Hydrogen Bonding and Density Functional Calculations: The B3LYP Approach as the Shortest Way to MP2 Results

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As a test for the applicability of the density functional theory to the system containing intramolecular hydrogen bonds, calculations were performed on propen-1,2,3-triol, the feasible intermediate in the epimerization of dihydroxyacetone and glyceraldehyde enantiomers. A comparison is made between results obtained by Becke's three parameter hybrid functional (for exchange) with gradient corrections provided by the LYP correlation functional (B3LYP) and those predicted at the ab initio Møller−Plesset second-order (MP2) level. The calculated minimum energy structures are in excellent agreement with respect to both energy and geometries of hydrogen-bonded structures. Earlier and recent studies suggest that, generally, the nonlocal B3LYP approximation leads to a very accurate overall description of intramolecular hydrogen-bonded systems. We propose a new, more efficient computational protocol, which may be useful in the study of the biologically important molecules at a level of accuracy usually only provided by traditional post-Hartree−Fock ab initio methods.

Introduction

One of the exciting developments based on density funtional theory (DFT)[1−5] is undoubtedly the emergence of methods that can provide a perspective on the exact characterization of hydrogen-bonded systems. Such computational approaches could be used to determine structures of biological importance. In addition, they might even be used to treat the transition state or activation barriers of important enzymatic reactions. As yet, some attempts were made to allow calculation for systems of 10^3-10^4 atoms.[6,7] The application of ab initio methods to the hydrogen bond problem has indicated that the Hartree−Fock (HF) method inaccurately predicts geometries of hydrogen-bonded structures. Ab initio approximations, in which electron correlation is taken into account, provide data in good agreement with experimental results (f.i. for the most intensively studied water dimer see refs 8−13). However, the high computational costs of correlated ab initio methods [e.g., at the Møller−Plesset (MP2) level] restricts their usefulness to rather small systems. Today, much interest is focused on nonlocal density functional approximations as an alternative to ab initio schemes in the hydrogen-bonding studies. This alternative offers the opportunity to suggest more efficient and simpler schemes, which significantly will shorten the classical procedure[14] and that will provide a reasonable compromise between the accuracy of the results and the computational effort.

Recently, we have studied D-glyceraldehyde **1** and dihydroxyacetone **2** (Figure 1) as model systems for the main part of natural sugar molecules.[15] We found that there are two predominant factors that govern hydrogen bonds: the size of the ring, in which hydrogen bonding is arranged, and the hybridization of the oxygen atom toward which the hydrogen bond is directed.[15] Moreover, all stable structures obtained revealed a cooperative effect. Although such effects have been extensively studied theoretically,[15−20] uncertainties still exist concerning the nature of hydroxyl group(s) and/or the access to neighboring proton acceptors on hydrogen bond arrangements. Because the structure of propen-1,2,3-triol is both tautomeric to model trioses and structurally significantly different, we recognized that corresponding calculations for this molecule are of interest. Although the potential for tautomerism and, consequently, for epimerization (i.e., the formation of a diastereomeric mixture from pure enantiomers by a change in configuration on one stereocenter in a molecule possessing several stereocenters) represents an old concept of sugar chemistry, this aspect has not been investigated to its full extent. Probably, the most extensive study was that by Ventura et al.[21] who investigated mechanisms for the conversion of vinyl alcohol to acetaldehyde (i.e., the simplest system for keto−enol tautomerism at all). Very recently, theoretical studies on keto−enol tautomerization involving carbonyl derivatives were also reported.[22] The importance of enoles as intermediates in synthesis, currently in enantioselective protonation, where only

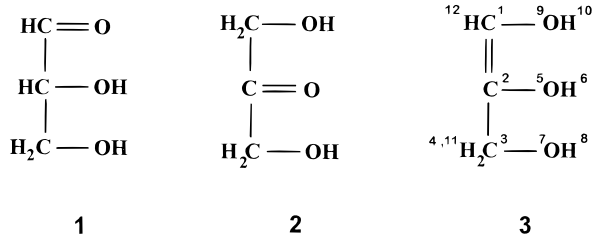

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Figure 1. Structures of D-(+)-glyceraldehyde (**1**) and dihydroxyacetone (**2**) and structure with atom numbering for propene-1,2,3-triol (**3**).

