarboxylic Acid Derivatives

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Received: February 21, 2004; In Final Form: April 27, 2004

We investigated the decarboxylation of 2-phenylcyclopent-3-ene-1,1-dicarboxylic acid (**1**) and its derivatives from the ab initio calculations. The reaction pathway starting from the R-configuration of **1** has been researched, and the transition states and endiol intermediates are computationally identified based on the imaginary frequency and its normal mode. The six membered ring transition states show the concerted mechanism for the C−C bond breaking and O−H bond formation. The intermediates are converted into the (R,R)- or (S,R)-2-phenylcyclopent-3-ene carboxylic acid. It has been found that the energy difference between two reactants (R1 and R2) is small (∼1.1 kcal/mol) and is virtually the same as that between two transition states (TS1 and TS2), while the energy difference between the (R,R) and (S,R) isomers of the product is much larger (∼7.39 kcal/mol). Thus, the stereochemistry of the product can be determined from the relative stability of the products as well as that of the transition states. The trans isomer is found to be favored due to its less steric hindrance than the cis isomer, which is consistent with previous experimental observation. However, the intramolecular interactions such as hydrogen bonding and π-hydrogen interaction also play a role to a certain extent.

Introduction

The ring compounds with chiral centers have served as potential drug candidates for the treatment of a variety of diseases, thus many stereoselective cyclic compounds have been synthesized.[1−6] The asymmetrically functionalized cyclopentene rings were synthesized through the [3+2] cycloaddition reaction of 2,3-butadienoates with electron-deficient olefins,[6,7] and several stereoselective ring compounds have been synthesized through the alkylations starting from the chiral pyrrolidines.[8]

Use of readily available reagents to creat densely functionalized structures in a highly diastereoselective fashion is important to enhance synthetic efficiency. There have been extensive studies on the diastereoselective cyclic compounds for recent years. Walsh and co-workers generated quite reactive organozinc species, which in turn adds to ketones and aldehydes to produce diastereoselective *meso*-1,6-enediols with efficient control.[9] Jeon and Walsh reported the successful enantioselective 1,2-addition reactions of cyclic α,β-unsaturated ketones, and developed a one-pot protocol for the enantioselective addition/diastereoselective epoxidation.[10] Yokoyama et al. explained the diastereoselective photochromism of a bisbenzothienylethene based on the steric effect and electronic interactions.[11] Sanji et al. first reported the successful diastereoselective addition of alcohols to diastereotopic silyenes.[12] Additionally, diquinanes from acyclic precursors,[13] 4-phenyl-1,2,3,4-tetrahydroisoquinolines from chiral lactam enolates,[14] and 1-benzyltetrahydroisoquinolines from amino acids[15] have been synthesized diastereoselectively. The diastereoselective products were also achieved by Evans asymmetric alkylation of oxazolidinone glycolates[16] and by Grignard addition to 2-acylindoline.[17] A method for the diastereoselective 2,4-disubstituted piperidines was developed by Watson et al. and was able to control the reaction selectively by changing the order of reaction sequence.[18] The enantioselectivity/diastereoselectivity has also been found in enzyme catalytic reactions in conversion of ketones or enol acetates to chiral acetates,[19] and the enantioselectivity was much more enhanced in ionic liquids than in conventional organic solvents.[20] The enzyme memory based approach was reported to give further enhancement of the enantioselectivity.[21]

Decarboxylation is an important practical reaction of carboxylic acids in organic chemistry, biochemistry, and geochemistry, and it is an important method for the stereoselective ring compounds. Some examples synthesized through decarboxylation are naproxen derivatives[22] known as nonsteroidal antiinflammatory drugs, β-trifluoromethyl-*N*-acetyltryptophan,[23] *N*-aryltrisubstituted pyrroles,[24] 3,6-dihydro-1*H*-pyridin-2-ones,[25] 1-arylpiperazyl-2-phenylcyclopropanes,[26] etc. The stereochemical study was done on the decarboxylation of 2-phenylcyclohexane-1,1-dicarboxylic acid 47 years ago.[27] In their experimental condition, pH 7, the cis conformer was found to be 65.6%; however, it was reduced to 8.7% after heating to 200 °C for 102 h. Sakito and Suzukamo synthesized a cyclopentenecarbonyl compound from a vinylcyclopropanecarbonyl chloride.[28] Interestingly, they found that the sterically hindered cis configuration was established on the NMR data. After thermodynamic treatment (60 °C for 4 h in the presence of NaOMe in methanol), the cis conformer changed to the sterically less hindered trans conformer, consistent with previous experimental results.[27] For a different system, 3-[(*tert*-butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone, the trans stereochemistry was observed for the functional groups at C3 and C5

