Articles

The Exceptional Conformational Bias of 1,5-Diene-3,4-diols Is Controlled by Electrostatic Interactions: A Theoretical Elucidation of the Origin in Rotational Isomer Stability

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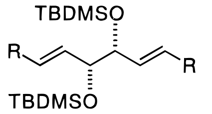
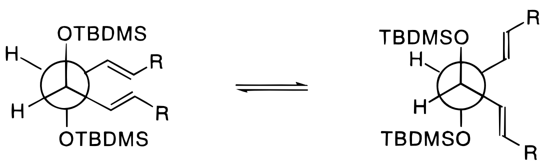
A conformational study of 1,5-hexadiene-3,4-diol (**1**) and 3-buten-1-ol (**2**) with the ab initio molecular orbital methods reveals that electrostatic interactions, rather than steric or tosional effects, control the conformational preferences of these compounds. It is found that the 1,2-dioxygen function prefers the anti arrangement due to the lone pair electron repulsion. A pseudo 1,3-diaxial oxygen/π bond repulsion and a 1,3-diaxial attraction between an oxygen lone pair and a vinyl H are found to be responsible for the profound preference for the CO-eclipsed form in diol **1**. Quantitatively, the repulsion between two gauche oxygen atoms is calculated to be ~1.5 kcal/mol at the MP2/6-31G**//HF/6-31G* level of theory. The repulsion between an oxygen atom and a π bond at the pseudo 1,3-diaxial position is ~1 kcal/mol, and the attractive interaction between an oxygen atom and a vinyl H at the pseudo 1,3-diaxial position is ~0.5 kcal/mol, respectively, at the MP2/6-31G*//MP2/6-31G* level.

Introduction

The derivatives of 1,5-diene-3,4-diols have been found to give near perfect diastereofacial selectivity in a number of reactions.[1,2] The origin of the superior π-facial selectivity was attributed to conformational bias in the bis(*tert*-butyldimethylsilyl) (TBDMS) derivative of 1,5-diene-3,4-diol. The steric bulk of the TBDMSO groups was believed to be responsible for holding each other apart at anti position (**Ia** or **Ib**). The two vinyl groups are assumed to be eclipsed with the CO bond (**Ia**). This conformation creates a mutually shielded environment for one of the π-faces, which Saito has termed the "inside faces". It is therefore only possible for reagents to attack from the "outside faces". All results reported thus far are consistent with this analysis.



I (R = CO_2Et, CH_2OAc, CH_3, etc.)



Ia CO-eclipsed

Ib CH-eclipsed

These reports are intriguing and closely related to our studies in the area of conformational analysis of chiral alkenes.[3] No rigid conformation, however, was observed throughout our investigation. The suggested rigidness of compound **I**[1] prompted us to carry out a series of studies. First, the conformations of a number of 1,5-diene-3,4-diols were investigated with the variable temperature (VT) NMR technique.[4] The results from the VT-NMR study provided the following information: (1) the data are consistent with the suggestion that **Ia** is the most populated form for compound **I** (R = CO_2Et); (2) rapid equilibra are occurring among several forms, thus no rigid conformation should be assumed for **I** at ambient temperatures.

More recently, we studied the conformations of 1,5-hexadiene with the *ab initio* molecular orbital methods.[5] Unlike *n*-butane, the gauche conformations of 1,5-hexadiene are equally or more stable than the anti forms. This result partially explains why conformation **Ia** is among the most stable forms for compound **I** since the face-to-face π-interactions of the 1,2-divinyl groups in 1,5-hexadiene are minimally repulsive.[5] However, one question remains: why should the CO-eclipsed form **Ia** be more stable than the CH-eclipsed conformation **Ib**? The favorable conformational arrangements in **Ib** include (1) anti relationship between two bulky TBDMSO groups, (2) the staggering of each single bond with other single bonds, and (3) the eclipsing of the CH bond with the double bond. In normal allylic compounds, the CH eclipsed conformation is favored for those double bonds that have donor substitution.[6] However, some donor-

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substituted 1,5-diene-3,4-diol derivatives (e.g. **I**, R = CH_3) still give high diastereofacial selectivity in the same direction as that shown by **Ia**.

