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Conformational Analysis of 4-Tetrahydropyranones: A Combined Molecular Mechanics (MM2) and ab Initio MO Study

Benjamin W. Gung,* Zhaohai Zhu, and David A. Mareska

Department of Chemistry, Miami University, Oxford, Ohio 45056

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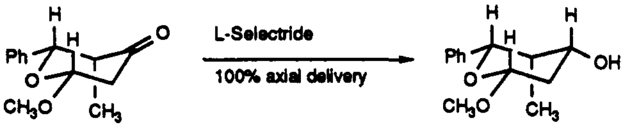
Studies by both MM2 and ab initio MO methods indicate that the "anomeric effect" observed in carbohydrates and tetrahydropyrans (THP) is also present in 4-tetrahydropyranones (THPN). The α-methyl group in a 4-THPN ring favors the equatorial orientation to a greater extent (2.4 kcal/mol) than it would in a cyclohexane system. A 2-phenyl group has a modest preference (1.1 kcal/mol) for the equatorial orientation.

Introduction

Substituted 4-tetrahydropyranones (THPN) are versatile intermediates in natural product synthesis.[1,2] The hydride reductions of 4-THPNs have been reported to give significantly higher proportions of "axial" approach products than normal cyclohexanones.[1,2,3] Most notably is the study reported by Danishefsky and Langer in 1985,[1] which involved the highly stereoselective reduction of pyranones with L-selectride. The results were described as "*in each case, the major product has arisen via axial hydride delivery*". The conclusion was surprising since the bulky L-selectride is known to reduce cyclohexanones through exclusive equatorial attack.[4] The observation was suggested to be an example of electronic effect overriding steric approach and to be consistent with "the theoretical construct recently proposed by Cieplak",[1,5b] which at the time was little known in the organic community.[5a] Since then, widespread interest has arisen with regard to the validity of the theory.[6] Therefore, our study of the conformational preferences of THPNs is directly relevant to the current interest in the origins of the stereoselectivity in asymmetric addition reactions.



I

Although the conformations of cyclohexanones and tetrahydropyrans have been studied extensively,[7] the conformational profiles of 4-THPNs, to the best of our knowledge, are unknown. The implication that the ground-state conformation of **I** is a chair form, such as shown above, seems to have overlooked the anomeric effect.[8] It is known from numerous examples in carbohydrate chemistry that pyranose sugars with an electron-withdrawing substituent such as the methoxy group at C1 are often more stable when the substituent has an axial orientation, rather than an equatorial one. This tendency is carried over to simpler ring systems such as 2-substituted tetrahydropyrans.[9] Therefore, in a compound such as **I**, the preference of the phenyl group in the equatorial orientation is opposed by the anomeric effect. Indeed, according to a MM2 calculation, without a phenyl group at the C6 position the C2-methoxy prefers to be in the axial orientation even in the 4-pyranone system. We therefore extended our study to the ground-state conformations for the substituted 4-THPNs in ref 1 by molecular mechanics[10] and for 2-hydroxy-THPN by ab initio MO methods. Our study shows that the THPNs have a rather flexible ring system and that the original implied ground state conformation is not the global minimum according to MM2. Consequently, the result from the reduction of THPNs may not be a good example to support the Cieplak model.

A. MM2 Study of the Conformational Preferences of THPN

Computational Method. The six substituted THPNs (Table I) from the study of Danishefsky and Langer were subjected to a conformational search, which was performed through the Multiconformer submode of the MacroModel program.[11,12] The minima were found through a complete geometrical optimization of the initial conformers generated by the program. The default of MacroModel was used, which rotates each marked dihedral angle by 60° intervals. The torsional angles specified for rotation included those about the C–Ph and the C–OMe bonds. It is known that the "anomeric effect" was implicated in the

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[1] Danishefsky, S.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3672.

[2] Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 75, and refs therein.

[3] Wigfield, D. C.; Feiner, S. *Can. J. Chem.* **1978**, *56*, 789.