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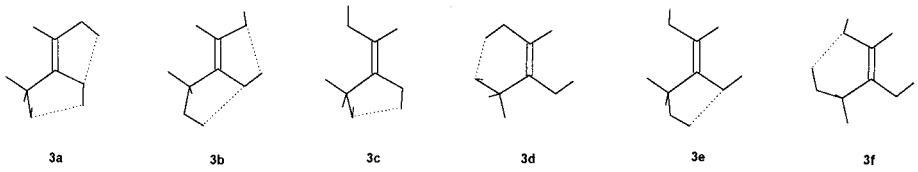


Figure 2. Projections of propene-1,2,3-triol **3a**−**3f** conformers. Dotted lines denote hydrogen bond contacts.

TABLE 1: Selected Bond Lengths and Intramolecular Hydrogen Bond Parameters for Propen-1,2,3-triol Conformers As Obtained by the Various Computational Approaches[a]

conformer	config.	B3LYP/3-21G	B3LYP/6-311G	B3LYP/6-311++G(d,p)	MP2/6-311++G(d,p)	hydrogen bond type
3a						cooperative system
H10···O5		2.202	2.243	2.255	2.217	5-memb. ring
O9-H10···O5	(*Z*)-	113.4	109.8	110.7	112.8	enol-to-enol, and
H6···O7		1.983	2.309	2.411	2.426	5-memb. ring
O5-H6···O7		121.9	111.5	109.9	110.0	enol-to-alchol
3b						cooperative system
H6···O9		2.077	2.218	2.235	2.208	5-memb. ring
O5-H6···O9	(*Z*)-	116.2	110.0	111.0	112.8	enol-to-enol, and
H8···O5		2.162	2.450	2.534	2.460	5-memb. ring
O7-H8···O5		113.9	104.5	102.6	105.0	alcohol-to-enol
3c						
H6···O7	(*E*)-	1.852	2.149	2.279	2.313	5-memb. ring
O5-H6···O7		125.9	116.1	113.8	113.3	enol-to-alcohol
3d						
H10···O7	(*E*)-	1.724	1.902	1.969	1.953	6-memb. ring
O9-H10···O7		145.2	139.1	139.7	141.4	enol-to-alcohol
3e						
H8···O5	(*E*)-	2.162	2.340	2.435	2.383	5-memb. ring
O7-H8···O5		113.0	105.9	103.9	106.0	alcohol-to-enol
3f						
H8···O9	(*E*)-	1.759	2.021	2.183	2.232	6-memb. ring
O7-H8···O9		147.0	132.0	128.5	127.5	alcohol-to-enol

[a] Bond lengths in Å; angles in degrees.

catalytic amount of the chiral reagent is required,[23] is another important reason for obtaining a better understanding of structures and reactivities of enoles and enolates.

In this work we attempt an analysis of all possible conformers of (*E*)- and (*Z*)-stereoisomers of propen-1,2,3-triol. Relative energies of these structures are calculated using both DFT and MP2 approaches.

Method

The standard 6-311++G(d,p) contracted basis set for the Becke3-LYP (B3LYP) exchange-correlation energy hybrid functional and for Møller−Plesset second-order (MP2) calculations was used, according to earlier suggestions.[16,24−26] All calculations were performed using the GAUSSIAN 94 program system.[27] Other computational details are given in ref 15.

Results and Discussion

Geometries of MP2 Structures. Contrary to triose **1** and **2** structures (see Figure 1), which possess carbonyl oxygen atoms (i.e., acceptor-only atoms for hydrogen bonds), the enol molecule possesses three nonequivalent hydroxyl groups with both proton donor and proton acceptor character. This structure means that in the case of propen-1,2,3-triol (optimized structures presented in Figure 2) two different major hydrogen bond interactions can be expected: enol-to-enol (or alcohol) and alcohol-to-enol. We deal with two kinds of hydroxyl groups: O9H10 and O5H6 bonded to C1 and C2 sp^2 carbon atoms are enolic in nature, whereas the O7H8 group at the C3 sp^3 carbon is rather alcoholic, although its allylic feature ought to be noticed (for atom numbering see Figure 1). In addition, cooperativity can develop in two contradictory directions (structures **3a** and **3b**). The computational study of α-L-fucose, an α-L-glucose derivative, seems to support the suggestion that in the two most stable rotamers, the number of possible OH···O is maximal, leading to the formation of counterclockwise or clockwise conformers with respect to the aldopyranosyl ring.[18] It is obvious that the *trans* position of enol hydroxyls in (*E*)-propen-1,2,3-triol conformers **3c**−**3f** prevents the formation of the cooperative chain.