There is no obvious reason why form **Ib** should not be as stable as **Ia** on the basis of steric and torsional strains. Conformation **Ib** was not considered by Saito because it would lead to products with stereochemistry opposite to what was observed. Our VT-NMR study supports their conclusion.[4]

Why do alkenes with the 1,5-diene-3,4-diol structural unit prefer the CO-eclipsed form (**Ia**) to a greater degree than normal allylic compounds?[4] Our study on 1,5-hexadiene did not address this question. In this manuscript, we wish to report that some features unique to the structure of 1,5-hexadiene-3,4-diol (diol **1**) are responsible for this phenomenon. Through a study with the *ab initio* molecular orbital methods, we have found that electrostatic interactions are important for the relative stability of conformational isomers in the oxygen-substituted alkenes. Although conformational preference in some small organic molecules have been attributed to dipole induced-dipole interactions,[7] currently these effects are not widely recognized. Recognition of these interactions, however, should be useful for understanding and predicting conformational preferences in organic molecules.

Computational Method

The initial conformational isomers were found through the molecular mechanics program MacroModel 4.0[8] on the SiliconGraphics Indigo2 work station. When the conformational search was done on diol **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, and the two C−O bonds. The conformations with intramolecular hydrogen bonds were discarded because the system (compound **I**) modeled cannot form such bonds. The conformations in which the O−H bonds are pointed away from the other OH group and to the most open space are kept for geometry optimization. Complete geometrical optimization of the initial conformers generated by the program was then carried out at a progressively higher level of *ab initio* molecular orbital theory[9] using the GAUSSIAN 90 and 92 programs.[10]

Ab initio calculations using the STO-3G and 3-21G basis sets at the Hartree-Fock level were performed on the SiliconGraphics Indigo2 work station. Higher level (MP2/6-31G*) of computations were carried out on the Cray Y-MP/8 supercomputer. The conformational minima of 1,5-hexadiene-3,4-diol (diol **1**) were fully optimized up to the extended 6-31G* basis set. Harmonic frequencies were calculated for each conformer using the 6-31G* basis set. The minimum conformations all have positive frequencies, which is an indication of a true minimum on the potential surface. Single point calculations were performed with the Moller−Plesset electron correlation (MP2/6-31G*) using the 6-31G* optimized structures. Attempted geometric optimization of diol **1** at the MP2/6-31G* level failed due to disk space and memory limitations. However, the conformers of 3-buten-1-ol (**2**) were completely optimized up to the MP2/6-31G* level.

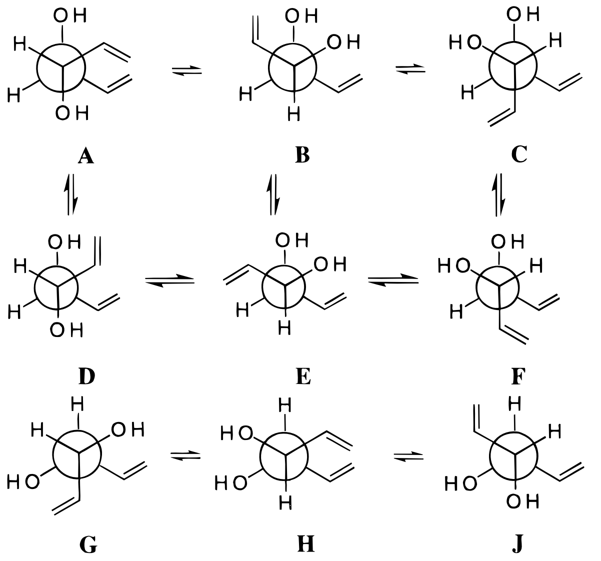

Figure 1. Newman projections for the conformers of 1,5-hexadiene-3,4-diol (diol **1**).