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10.1021/jp0492063 CCC: $27.50
Published on Web 06/05/2004

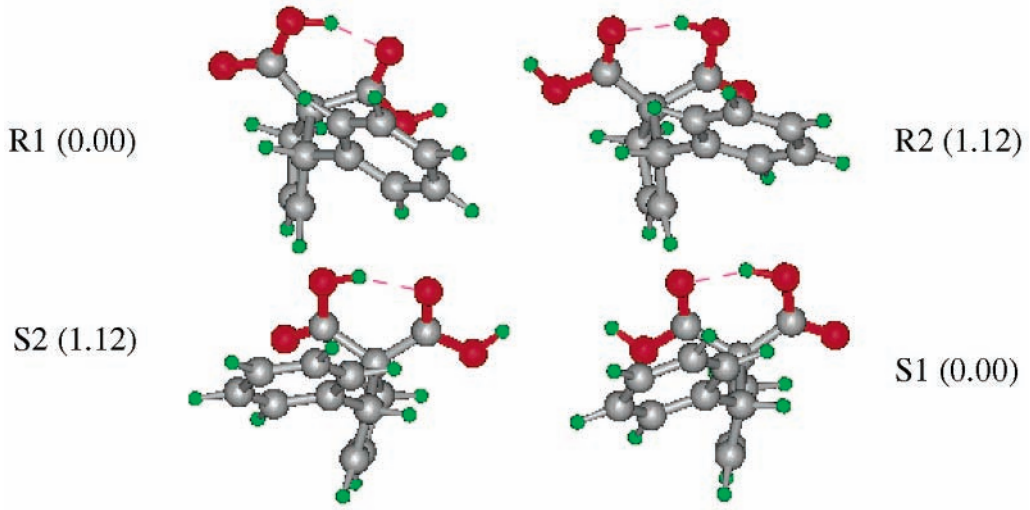
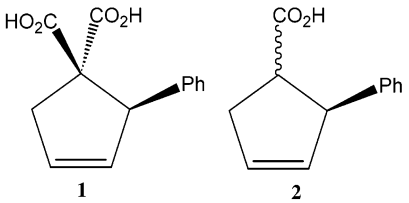


Figure 1. Four possible conformers and their relative energies (in parentheses in kcal/mol) of **1**.

positions.[29] Most of the trans selectivity was achieved at low-temperature with bulky substituents such as CO_2tBu, CH_2-$OSiMe_2t$Bu, or trityl groups at C5. Despite the tremendous volume of synthesized stereoselective ring compounds, the mechanistic studies that are essential for the design of new compounds are very limited.[30,31]

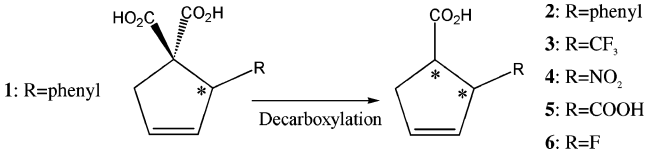
During our recent studies on the stereoselective synthesis of cyclopentene carboxylic acids via the ring-closing metathesis (RCM) reaction and the following decarboalkoxylation, we were faced with the problem of stereoselective decarboxylation of a suitably substituted cyclopentene dicarboxylic acid system. Recently, there have been several theoretical[32−34] and experimental[34−36] studies on the decarboxylation reactions which are involved in the biosynthesis of nucleic acids,[37,38] irreversible destruction of amino acids,[39] enzymatic reaction of OMP decarboxylase,[40,41] etc. In particular, the theoretically studied mechanisms have given a lot of information on the reaction pathways that make it possible to control the reactions. Despite such theoretical investigations, there is still lack of mechanistic study on the stereoselective decarboxylation. In these contexts, we intended to investigate the possibility of stereoselective decarboxylation of cyclopentene dicarboxylic acid system. As an initial model we chose 2-phenylcyclopent-3-ene-1,1-dicarboxylic acid (**1**) in order to grasp the effects of steric factor and intramolecular interactions on the stereochemistry of cyclopentene carboxylic acid **2**. Compound **1** was recently synthesized by rhodium catalyzed allylic alkylation/ring-closing metathesis to carbocycles[42] and by oxidation of diethyl ω-phenylalkenylmalonates by $Mn(OAc)_3$ under the N_2 and AcOH at 60 °C.[43]