The arrangement of hydrogen bonds has no effect on the carbon−carbon double bond length (1.344 and 1.340 Å, for **3a** and **3b**, respectively). This situation is not true for the bond lengths of carbon−oxygen bonds in the considered conformers: for both enol and allylic hydroxyls, acting as proton donors, the C−O bonds are distinguishably shorter than that engaged as proton acceptor group. For example, for conformer **3a**, the bond lengths are as follows (in parentheses the corresponding values for conformer **3b**): C1O9 1.359 Å (1.386 Å) and C3O7 1.434 Å (1.423 Å) (cf. also the C4O4 and C6O6 bond lengths obtained at the MP2/cc-pVDZ level for **1** and **2** in ref 19).

The geometry optimization we performed for a number conformers of **3** at the MP2/6-311++G(d,p) level of theory allow us to examine the effects of hydrogen bonding over a wide range of its arrangements. In an attempt to elucidate some of the important features of intramolecular hydrogen bonding in such structures we point out as essential factors cooperativity, the kind of interaction (enol-to-enol or alcohol-to-enol) and the size of the rings formed. A comparison of the structural parameters of hydrogen bonds is presented in Table 1. The calculations clearly show that if a ring of the same size is formed independently of cooperativity, the hydrogen bond of an enol group (being the stronger proton donor) to an alcohol oxygen atom is always shorter than in the case of the interaction of the alcohol hydroxyl with enol oxygen (cf. **3a** and **3b**; **3c** and **3e**).

TABLE 2: Calculated Energies for the Propen-1,2,3-triol (3) Conformers[a]

method	absolute energy	relative energies [kcal/mol]					
		3a	**3b**	**3c**	**3d**	**3e**	**3f**
B3LYP/3-21G	−341.650 123 4	0.00	3.83	3.66	−0.84	7.85	5.96
B3LYP/6-311G	−343.549 447 2	0.00	2.00	4.30	3.18	7.16	7.64
B3LYP/6-311++G(d,p)	−343.682 380 5	0.00	1.95	5.43	5.30	7.32	8.35
MP2/6-311++G(d,p)//B3LYP6-311++G(d,p)	−342.902 374 1	0.00	1.63	5.76	5.66	7.13	8.05
MP2/6-311++G(d,p)[b]	−342.902 790 7	0.00	1.62	5.65	5.66	7.16	8.03

[a] Absolute energy of **3a** (in hartrees) and relative energies of **3a**−**3f** as obtained by various computational procedures. [b] The absolute energy (in hartrees) and relative energy (in kcal mol^{-1}) for **1a** (ref 15) are −342.915 704 7 and −8.10; for **2a** (ref 15), the corresponding energies are −342.915 540 9 and −8.00, respectively.

It is also evident that noncooperative structures possess shorter hydrogen bond lengths than cooperative motifs (cf. **3c** and **3a**; **3e** and **3b**). This result is in line with the reasoning based on the observation that hydroxyls in noncooperative structures exhibit an essentially strain-free environment, whereas the interacted hydrogen bond systems may cause a distortion of the system that leads to longer contacts and, possibly, less stable individual bonds.

For the cooperative structures **3a** and **3b** OH···O enol-to-enol bond lengths of 2.217 and 2.208 Å with an identical value for the hydrogen bond angles of 112.8° were obtained. This effect is not sensitive to the basis set applied. These findings are consistent with the prediction indicating that the same kind of interaction as well as the ring size determine the degree of freedom and, finally, define the geometry of hydrogen bond formed. To a lesser extent it is apparent for the neighboring ring, where the intramolecular parameters are somewhat different, probably due to the weaker interaction in **3b** because of the alcohol-to-enol fashion (2.460 and 2.426 Å for **3b** and **3a**, respectively).