[4] Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

[5] (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

[6] For a leading reference, which supports the Cieplak thesis, see: Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001. For a leading critic, see: Wu, Y. D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

[7] cf., (a) Allinger, N. L.; Chung, D. Y. *J. Am. Chem. Soc.* **1976**, *98*, 6798. (b) Allinger, N. L.; Rahman, M.; Lii, J-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293.

[8] (a) Durrette, P. L.; Horton, D. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 49. (b) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527. (c) Szarek, W. A.; Horton, D. *Anomeric Effects*; ACS Symposium Series, No. 87; American Chemical Society: Washington, D.C., **1979**.

[9] de Hoog, A. J.; Buys, H. R.; Altona, C.; Havingga, E. *Tetrahedron*, **1969**, *25*, 3365.

[10] Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982. For a discussion of the implication of anomeric effects in MM2, see: Norskov-Lauritsen, L.; Allinger, N. L. *J. Comput. Chem.* **1984**, *5*, 326.

[11] For other MM2 studies of the conformations for compounds having anomeric carbons, see: (a) Navio, P. F.; Molina, J. M. *J. Mol. Struct.* **1990**, *222*, 387. (b) Entrena, A.; Gallo, M. A.; Espinosa, A.; Jaime, C.; Campos, J.; Dominguez, J. F. *J. Org. Chem.* **1989**, *54*, 6034.

[12] Still, W. C. MacroModel 2.5, Columbia University. For the performance of the MacroModel program in locating conformational minima, see: Saunders, M.; Houk, K. N.; Wu, Y. D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

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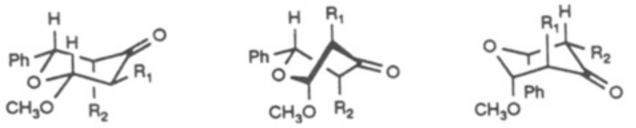
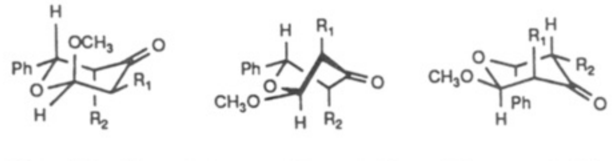
Table I. Relative Energies (MM2) of 2-Methoxy-6-phenyl-4-pyranones





			energies of individual conformation (kcal/mol)			ax/eq attack[a,b]	
compd	R1	R2	EC	TB	AC	$NaBH_4$	L-selectride
II	H	H	0.0	0.04	0.43	26:1	4:1
I	H	Me	0.51	0.61	0.0	100:0	100:0
III	Me	Me	0.0	2.23	1.37	33:1	13:1
IV	H	H	0.0	1.72	1.22	1:2	0:100
V	H	Me	0.0	0.65	0.49	2.5:1	1:2
VI	Me	Me	0.0	1.71	2.30	3:4	mixt

[a] Assuming that the **EC** form is the only conformation that is being attacked. [b] Reference 1.

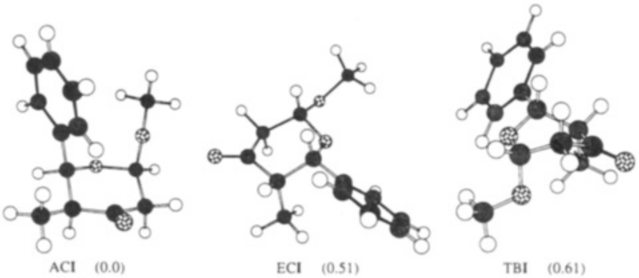


Figure 1. MacroModel-optimized structures of compound **I**. The relative energies are in the parentheses (kcal/mol).

MM2 force field,[10] and the parameters in the original MM2 force field were used in this study without modification.

Results and Discussion

Three stable conformers with lowest steric energies were found for each compound. These are the chair form with an equatorial phenyl group (EC), the twist boat (TB), and the chair form with an axial phenyl group (AC), Table I. The calculated relative energies for compounds **IV–VI** are expected on the basis of steric and anomeric effects. Incidently, these compounds did not give abnormal reduction results, Table I. However, the MM2 stability of compound **I**, which reportedly gave 100% axial attack, is opposite of what was previously implied.[1] The most stable conformer for compound **I** is the AC form according to MM2.

