Conformational Study of 1,5-Hexadiene and 1,5-Diene-3,4-diols

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Abstract: *Ab initio* MO study of 1,5-hexadiene at the MP2/6-31G* level shows that, unlike *n*-butane, there is little energy difference between the anti and the gauche conformations. However, molecular modeling using either MM2 or MM3 gives an energy that is too high for the gauche conformations of 1,5-hexadiene. The overestimation of the energy for the gauche conformations in 1,5-hexadiene was identified as the reason for the failure of molecular mechanics in predicting conformational energies of compounds involving the 1,5-diene-3,4-diol structural unit.

Introduction

Recently we have reported a series of studies of chiral alkene conformations using the variable temperature (VT) NMR technique,[1,2] and in some cases a combination of *ab initio* MO methods plus the VT NMR experiments.[3,4] In accordance with an early theoretical study,[6] it was found that an electron-withdrawing group (EWG) at the vinyl position promotes the conformation where the CO linkage is eclipsed with the C=C bond.[1,2] Furthermore, a silyl ether protective group of the allylic OH enhances the preference for the CO-eclipsed form by reducing the size of the allylic oxygen lone pairs[3-5] (eq 1).
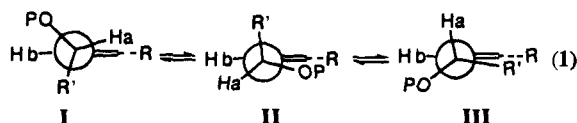
case a: I is favored when R = alkyl; II is favored when R = EWG
case b: I is favored when P = alkyl; II is favored when P = SiR₃

Saito and co-workers have observed unusually high diastereofacial selectivity for reactions on a tartrate-derived 1,5-diene-3,4-diol derivative, **1**, and proposed a rigid conformation **1a** to account for the π-facial selectivity.[7] Since compound **1** is closely related to the chiral alkenes that we were studying, we have carried out a VT NMR investigation of **1** and its derivatives.[5] Our study supports Saito's suggestion in that the CO-eclipsed conformation was found to be preferred, but the VT NMR data could not distinguish between **1a** and **1b**.[5] The previously found rules that a vinyl EWG promotes the CO-eclipsed form and an allyl silyl ether enhances this preference apply also to the 1,5-diene-3,4-diol derivatives.[5] However, molecular modeling using either MacroModel or Insight II was

1

1a   **1b**
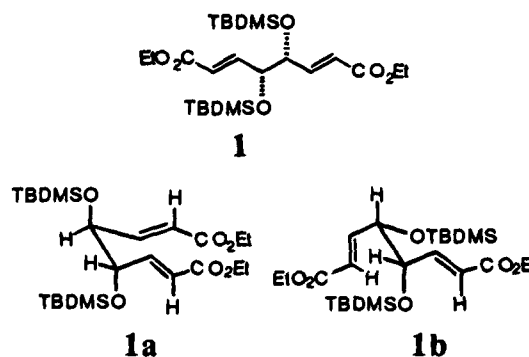
unsuccessful in identifying the conformation **1a** as the global minimum (*vide infra*). We reasoned that there must be unique structure units in **1** for which the force fields employ poor parameters. Compound **1** contains two chiral fragments joined at the allylic position. If the CO₂Et group is treated as a substituent, compound **1** also contains the 1,5-hexadiene fragment, which is an important structural unit and is present in many biologically important compounds. For example, squalene, the precursor to cholesterol, contains three 1,5-hexadiene units.[9] The preeminent Cope rearrangement involves the 1,5-hexadiene structure.[10] Although extensive studies have been done on the transition state of the rearrangement,[11] little is known about the ground state conformational profile of 1,5-hexadiene. Since molecular mechanics depends on experimental or *ab initio* results for parameterization, lack of information on the 1,5-hexadiene structure could have caused the poor performance exhibited by the molecular-modeling packages. In light of its importance in biological and organic chemistry, we have carried out an *ab initio* MO study on the conformations of 1,5-hexadiene. In this report, we will show that, unlike *n*-butane, the gauche conformations of 1,5-hexadiene are as stable or more stable than its anti forms, which, we think, is the primary reason

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Table 1. *Ab Initio* Relative Energies (kcal/mol) for the Conformers of 1,5-Hexadiene

		conformer									
entry	basis set	A (total E in aju)	B	C	D (F)	E	G	H	I	J (L)	K
1	6-31G*	0.66 (−232.982 353)	0.0	0.95	0.34	0.05	2.2	0.90	2.03	3.07	1.93
2	6-31G**	0.63 (−232.999 186)	0.0	0.95	0.33	0.05	−	−	−	−	−
3	MP2/6-31G* ^{a}	0.36 (−233.745 996)	1.01	0.55	0.0	0.13	−	−	−	−	−
4	MP3/6-31G* ^{a}	0.37 (−233.798 282)	0.65	0.62	0.05	0.0	−	−	−	−	−
5	MP2/6-31G*	0.32 (−233.747 944)	0.17	0.58	0.0	0.23	1.55	0.82	1.44	2.05	1.61
6	MP3/6-31G* ^{b}	0.37 (−233.799 690)	0.0	0.66	0.07	0.04					
7	MP4/6-31G* ^{b}	0.30 (−233.840 826)	0.05	0.57	0.0	0.10					