Results and Discussion

The Newman projections for the conformers of 1,5-hexadiene-3,4-diol (diol **1**) are depicted in Figure 1. There are a total of five free-rotating single bonds in **1** and three minima around each bond. To model the hydroxy-protected 1,5-hexadiene-3,4-diol, such as **I**, only one of the three conformers generated by rotating around the two C−O bonds in **1** is considered to be suitable. In these eligible conformations, the O−H bonds are pointed away from the other OH group and to the most open space. No intramolecular hydrogen bonded species was accepted. This criteria reduces the number of free rotating bonds to three, one of which is the central C_{sp^3}-C_{sp^3} bond and the other two are the adjacent C_{sp^2}-C_{sp^3} bonds. Rotation around the C_{sp^2}-C_{sp^3} bond gives three groups of stable conformers: (1) conformations with the CO bond eclipsing the C═C bond (**A**, **B**, and **C**), (2) conformations with the CH bond eclipsing the C═C bond (**G**, **H**, and **J**), and (3) conformations with the CC bond eclipsing the C═C bond (none is shown). Based on previous studies,[4−6] the CC-eclipsed forms are usually much higher in energy, they are therefore excluded from calculation. This leaves twelve (3 × 2 × 2) stable conformers, three of which are enantiomers of **D**, **E**, and **F** and are not listed. Thus when both CC_{sp^2}-C_{sp^3} bonds are in the CO-eclipsed form, rotation around the central C_{sp^3}-C_{sp^3} bond generates conformers **A**, **B**, and **C**. When one CC_{sp^2}-C_{sp^3} bond is in the CO-eclipsed form and one in the CH-eclipsed form, center bond rotation gives **D**, **E**, and **F**. Conformers **G**, **H**, and **J** are produced by rotation around the C_{sp^3}-C_{sp^3} bond while the two CC_{sp^2}-C_{sp^3} bond are both in the CH-eclipsed form.

A. 1,2-Dioxygen Functional Groups Prefer To Be at an Anti Position. The calculated relative energies for conformers **A**−**J** are listed in Table 1. The optimized structures of **A**−**J** are displayed in Figure 2. The relative energies underneath each conformer are single point energies calculated at the MP2/6-31G* level of theory using the optimized structures at the 6-31G* level. In

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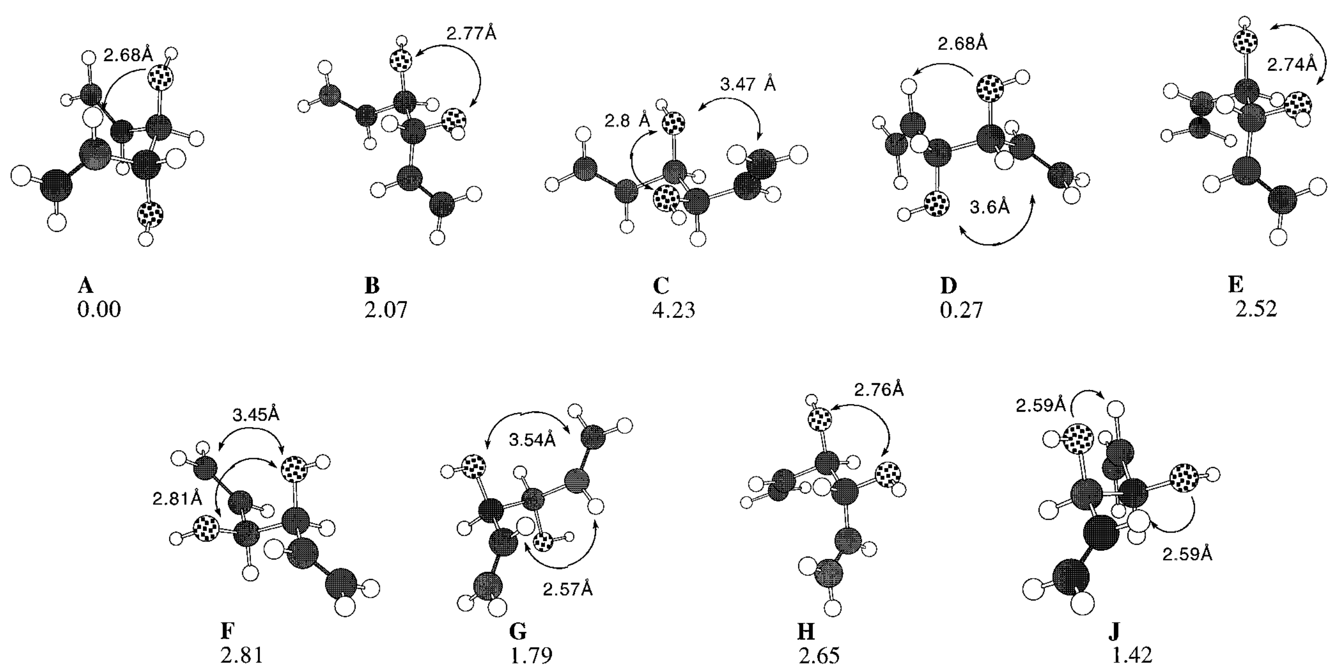