Usually, superior hydrogen bonding geometries are available in the six-membered rather than in the five-membered ring. Manifestations of large steric strain in the calculated structures include longer OH···O bonds and more acute bond angles. For example, Polavarapu and Ewig[28] reported a difference of 0.29 Å in the (O)H···O distances between similar rotamers of the $^4C_1$ conformer of β-D-glucose (cf. O5H6 in **a′** and O4H6 in **b′**, Table 1, ref 20). We also found that intramolecular hydrogen bonds better adopt the six-membered ring geometry. Structure **3d** possesses a rather short hydrogen bond with a length of 1.953 Å and an angle of 141.4° (i.e., extreme values in the set of structures we have studied). These parameters for the other structure **3f** with a six- membered ring are also distinct (2.232 Å and 127.5°). In the case of the latter conformer, the oxygen atoms lie approximately in the plane of the double bond (the actual value for the torsional angle is 4.5°). The methylene hydrogen atoms H4 and H11 at the C3 carbon atom are in truly equatorial or axial positions (∠H4−C3−C2−C1 = 178.8° and ∠H11−C3−C2−C1 = 60.3°). A different situation arises for the rotamer **3d**: the torsional angle H4−C3−C2−C1 amounts to 81.8°, whereas the angle H11−C3−C2−C1 has a value of 159.4°, indicating that these ligands are rather in pseudoaxial and pseudoequatorial positions, respectively. As follows from Table 2, according to the MP2/6-311++G(d,p) calculations, rotamer **3f** is by 2.37 kcal/mol less stable than **3d**. This result supports the hypothesis that stressless steric interactions are remarkably less important than the electrostatic influence on the hydrogen bond strength,[29] which seems to be the critical factor. Moreover, none of the enol six-membered rings resembles the half-chair form proposed for cyclohexene.[30] It seems that the interaction of π bond-n lone pairs of oxygen atoms and hydrogen bonding are far more complicated than simple torsional repulsion in common hydrocarbon rings.

For structures **3d** and **3f** the most stable conformation is that in which the carbon−carbon double bond is eclipsed to the O5H6 bond (torsional angles H6−O5−C2−C1 are 16.1° and 1.7°, respectively). It is interesting that such a conformer has been found for the propene molecule,[31] because the alternative one, with eclipsed hydrogen atoms, seems to be destabilized by the unfavorable overlap interaction between the bond orbitals. Because of this finding, the evident structure dependence of the conformation of this hydroxyl group is perhaps not surprising. It is possible that the C3H11 and C3H4 bonds, which are spatially fixed due to hydrogen bonding, simply affect the lone pairs on the O5 oxygen atom (structures **3d** and **3f**). An alternative explanation would be a corresponding attractive 1,3-interaction due to n→s* overlap of one of the n orbitals of O5 atom with the σ* orbital of the C3−O7 bond. Indeed, with respect to the mutual H6−O5 and C3−O7 orientation (76.8° and −75.6° H6−O5−C3−O7 dihedral angles for **3d** and **3f**, respectively), this overlap is nearly maximal and the so-called "anomeric effect" works. (The leading references for the anomeric effect comparing computational and experimental data are ref 28 and 32; see also ref 33).

Geometry Performance in DFT. To assess the accuracy of DFT-based calculations for this system, we fully optimized the B3LYP geometries using the MP2 approach. The six obtained structures are shown in Figure 2. The obtained *atomic* bond parameters are in principle identical or quite similar. There are only systematic differences in the carbon−carbon double bond lengths. The C═C bonds in structures optimized by the MP2 method are always shorter than in the corresponding conformers obtained by B3LYP with the same 6-311++G(d,p) basis set, but the difference never exceeds 0.01 Å (data not shown; for example the C═C bond length for **3a** at the B3LYP/6-311++G(d,p) level amounts to 1.337 Å). Other differences for C−O and O−H bond lengths and bond angles are usually <0.05 Å and 2°, respectively.