^{a} Single-point calculation using 6-31G* structure. ^{b} Single-point calculation using MP2/6-31G* structure.
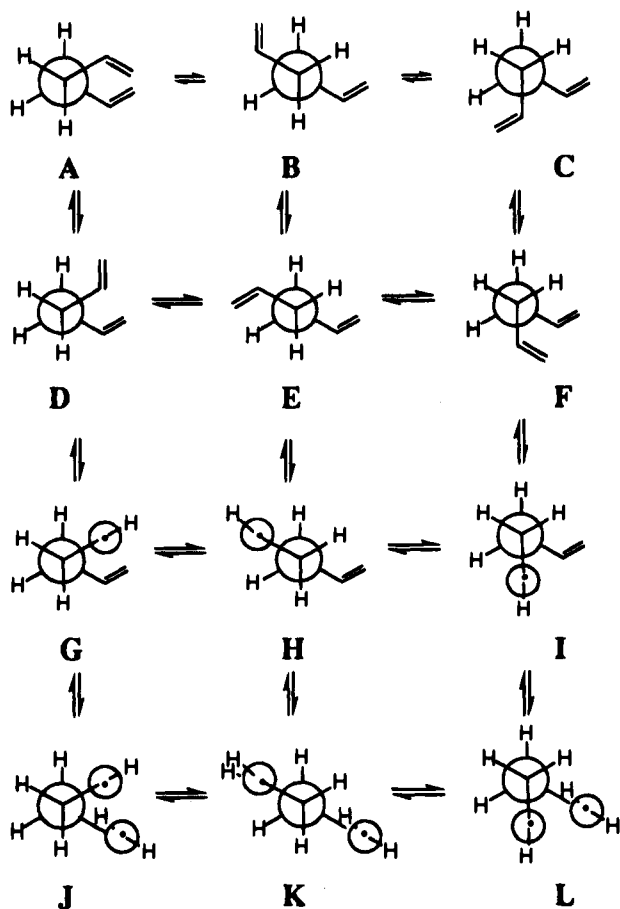
Figure 1. Newman projections for the conformers of 1,5-hexadiene.

why the current force fields fail to locate the correct global minimum for compound **1**. The calculated unusual stability of the gauche forms may also have implications on the folding of squalene and the reactivity of the Cope rearrangement.

Computational Method

Molecular mechanics calculations were performed on the Silicon-Graphics Indigo2 workstation using MacroModel 4.0[8] and Insight II 2.3. The force fields MM2 and MM3 implemented in the program MacroModel were employed,[12] and the force field cff91 was provided by Biosym Technologies Inc. through the program Insight II. The energy minima were found through complete geometrical optimization of the initial conformers generated by the programs. When a conformational search was done on compound **1**, the multiconformer submode of MacroModel was used, and the torsional bonds marked for rotation included the central C_{sp^3}–C_{sp^3} bond, the two adjacent C_{sp^3}–C_{sp^2} bonds, the two C–O bonds, and the two O–Si bonds. All energy minima

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were verified through force constant calculations. This was done in MacroModel by using the command Mtest (minimum test) in the Energy menu and in Insight II by the calculation of the derivatives in the Discover menu.

Ab initio calculations[13] were carried out by the GAUSSIAN 90 and 92 programs[14] implemented on the Cray Y-MP/8 supercomputer. The conformational minima of 1,5-hexadiene were fully optimized with the extended 6-31G* basis set and with the Moller−Plesset electron correlation (MP2/6-31G*). Harmonic frequencies were calculated for each conformer. The minimum conformations all have positive frequencies, which is an indication of a true minimum on the potential surface. Single-point calculations are performed for selected conformations with electron correlation up to MP4 using the MP2/6-31G*-optimized structures. The barrier for interconversion of the conformers was studied by constraining only the $\tau_{C2C3C4C5}$ torsional angle, which maintains the eclipsed conformation.