The MM2 structure of AC**I** (Figure 1) has the phenyl group nearly perpendicular to the C–O bond in the ring. Both the phenyl and the methoxy group bend outwards slightly to avoid the Van der Waals (1,3-diaxial) interaction, which leads to the distortion of the ring C–O–C bond angle to 117°. This value is not far from the 113.7° reported for the bond angle of D-glycopyranoses.[11a] Thus, the energy cost of the bending is more than compensated by the relief of the torsional strain according to MM2, Table II.

The L-selectride reduction of THPNs could have occurred through the normal equatorial attack if the chair form with axial phenyl is indeed more stable. The seemingly abnormal stability of the AC**I** is reasonable if one considers the following facts. It has been experimentally determined that the methoxy group prefers the axial orientation in a tetrahydropyran by 0–1 kcal/mol (solvent dependent).[9] Both experimental[13] and theoretical[14] studies have shown that β-heteroatom-substituted cyclohexanones prefer the axial orientation. The methyl group, which is in the equatorial orientation in the AC form, has an *A* value of 1.74 kcal/mol in cyclohexane.[15] Thus the orientational preferences of both the methoxy and the methyl groups could have counter-balanced the tendency for the phenyl group to be in the equatorial position. The phenyl group has an *A* value of 2.9 kcal/mol in a cyclohexane system.[16] However, inspection of the optimized structures (Figure 1), and the origins of the MM2 steric energy (Table II) reveals a much smaller axial preference of the phenyl group in a THPN system.

The EC**I** has a high torsional strain (23.8 kJ/mol), which, by analysis of the printout from the MacroModel program, stems from three unfavorable interactions: (1) the gauche interaction of the 5-methyl group with the ring; (2) the nearly 90° dihedral angle of the CH_3–C–C=O moiety, Figure 1 (the α-alkyl ketone effect);[17] (3) the anomeric effect which is evident in two dihedral interactions: (a) the dipole–dipole interactions from the O–C–O–LP (lone pair)[10] and (b) the absence of the favorable $n \rightarrow \sigma^*$ interaction.[22] The conformation AC**I**, on the other hand, is free of all three unfavorable interactions. The first two effects do not exist in AC**I** since the 5-methyl is equatorially oriented, Figure 1, and this conformation enjoys the favorable anomeric effect because the 2-methoxy group is axially oriented. It is clear that the 5-methyl and the 2-methoxy group prefer the AC**I** form much more than the EC**I**. The remaining question is how much strain does a 6-axial phenyl group cause in AC**I**? According to the results in Table I, it apparently does not override the preferences of the other two substituents. Therefore it can be expected to be less than its *A* value (2.7 kcal/mol) which is determined in a cyclohexane system. Quantitatively how much strain does an axial phenyl group create in a THPN system? This will be estimated by later calculations using single substituted THPNs.

Compound **II** does not have a 5-methyl group. Therefore its EC form does not have either the gauche interaction with the ring caused by the methyl group or the α-alkyl ketone effect.[17] In EC**III**, these unfavorable interactions are canceled out by the trans relationship between the 3- and the 5-methyl groups. Thus, the EC forms are still favorable for compounds **II** and **III** even though they suffer from the dipole–dipole repulsion from the OCOLP fragment. In contrast, compound **I** suffers from all three unfavorable interactions when it assumes the EC form.

In addition to having a stable chair form with diaxial substituents, two forms of twist boat conformation were also found for compound **II**. Only one TB form was found for compounds **I** and **III**. The more stable TB form of **II** has a modest torsional strain energy (Tor = 4.8 kJ/mol,

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(13) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.*, **1985**, *50*, 4173.

(14) Bowen, J. P.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 1830.

(15) (a) Booth, H.; Everett, J. R. *J. Chem. Soc. Chem. Commun.* **1976**, 278. (b) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.*, **1966**, *31*, 894.

(16) Eliel, E. L.; Manoharan, M. *J. Org. Chem.*, **1981**, *46*, 1959.