Figure 2. Optimized structures and relative energies (kcal/mol) for the conformers of 1,5-hexadiene-3,4-diol (diol **1**). Double-headed arrows indicate repulsions, and single-headed arrows represent attractive interactions.

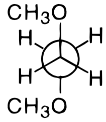
Table 1. Relative Energies (kcal/mol) and Dipole Moments (Debye) for the Conformers of 1,5-Hexadiene-3,4-diol (Diol 1)

conformer	dipole moment	relative energy		
		3-21G*	6-31G*	MP2/6-31G*[a]
		Both C−O Eclipsed		
A	0.34	0.00	0.00	0.00
		(−380.56907)[b]	(−382.68445)[b]	(−383.80197)[b]
B	1.57	3.02	2.01	2.07
C	2.11	7.74	4.25	4.23
		One C−O Eclipsed, One C−H Eclipsed		
D	0.13	1.89	0.08	0.27
E	2.90	5.32	2.25	2.52
F	1.96	6.18	2.56	2.81
		Both C−H Eclipsed		
G	0.39	4.77	1.22	1.79
H	2.02	6.98	2.22	2.65
J	1.74	4.37	0.81	1.42

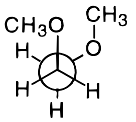
[a] Single point calculations. [b] Total energies in atomic units.

general, the conformations with the oxygen atoms at an anti position (**A**, **D**, **G**) are more stable than the ones with gauche dioxygen functions. The only crossover to this rule is the CH-eclipsed forms **G** and **J**. This exception will be discussed later in this manuscript. The oxygen-anti, CO-eclipsed conformer (**A**) was found to be the global minimum, which is the same as **Ia**, the conformation previously suggested by Saito.[1] It is remarkable that the ground state form of diol **1** remains the same even though it does not have bulky protecting groups on the hydroxy functions. The second most stable conformer is also an oxygen-anti form (**D**). Significantly higher energies were found for the rest of the conformers.

The first and the most obvious result of this study confirms our initial suggestion: it is not necessary to have bulky groups, such as the TBDMS group, in order for the 1,2-dioxygen function to assume the anti position.[4b] This conclusion is consistent with the results from a recent study on 1,2-dimethoxyethane (**II**).[11a] Both experimental (IR) and theoretical (*ab initio* MO) studies led to the conclusion that the anti conformation of 1,2-dimethoxyethane is more stable than the nearest gauche form by 1.44 kcal/mol.[11a] Similar results were found for 1,2-dichloroethane.[11b] In the gas phase, the anti conformation of 1,2-dichloroethane is preferred by 1.2 kcal/mol.