Results and Discussion

A. *Ab Initio* MO Study of 1,5-Hexadiene. The Newman projections for the conformers of 1,5-hexadiene are depicted in Figure 1. There are three free rotating C−C bonds in 1,5-hexadiene and three rotational minima around each bond. Twenty-seven conformations can be counted for 1,5-hexadiene theoretically. However, the symmetry of 1,5-hexadiene and the enantiomerism of the conformations leave only 10 energetically distinct conformers. Twelve rotational isomers are depicted in Figure 1. Table 1 contains the relative energies for calculations at various levels of theory. Among them, **D** and **F** and **J** and **L** are enantiomeric pairs. Rotation about the central C_{sp^3}–C_{sp^3} bond of 1,5-hexadiene with antiparallel vinyl groups generates rotamers **A**, **B**, and **C**, while rotation with parallel vinyl groups gives isomers **D**, **E**, and **F**. If one of the C_{sp^2}–C_{sp^3} bonds has an *s-cis* conformation (CC eclipsing C=C), rotation about the central C_{sp^3}–C_{sp^3} bond produces the conformers **G**, **H**, and **I**. If both C_{sp^2}–C_{sp^3} bonds have the *s-cis* conformation, rotation about the central C_{sp^3}–C_{sp^3} bond gives the conformers **J**, **K**, and **L**. Since the conformers **G−L** have relatively high energies (Table 1), their populations are expected to be low (Figure 2). The discussion will be concentrated on the more populated isomers **A−F**.

The optimized structures of **A−K** are shown in Figure 2. The relative energies underneath each conformer are calculated at the MP2/6-31G* level of theory. The global minimum is the gauche conformer **D** (**F**), in which an attractive interaction may be present between the π orbital and the vinyl proton.[16]

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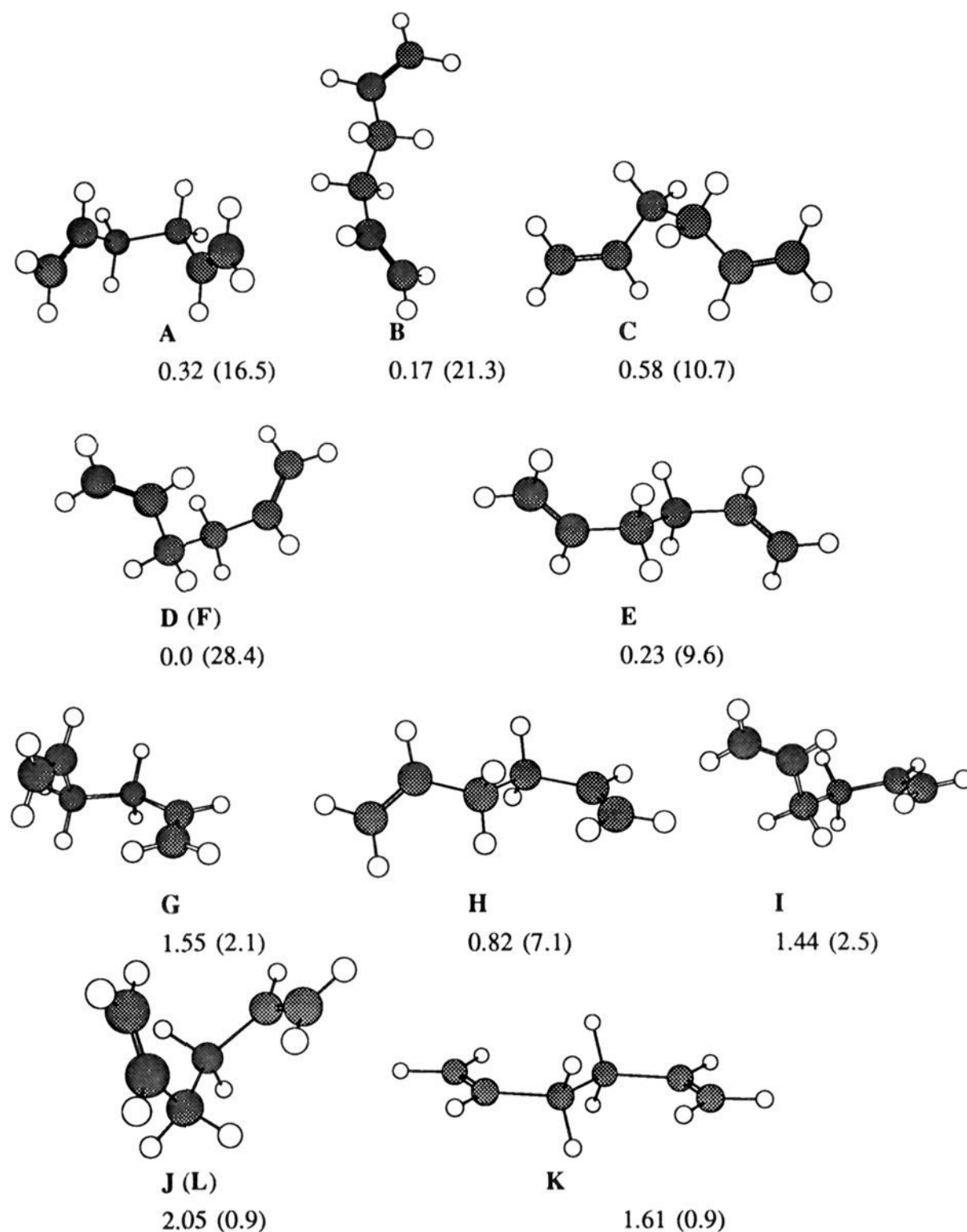
A
0.32 (16.5)