The maximum error in *hydrogen* bond lengths is 0.074 Å and for *hydrogen* bond angles 2.4°; that is, slightly larger than that for the *atomic* parameters. This result supports our earlier conclusion[15] that the B3LYP approach appears to be accurate enough to model hydrogen bonding in compounds containing oxygen proton donors and oxygen proton acceptors irrespectively of hybridization, stereochemical arrangement, and spatial surrounding.

Relative Energies. Total and relative energies for the six propen-1,2,3-triol rotamers with different hydrogen bonding as obtained by the B3LYP and MP2 calculations are collected in Table 2. The minimal 3-21G basis set approximation predicts energies that differ drastically from the MP2 data. A distinct improvement occurs in going to the 6-311G split-valence basis set. The addition of diffuse and polarization functions to the 6-311G basis [the 6-311++G(d,p) calculations] results in improved agreement between the B3LYP and MP2 results. Probably, this improved agreement is a consequence of the

excellent description of the spatially diffuse regions of the high electron density when using the 6-311++G(d,p) basis set. Applying MP2 single-point calculations with B3LYP geometries slightly further improves the relative energies as compared to the MP2/6-311++G(d,p) predictions.

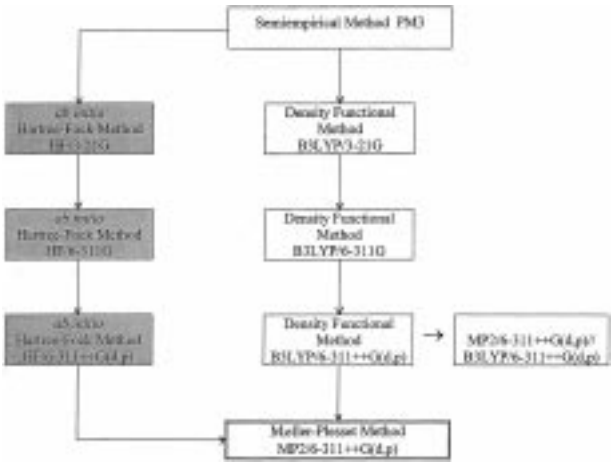
It is evident that because of the cooperative effect, the structures **3a** and **3b** become heavily favorable. Such preferences for a strikingly regular pattern of internal hydrogen bonding is well recognized for both α- and β-D-glucose anomers,[28] although for a glucopyranose only the one orientation ("information encoding", see ref 18) is energetically preferred according to NMR data.[34] The formation of hydrogen bonds by enol O9H10-to-the enol O5H6, and by enol O5H6-to-alcohol O7H8 in **3a** turns on the maximum cooperative interactions and leads to the global minimum structure, which is ∼1.6 kcal/mol (at the MP2/6-311++G(d,p) level) more stable than conformation **3b** with the opposite cooperative order. This result means that the result of the cooperative effect is strongest when both enol hydroxyls participate as proton donors. Similar conclusions apply for the other hydrogen-bonded, but noncooperative structures **3c** and **3d** with enol-to-alcohol interactions. In structures **3e** and **3f**, where proton donors and proton acceptors are arranged in the alternative fashion, the relative energies are ∼1.5 and ∼2.4 kcal/mol higher compared with **3c** and **3d**, respectively.

The position of the equilibrium for keto−enol tautomerism depends on the molecular structure, but for monofunctional compounds, usually the carbonyl form is highly favored. Our results at the at MP2/6-311++G(d,p) level of theory indicate that the carbonyl forms are indeed much more stable than enol tautomers [by up to 8.0 kcal/mol (Table 2)]. As expected, the aldehyde form is more stable, but the energy difference between glyceraldehyde and dihydroxyacetone is negligibly small [−0.10 kcal/mol for **1a** and **2a** isomers, ref 15; −0.20 kcal/mol at the MP2/6-31G(d,p) level, ref 15]. The ΔE value obtained may be related to the greater stabilization of aldehyde isomer **1** because of cooperative interaction (the central position of the oxygen atom in dihydroxyacetone **2** prevents the formation of a cooperative chain). Although a comparison of our computational results with experimental values is not possible, it is worthy to mention that the experimental gas phase energy difference between the pair acetaldehyde−vinyl alcohol is 9.9 ± 2.0 kcal/mol.[35] Similar differences between acetone and propen-2-ol of 13.9 ± 2.0[35] or 11.2 kcal/mol[36] are reported in the literature. In light of the study of Lee et al.,[22] it is evident that the quality of the MP2/6-311++G(d,p) level is sufficient to infer that the values of 8.0 and 8.1 kcal/mol (Table 2) for the glyceraldehyde/dihydroxyacetone-propen-1,2,3-triol system indicate an easier tautomerization. Thus, one cannot exclude that the epimerization in the sugar family is energetically less demanding than in simple carbonyl compounds.