II anti



gauche

Experimentally, it was shown that the bis(trimethylsilyl) (TMS) analogs of **I** and the TBDMS derivative (**I**) give both the same sense and the same ratio of π-facial selectivity.[1] Since the TMS group is considerably smaller than the TBDMS group, these results are inconsistent with the argument based on steric effects. Therefore, it is reasonable to conclude the following: the origin of the anti preference is due to polar effects, i.e., electrostatic repulsion between the lone pairs on the two oxygen atoms, rather than steric effects. This conclusion is consistent with the calculated dipole moments (Table 1) of each conformation. The oxygen-anti conformers (**A**, **D**, and **G**) have considerably smaller dipoles than the oxygen-gauche forms. Conformations **C**, **F**, and **J** are destabilized by the dipole−dipole interaction even though they have no obvious steric interactions (vinyl groups-anti).

Historically, dipolar interactions have been suggested to account for a number of conformational phenomenon. For example, dipolar interactions were proposed to cause

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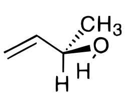
Table 2. *Ab initio* Relative Energies (kcal/mol) and Dipole Moment for Conformers of 3-Buten-2-ol

entry	conformer	dipole moment (Debye)	relative energy		
			HF/3-21G*	HF/6-31G*	MP2/6-31G*
1	**a**	1.88	0.11 (−229.674132)[a]	0.26 (−230.952896)[a]	0.01 (−231.644063)[a]
2	**b**	1.86	0.0	0.0	0.0
3	**c**	1.74	0.97	0.45	0.44
4	**d**	1.74	0.73	0.27	0.36
5	**e**	1.75	0.86	0.2	0.58
6	**f**	1.86	0.87	0.35	0.45
7	**g**	2.06	−0.22	−0.80	−1.62
8	**h**	1.98	2.45	1.10	1.02
9	**i**	1.86	1.45	0.84	0.56

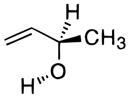
[a] Total energies in atomic units.

the anomeric effect.[12] The axial preference observed for 2-bromo- and 2-chlorocyclohexanones in nonpolar solvents was also believed to come from dipole−dipole interactions.[13] It should be noted that concerning the origin of the anomeric effect the alternative explanation based on electron delocalization seems to be preferred by many authors.[14] However, which mechanism is more important may depend on the substituents.[15] Finally, it has also been suggested that the origin for the high enantioselectivity in asymmetric allylboration reaction is the electron repulsion from oxygen lone pairs.[16]

B. Electrostatic Repulsions between the Oxygen Atom and the π Bond in a Pseudo 1,3-Diaxial Position. The second conclusion from this study, as described below, is directly related to the question posed earlier: why the CH-eclipsed form (**G**) is not favored in 1,5-diene-3,4-diols? In normal allylic alcohols, such as 3-buten-2-ol (**III**), the CH-eclipsed form, which corresponds to one half of **G**, is the most stable conformation.[3c] However, the doubly CH-eclipsed form **G** of diol **1** is almost 1.8 kcal/mol higher in energy than the doubly CO-eclipsed form **A**. Furthermore, there is an exception to the oxygen-anti rule in that conformation **J** with a gauche oxygen arrangement is more stable than the oxygen-anti isomer **G**. Two possible reasons for these observations are (1) the unfavorable interactions that are present in **G** but absent in the CH-eclipsed form of 3-buten-2-ol (**III**) and conformation **J**; (2) the attractive interactions that are present in **A** and **J** but absent in the CO-eclipsed form of **III**. The following discussion will show that both reasons 1 and 2 are true.