B
0.17 (21.3)

C
0.58 (10.7)

D (F)
0.0 (28.4)

E
0.23 (9.6)

G
1.55 (2.1)

H
0.82 (7.1)

I
1.44 (2.5)

J (L)
2.05 (0.9)

K
1.61 (0.9)

Figure 2. Optimized structures of **A**−**K** and their relative energies (MP2/6-31G*). The fractional populations based on the Boltzman distribution law are given in parentheses. The global minimum is the gauche conformer **D** (**F**), in which an attractive interaction may be present between the π orbital and the vinyl proton.[16] The CC-eclipsed forms (**G**−**K**) have higher energy than the CH-eclipsed forms (**A**−**F**). Conformer **C** has the highest energy among the CH-eclipsed forms, in which the two vinyl protons are only 2.5 Å apart.

The energy difference between the anti conformers **B** and **E** and the gauche forms **D** and **F** is negligible. This is in contrast to the conformations of *n*-butane, which has an energy difference of ~0.8 kcal/mol between the anti and gauche forms.[15] The origin of the instability in gauche *n*-butane is attributed to repulsive steric interactions.[15] The distance between the C1 and the C4 proximal hydrogen atoms is 2.35 Å in gauche *n*-butane.

However, there is no such close contact of hydrogen atoms in conformers **A**−**F**, not even for the gauche forms **A**, **C**, and **D**.[17] The distance between the two vinyl (C2 and C5) hydrogen atoms in the gauche form **C** is 2.5 Å, which causes the form to be ~0.5 kcal/mol higher in energy than the anti forms. Conformer **C** is the highest energy CH-eclipsed form. Therefore, unlike *n*-butane, the gauche forms (**A**, **C**, and **D**) of 1,5-hexadiene are comparable in stability to their anti conformations.

Conformation **A** interests us the most in that it was suggested as the reactive conformation of **1** (**1a**). **A** also plays a key role

in the Cope rearrangement and in the cyclization of squalene. Without electron correlation, conformer **A** is predicted to be ~0.6 kcal/mol higher in energy than the anti forms at the 6-31G* level of theory. With electron correlation (MP2/6-31G*), this difference drops to ~0.3 kcal/mol. We believe that it is important to include the electron correlation when π systems are involved.[13,18] The distance between the sp² carbon atoms C2 and C5 in **A** is 3.0 Å. The repulsive interaction caused by the face-to-face π electrons in **A** amounts to only ~0.3 kcal/mol judged by comparison with the anti conformers **B** and **E**, which are devoid of π−π interactions.

Table 2 lists the calculated energy barriers (MP2/6-31G*) for rotation around the central C_{sp^3}−C_{sp^3} bond. The optimizations for the barriers were carried out with constraint to the $\tau_{C2C3C4C5}$ dihedral angle only, which maintains the eclipsed conformation. The calculated *ab initio* energies in Table 2 allow us to apply the least-squares adjustment of a truncated Fourier series,[12a,19] which give the potential curves for rotation about

(17) The conformers **G**−**L** (CC-eclipsed forms) of 1,5-hexadiene have close contact between hydrogen atoms. The distance between the allylic and the terminal vinyl hydrogen atoms in the gauche forms **G** and **I** are 2.37 and 2.31 Å, respectively. In the anti forms **H** and **K**, this distance is ~2.44 Å. For the conformer with the highest energy, **J** (**L**), this distance is 2.35 Å.

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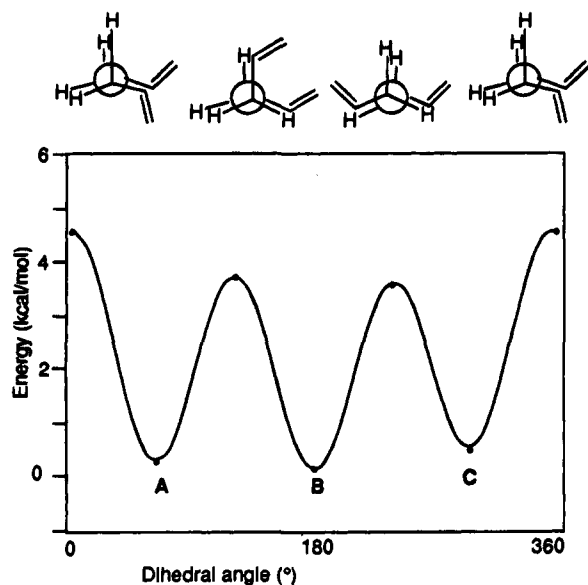
Figure 3. Rotational energy profile of 1,5-hexadiene with antiparallel vinyl groups. The potential constants are $V(0) = 4.65$, $V(1) = -0.76$, $V(2) = -0.39$, $V(3) = -3.72$, $V(4) = -0.04$, and $V(5) = -0.11$.