Calculational Methods

The four possible conformers (R1, R2, S1, and S2) of reactant dicarboxylic acid **1** were initially optimized by density functional theory (DFT) calculations using the nonlocal density function of Becke's three parameters employing the Lee−Yang−Parr functional (B3LYP) with 6-31G* basis sets.

SCHEME 1



The decarboxylation is proposed to be preceded by intramolecular hydrogen bonding between two acid groups. The transition states were optimized and confirmed by vibrational normal-mode analysis, which gave only one imaginary vibrational frequency corresponding to the proposed normal mode, that is, the C−C bond breaking and O−H bond formation to give an en-diol intermediate. The two isomers (cis and trans) of the product **2** were also fully optimized at the same level of calculations. The energy profile along the reaction coordinates of decarboxylation of **1** has been investigated.

To investigate the contribution of steric effect and intramolecular interactions, we calculated the relative stability of the cis and trans conformers for the derivatives of **2**. We carried out the MP2/6-311++G** optimization and B3LYP/6-311+G** single point energy calculation at the B3LYP/6-31G* optimized geometry (B3LYP/6-311+G**//6-31G*) and found that the B3LYP/6-311+G** single point energy is almost equivalent to the MP2/6-311++G** optimized energy. Therefore, we carried out the single point energy calculations with B3LYP/6-311+G** level for several product isomers (see Scheme 1) at the B3LYP/6-31G* optimized geometries. All ab initio calculations were carried out using the Gaussian 98 suite of programs.[44]

Results and Discussion

Figure 1 shows the four stable conformers and their relative energies of 2-phenylcyclopent-3-ene-1,1-dicarboxylic acid (**1**). R1 and R2 represent the same chirality at the phenyl substituted carbon but have different intramolecular hydrogen bonding directions, and S1 and S2 are in the same way. For both R and S chirality, slightly more stable conformers (R1 and S1) have the free hydroxy group (not attending H-bonding OH) pointing toward the phenyl. The stability of R1 and S1 conformers over the R2 and S2 conformers comes from the fact that the repulsion between π-electrons of phenyl and carbonyl of COOH is larger than the attraction between π-electrons of phenyl and hydroxy of COOH.