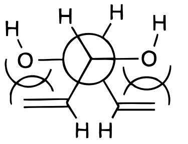


III CH-eclipsed



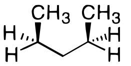
CO-eclipsed

First, we propose that the unfavorable interaction in conformation **G** is from the electron repulsion between the $\pi_{C1=C2}$ electrons and the C4 oxygen lone pairs, namely, electrostatic interaction. Each oxygen atom in structure **G** is in a pseudo 1,3-diaxial relationship with the sp^2 carbons of the π bond (see below). The distance between C1C$_{sp^2}$ and the oxygen in **G** is 3.54 Å, Figure 2. Clearly, the lone pair electrons on the oxygen and the π-electrons of the double bond are repulsive to each other. Supporting evidence for this analysis can also be found in other conformations. For example, the highest energy conformation of diol **1** is the vinyl-anti, CO-eclipsed form **C**. In this conformation, not only are the oxygen atoms gauche to each other, but also in a 1,3-diaxial relationship to the sp^2 carbons, Figure 2. Thus, electrostatic repulsion can explain the following facts: (1) conformation **C** is the highest energy form, (2) the oxygen-anti conformations are more stable, and (3) conformation **G** is the least stable oxygen-anti forms.

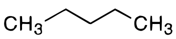


G

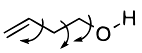
C. Structure of 3-Buten-1-ol (2). The relative position of the π bond and the C4 oxygen atom in **C** or **G** is similar to the two methyl groups of the syn-pentane conformation **K**. The syn-pentane conformation is about three kcal/mol higher in energy than the all-anti form **L**, according to molecular mechanics calculation (MM2 implemented in MacroModel).[8] In order to determine quantitatively the repulsive interaction involving this pseudo 1,3-diaxial oxygen-π bond, we have carried out an *ab initio* calculation on 3-buten-1-ol (**2**). This smaller molecular structure serves as a model for the interactions in one half of 1,5-hexadiene-3,4-diol (diol **1**). Stable conformers were found by rotating the three single bonds indicated below.



K



L



2

The calculated relative energies for **2** are listed in Table 2. The optimized structures are shown in Figure 3. After excluding the CC-eclipsed forms and enantiomers, nine conformations are obtained and divided into three groups. The first group (**a**, **b**, **c**) has a gauche OCCC fragment with the vinyl group pointing away from the oxygen atom. The second group includes conformations **d**, **e**, and **f**, which have an anti OCCC frame. The third group of conformations (**g**, **h**, **i**) have a gauche OCCC fragment,

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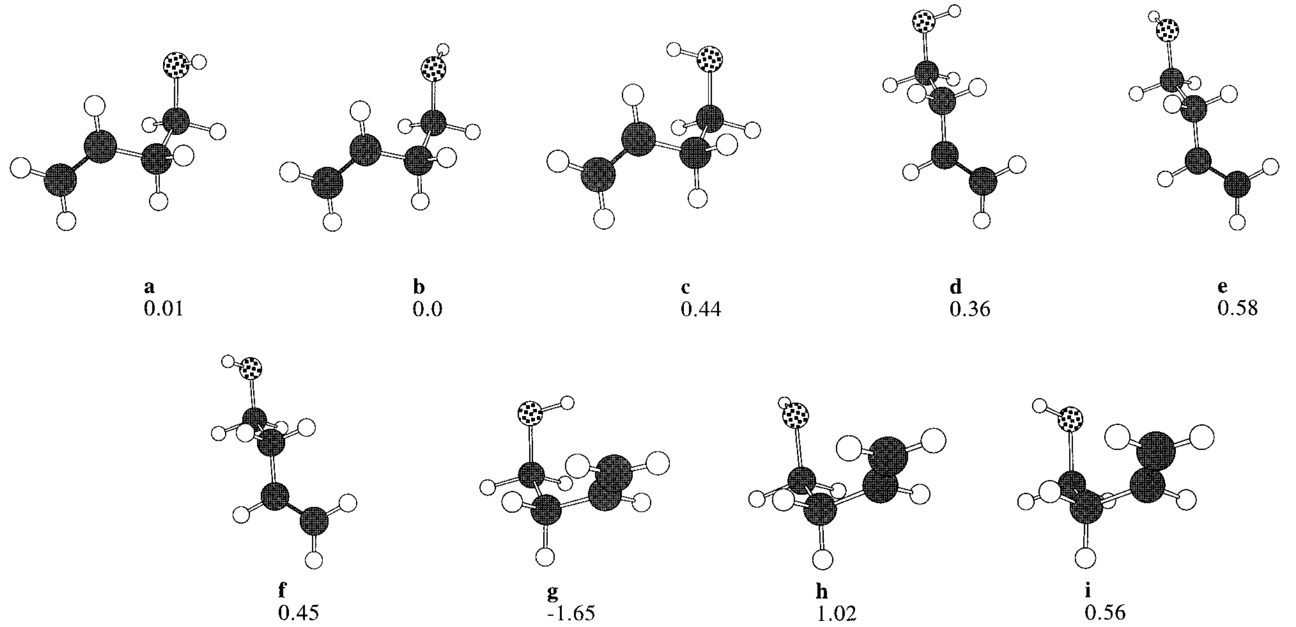