Table 2. Relative Energies (kcal/mol) for Rotational Barriers in 1,5-Hexadiene

entry	conformation (symmetry)	ϕ_1 (deg)	ϕ_2 (deg)	MP2/6-31G*
1	barrier (C_2)	0	−120	4.65
2	A (C_2)	60	−120	0.32
3	barrier (C_2)	120	−120	3.84
4	B (C_2)	180	−120	0.17
5	barrier (C_2)	240	−120	3.73
6	C (C_2)	300	−120	0.58
7	barrier (σ)	0	120	5.61
8	D (C_1)	60	120	0.00
9	barrier (C_1)	120	120	3.65
10	E (C_1)	180	120	0.23
11	barrier (C_1)	240	120	3.65
12	F (C_1)	300	120	0.00

the center $C_{sp^3}-C_{sp^3}$ bond of 1,5-hexadiene (Figures 3 and 4). The derived potential constants $V(i)$ are included in Figures 3 and 4. Two sine terms are needed in the potential function for

$$V(\omega) = V(0) + \sum_i Vi(1 - \cos i\omega)/2 + \sum_j Vj \sin j\omega$$

rotation with the antiparallel vinyl groups (Figure 3) to fit the asymmetric potential curve since the energy minima and barriers are not the same. On the other hand, only the cosine terms are needed for the potential function describing rotation with parallel vinyl groups since a symmetrical curve centered at 180° is sufficient (Figure 4).

As shown in Figures 3 and 4, if the central $C_{sp^3}-C_{sp^3}$ bond is rotated 360° starting from the eclipsed conformation ($\tau_{C2C3C4C5} = 0$), three barriers and three minima are on the potential energy surface. Figure 3 shows the potential energy curve for conformations A, B, and C and the barriers separating them. Figure 4 is the plot for conformers D, E, and F and the barriers between them. The highest barrier (5.61 kcal/mol) is the one separating conformations D and F (entry 7, Table 2), which is
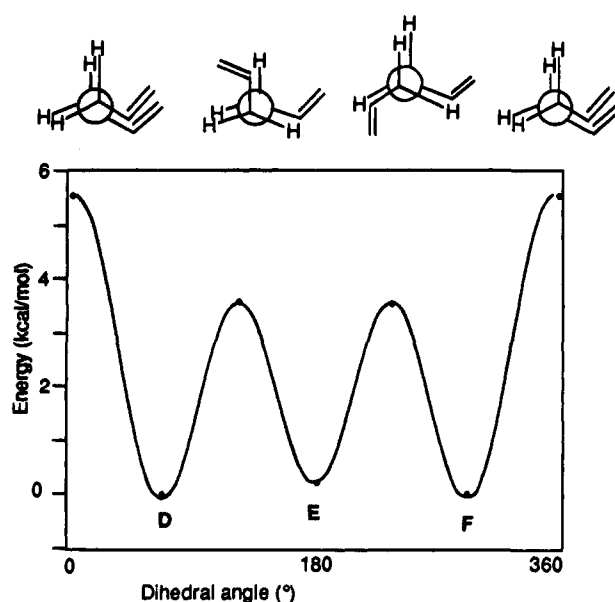
Figure 4. Rotational profile of 1,5-hexadiene with parallel vinyl groups. The potential constants are $V(0) = 5.61$, $V(1) = -1.15$, $V(2) = -1.46$, and $V(3) = -4.23$.
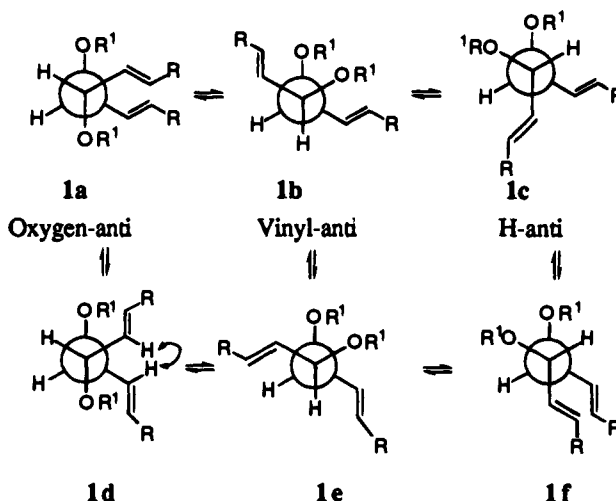