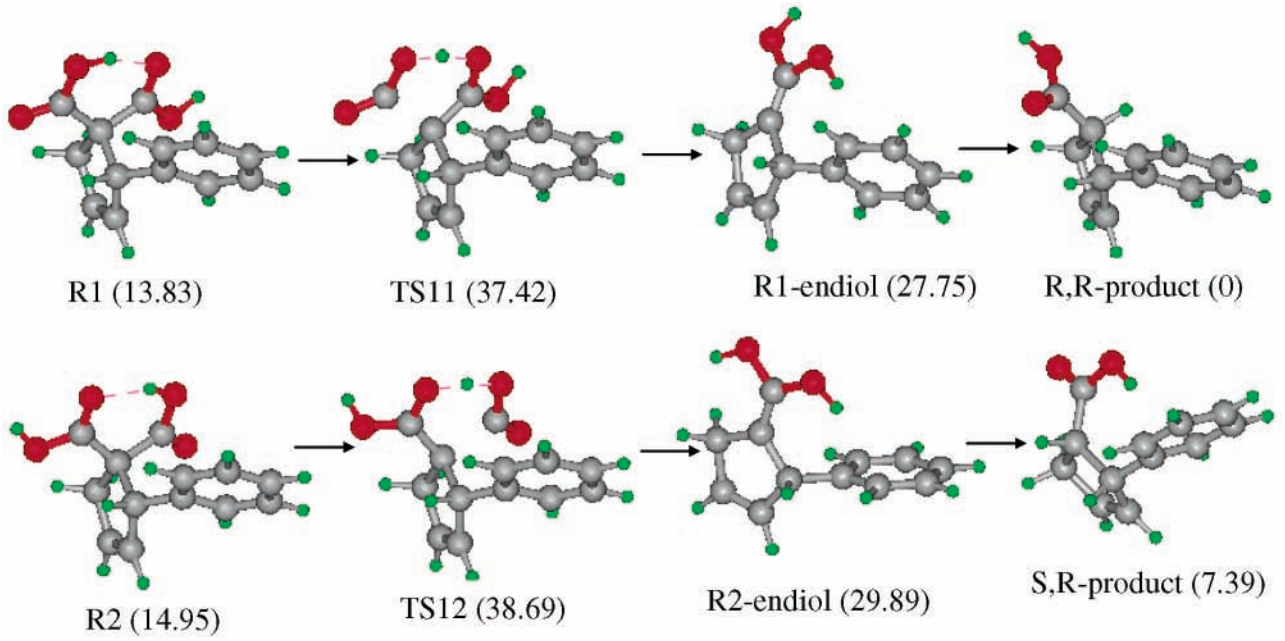


Figure 2. Reaction pathways of decarboxylation of **1** (relative energies are given in parentheses in kcal/mol).

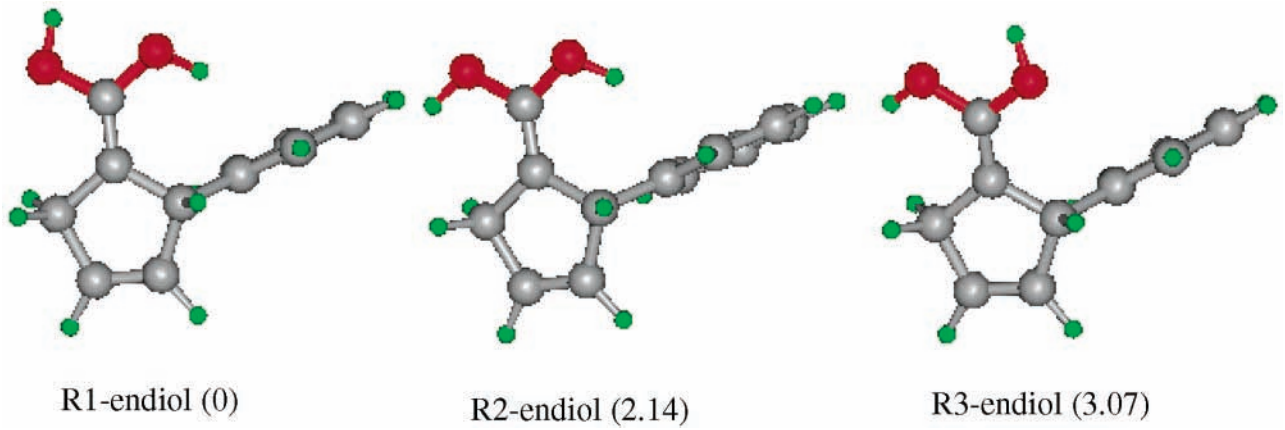


Figure 3. Different conformers of endiol depending on the orientation of hydroxyl groups (relative energies are given in parentheses in kcal/mol).