(17) Bowen, J. P.; Pathiaseril, A.; Proferta, S.; Allinger, N. L. *J. Org. Chem.*, **1987**, *52*, 5162.

Table II. Origins of the Steric Energies (kJ/mol) for Compounds I–III[22]

compd	conform	rel E (kcal/mol)	stretch	VDW	bend	torsion	str-bend	imp-torsion	H-bond	electrostatic
I	EC	0.51	3.1	47.0	16.0	**23.8**	1.1	0.1	0.0	−93.6
I	TB	0.61	3.2	48.5	24.2	13.1	1.5	0.0	0.0	−92.7
I	AC	0.00	3.3	44.4	34.0	**6.3**	1.8	0.3	0.0	−94.7
II	EC	0.00	2.5	46.2	14.4	13.2	0.9	0.1	0.0	−93.4
II	TB	0.04	2.6	47.3	22.7	4.8	1.3	0.0	0.0	−94.7
II	AC	0.43	2.8	41.7	29.4	4.8	1.5	0.3	0.0	−94.7
II	TB(C1)	2.4	2.7	46.0	28.2	9.1	1.6	0.0	0.0	−93.8
III	EC	0.00	3.5	48.8	17.1	25.3	1.3	0.0	0.0	−94.1
III	TB	2.23	3.4	49.6	31.6	23.0	1.8	0.0	0.0	−93.5
III	AC	1.37	3.7	46.3	34.3	16.0	1.9	0.3	0.0	−94.9

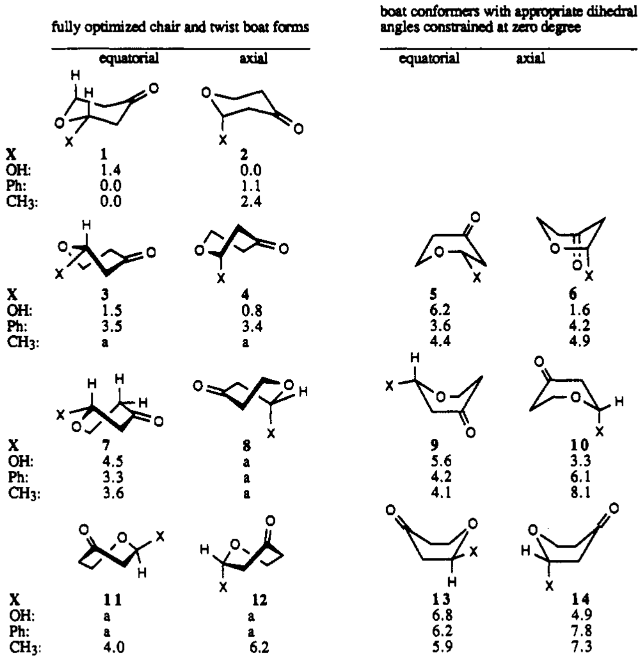

Figure 2. Relative MM2 energies (kcal/mol) of different conformations for 2-substituted THPNs (a = not a minimum).

Table II) which is as low as that of the corresponding AC form (4.8 kJ/mol). Its bending energy (22.7 kJ/mol) is higher than the EC form (14.4 kJ/mol) and lower than the AC form (29.4 kJ/mol). It is known that both 1,4-cyclohexadione and cyclohexane-1,4-dioxime exist solely as the twist-boat form.[18] The THPNs, **I–III**, do not have the same degree of preference for the twist-boat form. But this conformation does allow these 2,6-syn-disubstituted THPNs to have an axial methoxy group and an equatorial phenyl group, which appear to minimize the torsional strain and reduce the bending energy.

To further identify the effect of a single substituent on a 4-THPN, we have carried out MM2 calculations on three such compounds, each with a methyl, a hydroxyl, or a phenyl group at the β-position to the carbonyl. The schematic structures and the calculated energies are shown in Figure 2. All conformations are fully optimized with the exception of the boat forms, for which the appropriate dihedral angles were constrained to 0°. Due to the asymmetric carbon, three different boat forms are possible (see **5**, **9**, and **13**). Axial and equatorial orientations make a total of six boat forms (compare **5** and **6**; **9** and **10**; **13** and **14**). When these boat forms were freed of all the dihedral constraints, some of them become stable twist-boat forms. The structures in Figure 2 are so arranged so that the TB forms are on the left of the original boat forms. For example, TB forms, **3** and **4**, are originated from **5** and **6**, respectively.