Figure 3. Optimized structures (MP2/6-31G*) and relative energies (kcal/mol) for conformers of 3-buten-1-ol (**2**).

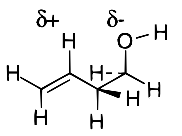
and the vinyl group is in the 1,3-pseudo diaxial relationship to the CO bond. It is interesting to note that the conformations with an anti OCCC frame (**d**, **e**, and **f**) are not the most stable forms even without considering the hydrogen bonded conformer (**g**). This fact is consistent with electrostatic interactions as described below.

Conformer **h** is the model for estimating the 1,3-diaxial repulsion between the oxygen and the π bond. When compared to conformer **a** or **b**, this amounts to ~1 kcal/mol in energy difference. The major part of this energy difference comes from the repulsion between the oxygen lone pair and the π electrons of the double bond in **h**, and part of it is from an attractive interaction in **a** and **b**. The reason for attributing part of the energy difference to an attractive interaction in **a** and **b** is because these conformers are more stable than the conformations with an anti OCCC fragment. These conformations with an anti OCCC fragment should not have any repulsive interactions and should be the most stable ones if there is no attractive interactions in **a** and **b**. This attractive interaction will be further discussed in the next section.

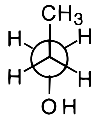
The global minimum for **2** is the hydrogen bonded form **g**. This conformer is more stable than the next nearest one by 1.62 kcal/mol (Table 2) at the MP2/6-31G* level of theory. It is consistent with previous observations of hydrogen bonding between an OH group and a π bond in 3-buten-1-ol.[17] Schleyer and co-workers determined that the hydrogen bond between the OH and the π bond in 2-arylethanols has a bond energy about 1.4 kcal/mol in CCl_4 solution.[18] Kirchner and Richter reported a hydrogen bonding strength of 2.6 kcal/mol in the gas phase for 2-arylethanols.[19] From the current results, a perfect geometry of OH to π bonding is present in the optimized structure of conformer **g** (Figure 3).

D. Attractive Electrostatic Interactions in 1,5-Hexadiene-3,4-diol (diol 1) and in 3-Buten-2-ol (2).

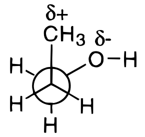
In order to model the doubly hydroxy group-protected compound **I**, the hydrogen bonded conformer **g** should be excluded in the following discussion. A more subtle electrostatic attraction (than a hydrogen bond) appears to be present in 1,5-hexadiene-3,4-diol (diol **1**) and in 3-buten-2-ol (**2**). Conformers **a** and **b** are the most stable forms of **2** without hydrogen bonding. Why are these conformers with a gauche OCCC fragment (**a**, **b**) more stable than those with an anti OCCC frame (**d**, **e**, **f**)? Here we suggest an attractive electrostatic interaction in conformations **a** and **b**. As shown below, the oxygen atom and the vinyl hydrogen atom are at a pseudo 1,3-diaxial relationship. The lone pair electrons on the oxygen atom are pointed toward the vinyl hydrogen atom, an optimal position for attractive electrostatic interaction. This may be the second reason why **A** is the global minimum of diol **1** because this stabilizing interaction should be twice as strong in conformation **A** of diol **1** as that in conformer **a** or **b** of **2**.