The decarboxylation of **1** is considered to give a product via an endiol intermediate as shown in Figure 2. In this study, only the R reactants (R1 and R2) are considered because the S1 and S2 should have the same reaction pathway. The reaction consists of decarboxylation at first and enol−keto tautomerization at second. TS1 and TS2 denote the transition states for the reactants R1 and R2, respectively. The relative energy of R2 to R1 is 1.12 kcal/mol, and that of TS2 to TS1 is 1.27 kcal/mol. Thus, the direction of intramolecular hydrogen bonding affects the stability of transition states almost equivalently to that of reactants. The endiol intermediates, R1-endiol and R2-endiol, are obtained by the removal of CO_2 from the transition states TS1 and TS2, respectively. The structural changes of bond lengths, C−C, C−O, O−H, H···O, O═C, and C−C (clockwise starting from the C1 position of R2) are noticeable. These are 1.554, 1.338, 0.990, 1.712, 1.224, and 1.522 Å in R2, respectively, while 1.900, 1.286, 1.144, 1.220, 1.252, and 1.473 Å in TS2, respectively. Almost the same numbers are obtained for R1 and TS1. The bond length changes from R2 to TS2 clearly reflect the concerted C−C bond breaking and O−H bond formation. In addition, the bond angle O−H···O is 148° in R2, while it is 164° in TS2, which implies that the O···H···O angle is quite linearized when the carbon dioxide is departing. The energy difference (7.39 kcal/mol) between R,R-product and S,R-product is slightly larger than that between reactants or transition states, and the stereochemistry of the final product is dependent on the thermodynamic stability of the two isomers as well as the relative energy of the transition states TS1 and TS2. In this case, the (1R,2R)-2-phenylcyclopent-3-ene-carboxylic acid corresponds to the trans conformer and the (1S,2R) product to the cis conformer. The R,S configuration depends on the priority of the atoms with connectivity, thus we simply denote cis and trans according to the relative arrangement of the two substituents COOH and phenyl. The S1 and S2 would give the same profile because the energy of the S isomer is the same as that of the R isomer.

For the endiol, there are three possible conformers, depending on the orientation of hydroxyl groups, as shown in Figure 3. The most stable conformer involves intramolecular weak hydrogen bonding between two −OH groups and π-hydrogen bonding between −OH and the phenyl group. The other two conformers involve either intramolecular weak hydrogen bonding or π-hydrogen bonding. From the relative energies, we may estimate the intramolecular hydrogen bonding energy is ∼2 kcal/mol, while the π-hydrogen bonding energy is ∼1 kcal/mol. The R1-endiol is considered to give R,R-product by enol−keto tautomerization, whereas the R2-endiol is considered to give S,R-product, comparing the fine structures before and after the

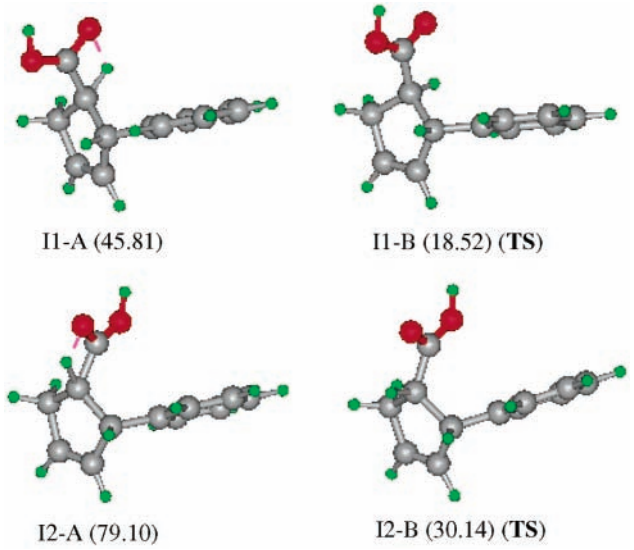


Figure 4. Intermediates for the enol−keto tautomerization (relative energies with respect to R,R-product are given in parentheses in kcal/mol).

endiols in the reaction pathways. One of the hydroxyl groups (OH) of the R1-endiol is pointing toward the phenyl ring through the π-H interaction, which plays an important role in the conformational stabilization in various chemical systems,[45−48] and the other OH has a syn type conformer with almost zero dihedral angle of H−O−C−O. The endiol intermediates convert to the carboxylic acid (**2**) by tautomerization.