Figure 5. Rotational isomers of 1,5-diene-3,4-diol derivative 1 (R = CO_2Et, R^1 = protective group). The CO-eclipsed forms are on the first row, and the CH-eclipsed forms are on the second row.

apparently due to the parallel orientation of the two vinyl groups (see Figure 4). The next highest energy barrier (4.65 kcal/mol) is the one with two eclipsing antiparallel vinyl groups separating forms A and C (entry 1, Table 2). It is interesting to note that the highest energy barrier in n-butane (in which two methyl groups eclipse) is about 6 kcal/mol.[15] It is surprising that even with the parallel orientation of the two C=C bonds, the barrier is lower than that in n-butane. The antiparallel orientation leads to a still smaller barrier. These results suggest that eclipsing 1,2-divinyl groups can arrange their orientation in space so that they cause less steric strain than eclipsing 1,2-dimethyl groups.

It is important to point out that not only the barriers, but also the minima, of 1,5-hexadiene are different from those of n-butane. n-Butane has a symmetrical rotational profile, in which the two gauche conformations are higher in energy than the anti form. In contrast, as shown in Figure 4, the gauche forms D and F of 1,5-hexadiene are slightly more stable than the anti forms according to calculations at the MP2/6-31G* level. The gauche form A is ~0.3 and C is ~0.6 kcal/mol higher in energy than the anti forms, respectively. Unfortu-

nately, there is no experimental data to support the current calculation results.[20] However, the ready cyclization of squalene derivatives under non-enzymatic conditions suggests the presence of gauche form A.[21]

B. Origins of the Conformational Preference in 1,5-Diene-3,4-diols. The extreme diastereofacial bias exhibited by the 1,5-diene-3,4-diol derivatives, such as **1**, has stimulated interests to search for the origin of the conformational preference.[5,7] Based on the current result from 1,5-hexadiene, the origin of the strong conformational bias of compound **1** starts to unfold. The rotational isomers of **1** are depicted in Figure 5. The CO-eclipsed forms are on the first row, and the CH-eclipsed forms are on the second row. According to our VT NMR study, the CO-eclipsed forms are considerably more stable than the CH-eclipsed forms for these bis(allylic) compounds.[5] In fact, for simple γ-hydroxy-α,β-unsaturated esters with a benzyl ether protective group, the CH-eclipsed forms are favored. However, the CO-eclipsed forms become preferred for the corresponding bis(allylic) compounds.[5] In our recent report, we have raised the question of why the bis(allylic) structure in **1** promotes the CO-eclipsed form.[5] On the basis of the current results for 1,5-hexadiene, one of the reasons for the added stability of the CO-eclipsed form might be the repulsive interaction between the vinyl hydrogens in the CH-eclipsed form **1d**. Although for 1,5-hexadiene conformer **A** is only 0.3 kcal/mol more stable than conformer **C**, we believe that this same effect would be much more important in compound **1** when the oxygen substituents are in place.

There is still the question of why the R[1]O-anti conformer (**1a**) is more stable than the vinyl-anti (**1b**) or the H-anti forms (**1c**). Saito has suggested that the preference of **1a** is the result of the steric bulk of the *tert*-butyldimethylsilyl (R[1] = TBDMS) group.[7] However, the analog of **1** with a smaller trimethylsilyl group gave virtually the same diastereofacial selectivity,[7b] a fact that is inconsistent with the argument based on steric effects. The following discussion will show that electronic interactions alone may be enough to make conformer **1a** more favorable by ~2 kcal/mol.

A recent study of 1,2-dimethoxyethane (**2**) by infrared spectroscopy and *ab initio* methods has shown that the anti form of **2** is more stable than the nearest gauche form by 1.44 kcal/mol.[22] Compound **1** contains the OCCO fragment, which can

2 anti   **2 gauche**
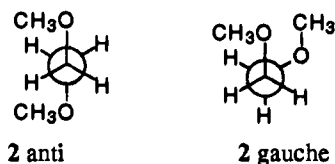
assume either the anti (**1a**) or the gauche form (**1b** and **1c**). The only major difference of **1** from **2** is that the double bonds are in place of hydrogen atoms.

The repulsive interaction caused by the face-to-face π electrons in **1a** is ~0.3 kcal/mol at the MP4/6-31G*//MP2/6-31G* level of theory (Table 1). Therefore, the face-to-face π interactions are offset by the anti preference of the 1,2-dioxygen unit by ~1.1 kcal/mol.