b



IV anti



gauche

This attractive interaction is similar to that reported recently by Houk on 1-propanol (**IV**).[7b] Kishi et al. reported experimental studies of the conformations of C-glycosides and discovered that these compounds exist in a gauche CCCO arrangement, rather than the anti arrangement.[20] Houk et al. studied this conformational phenomenon with the *ab initio* methods. It was found that a simple CCCO fragment, such as 1-propanol, prefers the gauche form by ~0.4 kcal/mol. The origin of this preference was attributed to electrostatic attraction. It should be noted that these polar interactions are from local dipoles. For example, in conformation **a** and **b** of

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(17) (a) Traetteberg, M.; Oestensen, H. *Acta Chem. Scand., Ser. A* **1979**, *33*, 491–7. (b) Marstokk, K. M.; Moellendal, H. *Acta Chem. Scand., Ser. A* **1981**, *35*, 395–401.

(18) Schleyer, P. v. R.; Wintner, C.; Trifan, D. S.; Backskai, R. *Tetrahedron Lett.* **1959,** *14*, 1.

(19) Kirchner, H. H.; Richter, W. *Z. Phys. Chem. Neue Folge.* **1972**, *81*, 274.

(20) (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.

3-buten-2-ol (**2**) the interacting dipoles are the C−O and the C−H bonds even though the calculated total dipole moments for the various conformers of **2** show little difference (Table 2).[21]

The second most stable conformer of diol **1** is the oxygen-anti, one CH-eclipsed and one CO-eclipsed form **D**. This conformation contains both a structure moiety of **b** and of **h**. The center OCCO torsional angle is 173.8°, which allows maximum attraction between the oxygen atom and the vinyl H and minimum repulsion between the oxygen atom and the sp^2 carbon. The vinyl group that is eclipsed with the CH bond turns slightly away from the oxygen atom to avoid repulsive interactions, Figure 2. These facts explain why conformer **D** is the second most stable isomer. On the other hand, it is not possible for the doubly CH-eclipsed conformation **G** to turn its vinyl groups away from the oxygen atoms because the vinyl hydrogen atoms will collide as indicated in Figure 2.

The third most stable form of Diol **1** is the oxygen-gauche conformation **J**. This crossover of stability can also be explained by the attractive electrostatic interactions. The repulsion from the gauche 1,2-dioxygen function is partially offset by the two attractive interactions between the oxygen atom and the vinyl hydrogen atoms. Unlike in conformation **G**, there is no pseudo 1,3-diaxial interactions between oxygen and π bond in conformation **J**. Thus, electrostatic effects should be considered the driving force for the relative stability of conformational isomers in 1,5-hexadiene-3,4-diols, including the anti preference of the 1,2-dioxygen function and the preference for the CO-eclipsed form.

Conclusions

From an *ab initio* MO study of 1,5-hexadiene-3,4-diol (Diol **1**) and 3-buten-1-ol (**2**), three types of electrostatic interactions are found to be responsible for the conformational preference of compound **I**. These are (1) the repulsion between oxygen lone pairs leading to anti preference of the 1,2-dioxygen function, (2) the repulsion between the pseudo 1,3-diaxial oxygen/π bond, and (3) the attraction between the oxygen lone pair and the vinyl H in a pseudo 1,3-diaxial position. Both interaction 2 and 3 lead to the preference for the CO-eclipsed form in 1,5-hexadiene-3,4-diols. The magnitude of these electrostatic interactions are in the order as presented above ranging from ~1.5 to ~0.5 kcal/mol. These repulsions and attractions among the polar groups will diminish if hydrogen bonding or polar solvent is present.[22] That is probably why they have not received much attention in conformational analysis, especially the third type which is weak and attractive. This study shows that these electrostatic interactions are important and responsible for exceptional conformational preference of organic molecules if several interactions work in concert.

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Supporting Information Available: The optimized parameters and Z-matrix for conformations of **A**−**J** (6-31 G*) and **a**−**i** (MP2/6-31G*) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[21] We thank the editor, Professor Andrew Streitweiser, for pointing out this difference.

[22] Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.