The second step (enol−keto tautomerization) is usually considered to be an equilibrium process under usual experimental conditions. We found some intermediates for the tautomerization and represented them in Figure 4. We denote I1's (I1-A and I1-B) as the intermediates to give the R,R-product, and I2's (I2-A and I2-B) as the S,R-products. Since our calculations are done in the gas phase, the relative energies cannot be compared with usual experimental results. In particular, the relative energies of I1-A and I2-A are almost meaningless because the hydroxyl group is easily deprotonated and the deprotonated proton can easily approach to the carbon atom next to the carbonyl carbon atom in common experimental conditions. In the calculated intermediates I1-A and I2-A, one of the imaginary vibrational frequencies corresponds to the proton shifting mode from oxygen to carbon atom, and another imaginary frequency involves a complicated mode over the whole molecule. The calculated high energies of the I1-A and I2-A intermediates apparently suggest that the tautomerization should be a rate-limiting step; however, in solution phase in usual experimental conditions, these barriers should be negligible due to the easy deprotonation and protonation (proton shift from oxygen to carbon). More interesting intermediates are I1-B and I2-B. These intermediates were confirmed to be transition states from the frequency calculations. The transition motion does not correspond to the direct enol−keto tautomerization, but it corresponds to the rotation of the carboxyl group after the shift of proton from oxygen to carbon. As a matter of fact, it is very difficult to find direct four membered transition states for the tautomerization in the gas phase. Considering that the barrier should be negligible in the existence of solvent, the rate determining step would be the first step, and the corresponding transition states have been identified as TS1 and TS2.

The transition states were confirmed by the single imaginary vibrational frequency and by matching the vibrational normal mode corresponding to the imaginary frequency and the actual

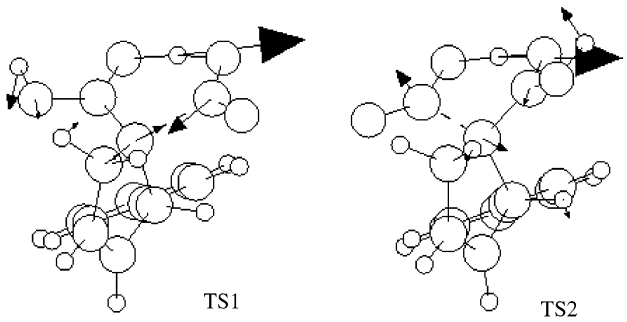


Figure 5. Vibrational normal coordinates of imaginary frequencies of TS1 and TS2 along the reaction coordinates.

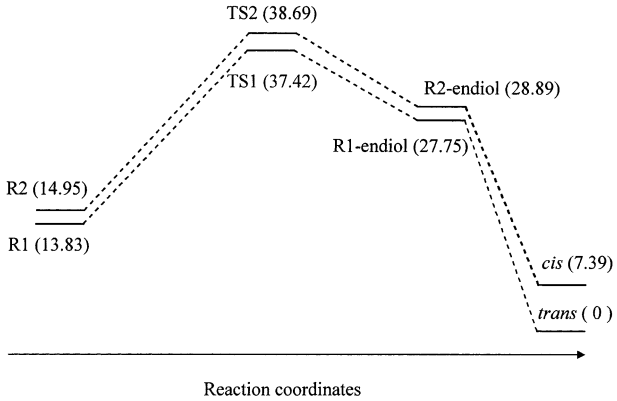


Figure 6. Relative energy diagram for the reactants (R1, R2), transition states (TS1, TS2), intermediates (R2-endiol, R2-endiol), and products (trans and cis) along the reaction coordinates.

proposed reaction coordinates. Figure 5 represents the normal coordinates of imaginary frequencies of TS1 and TS2 along the reaction coordinates. The normal coordinates of the transition states clearly show that the transition states are consistent with the C−C bond breaking and O−H bond formation as suggested that the decarboxylation would occur through the concerted mechanism. The relative stability of TS1 and TS2 arises from the same reason as the stability of R1 and R2 mentioned above.

Figure 6 represents the energy profile along the reaction coordinates for the decarboxylation of **1**. The cis isomer is more unstable than trans by 7.39 kcal/mol. Our results are consistent with previous experimental findings for the preference of the trans isomer.[28,29] As seen in Figure 2, the intramolecular π-H interaction is persistent in the cis product though the major product is trans due to the predominant steric effect. It would be expected that the energy difference between cis and trans isomers would be smaller when the intramolecular π-H interaction becomes stronger, and furthermore, the cis conformer could be more stable than the trans isomer if the system is intellectually designed. In this connection, we have investigated the stability of the cis and trans isomers of products (**3**, **4**, **5**, **6**) of the decarboxylation of several derivatives of **1**. The reaction pathway is assumed to be the same as **1**, and the preference for the trans isomer over the cis is determined by the thermodynamic stability.