Conclusion

Our earlier[15] and present investigations have demonstrated that nonlocal DFT methods with the exact exchange in the hybrid form (in particular B3LYP) offer geometrical parameters, also for hydrogen bonds, in better accordance with MP2 data than results of HF calculations. Similar conclusions have also been reported by other authors.[11,32,37,38] However, the extensive use of the B3LYP approach in getting to high quality results, up to now, has not been suggested as a general protocol for the study of hydrogen-bonded systems. Moreover, this suggestion would be motivated by computational expedience because the time required in DFT methods increases as N^3 (N = number of basis functions), as opposed to at least N^5 for ab initio methods including electron correlation. Therefore DFT methods, seem to be ideally suited for the study of larger size systems, especially for hydrogen-bonded clusters, and also for associates, where hydrogen bonding, often in a cooperative manner, is essential for the description of the ligand binding site. Scheme 1 illustrates the use of systematically improved basis sets up to 6-311++G(d,p) [optionally the 6-311++G(2d,2p)]. Increase of the basis set size beyond this level usually has no discernible effect on the calculated geometry profiles,[17,32,37] which in comparison with the experimental data are almost identical. This result suggests that inclusion of electron correlation effects through the B3LYP nonlocal functional is quite enough for correct modeling of the chemically sensitive lone pair spatial regions, at least in the case of oxygen atoms.

SCHEME 1: Suggested *versus* Practiced Protocol of Subsequent Calculations of Energy Differences at the *ab Initio* MP2 Level



Usually, a large number of stationary points obtained at the semiempirical level may be reduced by HF calculations with the standard split valence 3-21G basis set applying a rather loose convergence criterion for the gradient. In the case of propen-1,2,3-triol, the ranking order in the relative energies is not affected by the cooperative effect: the B3LYP/3-21G approximation does not predict properly even the most stable conformer. Also, a comparison reveals a lack of agreement between the hydrogen bond parameters as predicted by the B3LYP/3-21G and B3LYP/6-311++G(d,p) methods. However, the relative energies of the conformers obtained with the B3LYP method approaches converge quickly with increasing number of basis functions. The DFT method seems to be less sensitive to the basis sets than the HF approximation. Because the correlation energy correction MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p) is almost unaltered by the full geometry optimization at the MP2/6-311++G(d,p) level, the former approach may then be used alternatively. The limited effect of the grid size on the calculated structures allows the application of an economical grid instead of the most fine one.[19] The strategic use of the suggested abridged sequence shown in Scheme 1 may be the best route that can now be executed for a given molecular system (cf. ref 32). The proposed protocol may perform remarkably well in calculating certain molecular properties and allows achievement of "chemical accuracy" (≫1 kcal/mol) *inter alia* on the rational drug design area.

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References and Notes

(1) Labanowski, J. K.; Andzelm, J. W. *Density Functional Methods in Chemistry*; Springer-Verlag: New York, 1991.

(2) Parr, R. G.; Yang W. *Annu. Rev. Phys. Chem.* 1995, *46*, 701.

(3) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974.

(4) Ernzerhof, M.; Perdew, J. P.; Burke, K. *Top. Curr. Chem.* **1996**, *180*, 1.

(5) Ernzerhof, M.; Burke, K.; Perdew, J. P. In *Recent Developments in Density Functional Theory, Theoretical and Computational Chemistry*; Seminario J. M., Ed.; Elsevier: Amsterdam, 1996.