There is other evidence that also explains why **1a** is favored electronically. Kishi and co-workers have reported experimental

Table 3. Comparison of Force Fields: Relative Energies (kcal mol^{-1}) for the Conformations of **1**

	conformer		MM2	MM3	cff91	expt[5,7]
1a	oxygen-anti	CO-eclipsed	5.1	4.5	3.5	0.0
		CH-eclipsed	4.1	5.3	1.9	>1.0
1b	vinyl-anti	CO-eclipsed	0.0	1.8	3.9	a
		CH-eclipsed	1.4	0.0	3.1	>1.0
1c	H-anti	CO-eclipsed	2.4	4.5	3.7	>1.0
		CH-eclipsed	3.1	0.6	0.0	>2.0

[a] VT NMR data cannot distinguish **1a** and **1b**.[5]

studies of the conformations of C-glycosides and discovered that these compounds exist in a gauche CCCO arrangement, rather than the anti arrangement.[23] Recently, Houk *et al.* has studied this conformational phenomenon with *ab initio* methods.[24] It was found that a simple CCCO fragment, such as 1-propanol, prefers the gauche form by ~0.4 kcal/mol.

anti   **gauche**
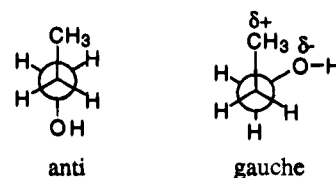
This gauche preference was attributed to electrostatic interaction between the oxygen and the methyl hydrogen atoms. It is conceivable that this type of interaction can operate in conformation **1a** since it has the gauche CCCO arrangement. Because compound **1** possesses the bis(allylic) structure, the CCCO gauche preference should be twice as much as if it contains only one CCCO fragment. Furthermore, a more positively charged hydrogen atom is expected at the β position of an α,β-unsaturated ester, such as **1**, than those of the methyl group of propane.

To summarize, conformation **1a** contains several favorable structural features: (1) the anti OCCO arrangement, (2) the gauche CCCO arrangement (twice), and (3) enhanced electrostatic interaction between the positively charged β hydrogens of the α,β-unsaturated ester and the allylic oxygen atoms. Counting these favorable interactions and taking into account that the only unfavorable face-to-face π interaction is only ~0.3 kcal/mol, we found that the preference of **1a** over other forms could be as high as 2 kcal/mol. This would explain the superior diastereofacial selectivity displayed by the trimethylsilyl analog of **1**, assuming that these favorable interactions also operate in the transition state. The bulk of the TBDMS group may help to achieve the superior diastereofacial selectivity, but it is not an absolute requirement.

C. Comparison of Force Field Calculations to the MP2/6-31G* Results. Table 3 shows the results of molecular mechanics calculations on compound **1**. It must be noted that the conformations depicted in Figure 5 for compound **1** are based on a staggered $C_{sp^3}-C_{sp^3}$ bond and an eclipsed $C_{sp^3}-C_{sp^2}$ bond. Saito and co-workers have collected strong evidence that suggests that **1a**, the TBDMSO-anti, CO-eclipsed conformation is the global minimum.[7] Our own VT NMR study has ruled out the possibility of a favored CH-eclipsed form and supports structures **1a** and **1b**.[5] However, the force fields, especially MM2, tend to find energy minimum, which puts the $C_{sp^3}-C_{sp^2}$ bond at a perpendicular, rather than an eclipsed conformation.

(20) We have searched the Cambridge Structural Database for the fragments C=C–C–C–C=C and C=C–C(OH)–C(OH)–C=C. All hits are either part of a cyclic structure or part of an organometallic compound.

(21) For a recent example, see: Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324.
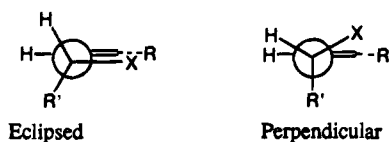
(22) Yoshida, Y.; Kaneko, I.; Matsuuro, H.; Ogawa, Y.; Tasumi, M. *Chem. Phys. Lett.* **1992**, *196*, 601.

(23) (a) Wu, T. C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. (b) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468.

(24) Houk, K. N.; Eksterowicz, J. E.; Wu, Y. D.; Fuglesang, C. D.; Mitchell, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 4170.

Eclipsed   Perpendicular

The conformers listed in Table 3 are those that have close resemblance to the eclipsed forms.

As shown in Table 3, each of the three force fields finds a different global minimum, but none comes close to locating **1a**. On the basis of experimental evidence,[5,7] these results are erroneous. As discussed above, the electronic effects related to structures of 1,5-hexadiene, the fragment OCCO, and the fragment CCCO were not known. Therefore, it is obvious that improvements are needed for the parameters related to these structures in these force fields.