Table 1 lists the relative energies of the cis isomer with respect to the corresponding trans isomer. The trend of the relative energies obtained by the B3LYP/6-311+G** single point energy calculation at the B3LYP/6-31G* optimized geometries are the same as those obtained by MP2/6-311++G** and B3LYP/6-31G* geometry optimization. In all cases, the trans isomers are more stable than the cis isomers, which is consistent with the previously reported experimental

TABLE 1: Relative Unstability of cis Conformers of Products (2−6) Compared with Corresponding trans Conformers[a]

	B3LYP/6-31G*	B3LYP/6-311+G**//6-31G*	MP2/6-311++G**
2	7.39	7.49	
3	8.15	10.19	9.02
4	7.75	8.97	
5	5.67	7.10	6.81
6	3.44	5.85	5.93

[a] Units are in kcal/mol.

results. The main reason for the trans preference is due to the sterical repusion between functional groups at the C1 and C2 positions. We expected that the relative energy would be smaller if a sterically less hindered functional group is substituted, replacing the phenyl group at the C2 position, or a functional group could enhance the intramolecular interactions with COOH at the C1 position. For **3**, **4**, and **5**, the relative stability of the cis conformers with respect to their corresponding trans isomers are almost the same. The COOH (**4**), NO_2 (**5**), and F (**6**) can form an intramolecular hydrogen bond with adjacent COOH group in a cis isomer. But, the seven membered ring is formed when the COOH at C1 forms a hydrogen bond with COOH or NO_2 at the C2 position, thus, the strength of the intramolecular hydrogen bonding is relatively weak and the steric effect is not much reduced compared with **2**. However, a very small substituent F reduces the relative energy of the cis conformer considerably due the reduced steric effect and increased intramolecular interaction through the hydrogen bonding between F and COOH. Our results suggest that the diastereoselectivity of dicarboxylic acids with adjacent substituents is determined by steric effect; however, the intramolecular interactions between COOH and the adjacent functional group also contribute to the governing of the stereoselectivity. As a matter of fact, in a similar system, the cis configuration was initially established; however, it was converted into a thermodynamically more stable trans isomer in previous experiments.[27,28]

Conclusion

We investigated the decarboxylation of 2-phenylcyclopent-3-ene-1,1-dicarboxylic acid (**1**) and its derivatives from the ab initio calculations. The reaction pathway starting from the R-configuration of **1** has been researched and has clearly shown the transition states and endiol intermediate, which in turn converted into the *trans*- or *cis*-2-phenylcyclopent-3-ene carboxylic acid. The energy difference between the two reactants is small and virtually the same as that between the two transition states. Transition states change to the en-diol intermediate after the loss of CO_2, and the subsequent equilibrium process (tautomerization) gives the product. The energy difference between the trans and cis isomers of the product is much larger than that between reactants, thus, the stereochemistry should be determined from the relative stability of the trans and cis isomers of the products. The stereochemistry of the product is trans isomer for all the cases investigated here, mostly due to the steric hindrance between adjacent substituents, which is consistent with previous experimental results. However, the intramolecular interactions such as hydrogen bonding and π-hydrogen bonding also play a role to a certain extent. For several cases, we investigated the interplay of steric hindrance and intramolecular interactions. In particular, for the small substituent F, F renders less steric hindrance with the adjacent carboxylic group as well as forms an intramolecular hydrogen bond, hence making the energy difference between trans and cis considerably reduced. Our results suggest that the decarboxylation is an efficient way to generate a diastereoselective synthesis, and the stereochemistry of the product of decarboxylation can be controlled by intellectual design of adjacent functional groups.

Acknowledgment. This study was financially supported by a special research fund of the Chonnam National University in 2004.

Supporting Information Available: The energies, number of imaginary frequencies, and Cartesian coordinates of **1** (R1, R2, S1, S2), TS1, TS2, R1-Endiol, R2-Endiol, **2** (trans, cis), **3** (trans, cis), **4** (trans, cis), **5** (trans, cis), **6** (trans, cis) (in plain text). This material is available free of charge via the Internet at http://pubs.acs.org.

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