(6) Kohn, W. *Int. J. Quantum Chem.* **1995**, *56*, 229.

(7) Dunlap, B. I. *Int. J. Quantum Chem.* **1996**, *58*, 123.

(8) Laasonen, K.; Csajka, F.; Parrinello, M. *Chem. Phys. Lett.* **1992**, *194*, 192.

(9) Laasonen, K.; Parrinello, M.; Car, R.; Lee C.; Vanderbilt, D. *Chem. Phys. Lett.* **1993**, *207*, 208.

(10) Sim, F.; St-Amant, A.; Papai, I.; Salahub, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 4391.

(11) Kim, K.; Jordan, K. D. *J. Phys. Chem.* **1994**, *98*, 10089.

(12) Lee, C.; Chen, H.; Fitzgerald, G. *J. Chem. Phys.* **1995**, *102*, 1266.

(13) Estrin, D. A.; Paglieri, L.; Corongiu, G.; Clementi, E. *J. Phys. Chem.* **1996**, *100*, 8701.

(14) Hehre, W. J.; Radom, L.; v. R. Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*; J. Wiley and Sons: New York, 1986.

(15) Lozynski, M.; Rusinska-Roszak, D.; Mack, H.-G. *J. Phys. Chem. A* **1997**, *101*, 1542.

(16) Csonka, G. I.; Csizmadia, I. G. *Chem. Phys. Lett.* **1995**, *243*, 419.

(17) Reiling, S.; Brickmann J.; Schlenkrich, M.; Bopp, P. A. *J. Comput. Chem.* **1996**, *17*, 133.

(18) Csonka, G. I.; Elias, K.; Csizmadia, I. G. *J. Comput. Chem.* **1996**, *18*, 330.

(19) Csonka, G. I.; Elias, K.; Csizmadia, I. G. *Chem. Phys. Lett.* **1996**, *257*, 49.

(20) Barrows, S. E.; Dulles, F. J.; Cramer, C. J.; French, A. D.; Truhlar, D. G. *Carbohydr. Res.* **1995**, *276*, 219.

(21) Ventura, O. N.; Lledos, A.; Bonaccorsi, R.; Bertran, J.; Tomasi, J. *Theor. Chim. Acta* **1987**, *72*, 175.

(22) Lee, D.; Kim, C. K.; Lee, B. S.; Lee, I.; Lee, B. C. *J. Comput. Chem.* **1997**, *18*, 56.

(23) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566.

(24) Neville, J. J.; Zheng, Y.; Brion, C. E. *J. Am. Chem. Soc.* **1996**, *118*, 10533.

(25) Ha, T. K.; Makarewicz, J.; Bauder, A. *J. Phys. Chem.* **1993**, *97*, 11415.

(26) Ding, Y.; Krogh-Jespersen, K. *J. Comput. Chem.* **1996**, *17*, 338.

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople J. A. *Gaussian 94*, Revision D.1, Gaussian: Pittsburgh, PA, 1995.

(28) Polavarapu, P. L.; Ewig, C. S. *J. Comput. Chem.* **1992**, *13*, 1255.

(29) Umeyama, H.; Morokuma, K. *J. Am. Chem. Soc.* **1977**, *99*, 1316.

(30) Anet, F. A. L. Conformational Analysis of Cyclohexenes In *Conformational Analysis of Cyclohexenes, Cyclohexadienes and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH: New York, 1989; p 1.

(31) Herschbach, D. R.; Krisher, L. C. *J. Chem. Phys.* **1958**, *28*, 728.

(32) Kneisler, J. R.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 757.

(33) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; J. Wiley and Sons: New York, 1994; Chapter 10.

(34) Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1984**, *25*, 1575.

(35) Holmes, J. L.; Lossing, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2648.

(36) Turecek, F.; Brabec, L.; Korvola, J. *J. Am. Chem. Soc.* **1988**, *110*, 7984.

(37) Novoa, J. J.; Sosa, C. *J. Phys. Chem.* **1995**, *99*, 15837.

(38) Gonzales, L.; Mo, O.; Yanez, M.; Elguero J. *J. Mol. Struct. (THEOCHEM)* **1996**, *371*, 1.