In order to locate the poor parameters in these force fields that produced the errors in the calculation of **1**, we have calculated the relative energies of 1,5-hexadiene by the three popular molecular mechanical force fields (Table 4). MM2[12] gives energies for the gauche forms that are too high and energies for the CC-eclipsed forms that are too low. MM3[12b] has significant improvement over MM2 but still overestimates the energy of the gauche forms by ~1 kcal/mol and slightly underestimates the energy of the CC-eclipsed forms. It is interesting to note that MM3 has been explicitly parameterized to reproduce high-level *ab initio* calculations on *n*-butane.[12c] The cff91 is the so-called "class II" force field, on the basis of the the derivation and parameterization of analytic representations of the *ab initio* potential energy surfaces.[25] In fact, the energies calculated by cff91 are similar to that obtained by the HF/6-31G* (Table 1, entry 1). However, as pointed out above, electron correlation is very important in the calculation of π interactions. On the basis of the results in Table 1, electron correlation must be included in the optimization. When single-point calculations, including MP2 and MP3, were performed on the HF/6-31G*-optimized structures, conformer **B** became abnormally higher in energy (see entries 3 and 4 in Table 1). Since the cff91 is based on the HF/6-31G* potential energy surface,[25] it also overestimates the energies of the gauche forms. In addition, cff91 overestimates the CO-eclipsed forms of the allylic fragment in **1** by >3 kcal/mol on the basis of the data in Table 3.

We further looked into the components of the steric energies for 1,5-hexadiene to locate the origins of the calculated strain. As shown in Table 5, the contributions to the difference in total energies of different conformations are mainly from torsional strain. Thus, the potential constants $V(i)$ (Figures 4 and 5) developed in this study should be useful in improving the torsional parameters.

Conclusions

At the MP2/6-31G* level of theory, there is little energy difference between the anti and the gauche conformations of 1,5-hexadiene. This is in direct contrast to the conformations of *n*-butane. The current finding is significant since 1,5-hexadiene has an important position in both biological chemistry and organic chemistry. Although molecular modeling by molecular mechanics has enjoyed great success over the last decade, the unique structure of 1,5-hexadiene presents a new

(25) The following articles describe a newer version (cff93, it has not been released commercially): (a) Sun, H.; Mumby, S. J.; Maple, J. R.; Hagler, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2978. (b) Maple, J. R.; Hwang, M.-J.; Stockfisch, T. P.; Dinur, U.; Waldman, M.; Ewig, C. S.; Hagler, A. T. *J. Comput. Chem.* **1994**, *15*, 162.

Table 4. Comparison of Force Fields: Relative Energies (kcal mol−1) of 1,5-Hexadiene

entry	conformer	MM2[a]	MM3[a]	cff91[b]	MP2/6-31G*
		CH-Eclipsed Forms			
1	A (gauche)	1.53	1.18	0.72	0.32
2	B (anti)	0.00	0.02	0.02	0.17
3	C (gauche)	2.12	1.20	0.83	0.58
4	D (gauche)	1.75	1.03	0.59	0.0
5	E (anti)	0.03	0.00	0.00	0.23
		CC-Eclipsed Forms			
6	G	2.48	2.27	1.61	1.55
7	H	0.57	0.67	0.80	0.82
8	I	0.57	2.26	1.61	1.44
10	J	3.02	3.02	2.15	2.05
11	K	1.18	1.42	1.75	1.61

[a] See ref 12. [b] See ref 17.

Table 5. Origins of the Steric Energies (kcal/mol) for the Conformers of 1,5-Hexadiene

force field	conformer	relative entry	stretch	bend	torsion	electrostatic	VDW
MM2	A	1.52	0.16	0.38	1.09	0.06	1.93
	B	0.00	0.16	0.34	−0.67	0.04	2.23
	C	2.12	0.17	0.44	1.25	0.06	2.28
	D	1.75	0.16	0.41	1.10	0.06	2.10
	E	0.02	0.16	0.33	−0.67	0.04	2.26
MM3	A	1.20	0.16	0.35	−1.29	7.29	3.04
	B	0.00	0.16	0.27	−2.09	6.71	3.32
	C	1.22	0.17	0.39	−1.15	6.81	3.36
	D	1.03	0.16	0.35	−1.27	6.92	3.22
	E	0.00	0.16	0.26	−2.09	6.69	3.34
cff91	A	0.72	0.42	1.62	−5.35	3.23	1.44
	B	0.02	0.29	1.45	−5.85	2.81	1.77
	C	0.83	0.40	1.75	−5.29	2.97	1.67
	D	0.58	0.41	1.64	−5.35	2.91	1.60
	E	0.00	0.29	1.44	−5.84	2.78	1.77

challenge for force field parameterization. The inadequacy of the three force fields tested against compound **1** and analyzed by comparing results from MP2/6-31G* calculations for 1,5-hexadiene shows that continued improvement of molecular mechanics force fields is very much desired and that the molecular modeling and dynamics studies that employ these force fields must proceed with caution. The stability of the gauche forms of 1,5-hexadiene suggests that the folding of squalene is energetically favorable. This conclusion is supported by the fact that the cyclization of squalene derivatives can be carried out in non-enzymatic conditions.[21]

Supplementary Material Available: Tables of the optimized parameters and Z-matrix for conformations of **A**—**F** (MP2/6-31G*) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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