Although, as expected, the 2-methyl and the 2-phenyl THPNs have a ground state conformation of the EC form, the most striking results are the relative stability of the AC (**2**) form for X = OH and Ph. The 2-hydroxyl-THPN (**2**, X = OH) prefers the axial orientation of the OH group by 1.4 kcal/mol and the twist boat conformation (**4**, X = OH) by 0.6 kcal/mol relative to the EC form. The 2-phenyl-THPN favors the equatorial form but only by 1.1 kcal/mol (compare **1** and **2**, X = Ph) while the 2-methyl-THPN favors the EC form by 2.4 kcal/mol (compare **1** and **2**, X = Me). The general trend is obvious not only for the chair forms but also for the boat and the twist-boat forms: the hydroxy group prefers the axial orientation and the methyl and the phenyl groups favor the equatorial position. A methyl group in general has a greater preference for the equatorial orientation than a phenyl group.

To help understand why a phenyl group does not cause as much strain as a methyl group in the axial orientation, the origins of the MM2 steric energies for the chair conformations (**1** and **2**) of the three substituted THPNs are listed in Table III. The axial 2-methyl-THPN has higher torsional and bending energy than its equatorial counterpart. The axial 2-phenyl-THPN has no excess torsional strain at all when compared to its equatorial form (**1**, X = Ph). It does have higher bending energy, indicating a distortion of the bond angles. However, the bond angle distortion allows the phenyl group to orient in such a way that the torsional strain is relieved and the total steric energy is reduced.

B. Ab Initio Study of the Conformations for THPN

Computational Methods. Ab initio calculations[19] were carried out by the GAUSSIAN 90 and 92 programs[20] implemented on the Cray Y-MP/8 supercomputer. All conformations were fully optimized with the STO-3G, the 3-21G, and the extended 6-31G* basis set, with the exception of the boat forms, for which the dihedral angle, C(O)CCO, was constrained to 0°. The barrier for interconversion of the conformers was studied by constraining the CC(O)CC torsional angles to 0°, (TSa and TSe). Harmonic frequencies were calculated for each conformer. The optimized structures other than the boat and the transition states for ring inversion have all positive

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(18) Kellie, G. M.; Riddell, F. G. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L. Eds., Wiley-Interscience: New York, 1974; Vol. 8, p 225.

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

(20) Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90, revision H*; Gaussian, Inc.: Pittsburgh, PA, 1990.

Table III. Origins of the Steric Energies (MM2, kJ/mol) for Conformations 1 and 2[22]

conformation	rel *E* (kcal/mol)	stretch	VDW	bend	torsion	str-bend	imp	H-bond	electrostatic
1, X = OH	1.4	0.9	25.5	8.2	**18.7**	0.5	0.1	0.0	−74.9
2, X = OH	0.0	0.8	24.6	15.0	**8.7**	0.7	0.2	0.0	−77.0
1, X = Ph	0.0	2.4	31.6	5.3	**13.0**	0.7	0.1	0.0	−13.3
2, X = Ph	1.1	2.6	31.9	10.4	**12.7**	0.9	0.1	0.0	−14.1
1, X = Me	0.0	1.6	20.1	5.4	13.0	0.7	0.1	0.0	−16.6
2, X = Me	2.4	1.7	19.9	10.0	18.3	0.9	0.1	0.0	−16.3

Table IV. Gaussian 90 Computed Energies

conformer	STO-3G//STO-3G au (kcal/mol)	3-21G//3-21G au (kcal/mol)	6-31G*//6-31G* au (kcal/mol)
1 (EC)	−413.2180248 (4.48)	−416.2454384 (3.44)	−418.5767289 (1.42)
2 (AC)	−413.2251632 (0.00)	−416.2509141 (0.00)	−418.5789945 (0.00)
3 (EB)	−413.214609 (6.62)	−416.2349549 (10.01)	−418.5607451 (11.45)[a]
4 (AB)	−413.2177717 (4.64)	−416.2427935 (5.10)	−418.5658694 (8.24)[a]
5 (TB)	−413.2208894 (2.68)	−416.2453278 (3.51)	−418.5746557 (2.72)
TSa	−413.2177967 (4.62)	−416.2417726 (5.74)	−418.5686934 (6.46)
TSe	−413.2164571 (5.46)	−416.236914 (8.79)	−418.5669724 (7.54)[a]

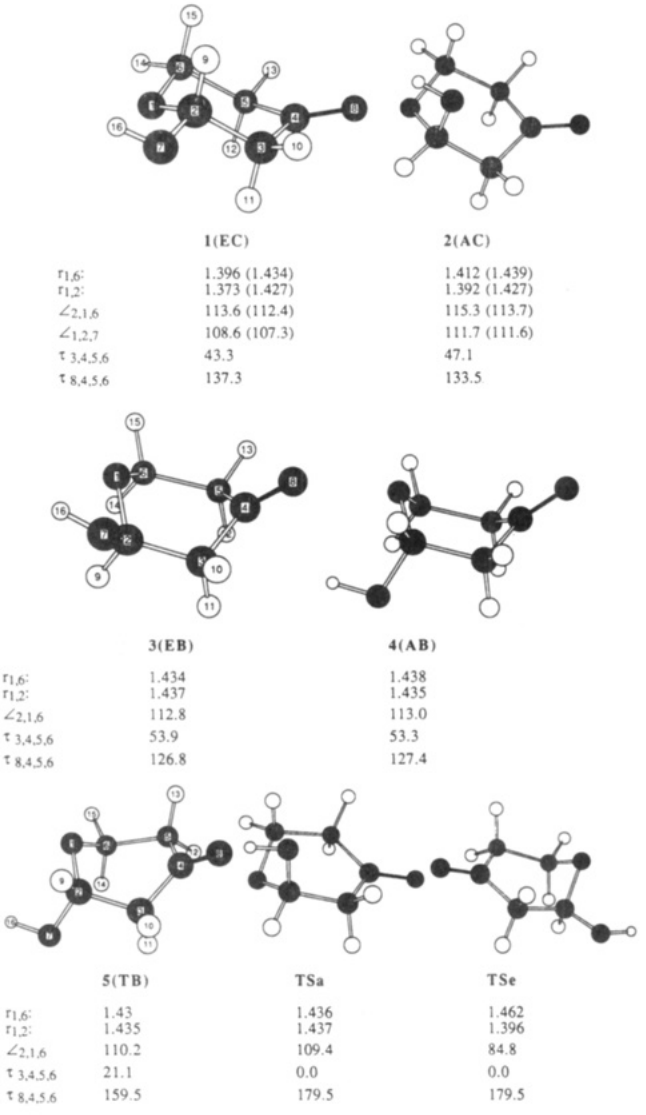
[a] Calculated at the 6-31G*//3-21G level of theory.

frequencies, which is an indication of true minima on the 6-31G* potential surface.

Results and Discussion

The total and relative energies of different conformations are listed in Table IV. The optimized structures and selected geometric data are listed in Figure 3. For each of these structures, three staggered rotamers about the dihedral angle, OC–OH, were initially optimized. The most stable conformation is shown here for each set of three calculations. In all of the ground state conformers, the dihedral angle OC–OH is either ca. 60° or ca. −60°. It appears that the minimization of the dipole–dipole interactions between the lone pairs on the ring oxygen and the lone pairs on the hydroxyl group is the origin for the preferred conformation. The calculated geometric data around the anomeric center for the THPN are in good agreement with the experimental data (X-ray structures) for the chair conformations of D-glycopyranoses.[11a] The ab initio calculations confirm the MM2 results. As expected, the chair conformation with an axially oriented hydroxyl group is more stable than that with an equatorial OH. The twist boat (**5**) form is only 1.3 kcal/mol higher in energy than the chair form with an equatorial OH (EC) at the 6-31G*//6-31G* level of theory. The flat conformations TSa and TSe were calculated to explore the barrier for ring inversion. The moderate inversion barrier (6.46 kcal/mol, 6-31G*//6-31G*), when compared to that for cyclohexane,[21] and the small energy difference between the conformers suggest a rapid equilibrium among the conformers at room temperature.

The calculation results for the 4-THPNs raise an interesting question about the conclusion drawn from the reduction of **I** with L-Selectride: was it 100% axial hydride delivery through the EC form,[1,5b] or was it 100% equatorial delivery through the AC conformer of **I**, Figure 4? As indicated in Figure 4, all three different conformations can provide the same reduction product. But the conclusion would be very different if the AC form is indeed more stable in solution. In which case, the products should arise from the normal equatorial approach, rather than the suggested axial approach.



	1(EC)	**2(AC)**
$r_{1,6}$:	1.396 (1.434)	1.412 (1.439)
$r_{1,2}$:	1.373 (1.427)	1.392 (1.427)
$\angle_{2,1,6}$	113.6 (112.4)	115.3 (113.7)
$\angle_{1,2,7}$	108.6 (107.3)	111.7 (111.6)
$\tau_{3,4,5,6}$	43.3	47.1
$\tau_{8,4,5,6}$	137.3	133.5

	3(EB)	**4(AB)**
$r_{1,6}$:	1.434	1.438
$r_{1,2}$:	1.437	1.435
$\angle_{2,1,6}$	112.8	113.0
$\tau_{3,4,5,6}$	53.9	53.3
$\tau_{8,4,5,6}$	126.8	127.4

	5(TB)	**TSa**	**TSe**
$r_{1,6}$:	1.43	1.436	1.462
$r_{1,2}$:	1.435	1.437	1.396
$\angle_{2,1,6}$	110.2	109.4	84.8
$\tau_{3,4,5,6}$	21.1	0.0	0.0
$\tau_{8,4,5,6}$	159.5	179.5	179.5

Figure 3. Optimized structures and selected geometric data for 2-hydroxyl-4-THPN (6-31G*). The values in parentheses are from crystallographic data for D-glycopyranoses.[11a]

From the reported ^{1}H NMR data for the reduction product from **II**, it appears that the twist-boat form was

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(21) Pickett, H. M.; Strauss, H. L. *J. Am. Chem. Soc.* **1970**, *92*, 7281, and references therein.

(22) As one referee pointed out, the force-field terms are far from reality. Caution should be excised not to over interpret the MM2 results. However, *ab initio* MO theory cannot handle effectively the large molecules at present time. In view of the continued success of molecular mechanics, it is justified to model the ground state conformations of these relatively large organic molecules with the empirical force field.

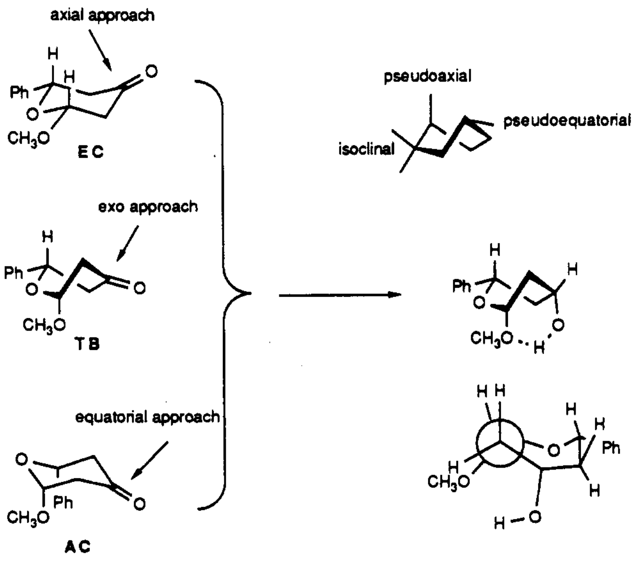

Figure 4. Three different conformations can provide the same π-facial selection; the Newman projection of the TB form of the product shows that the dihedral angles are consistent with the reported coupling constants.

predominant (δ 4.73 (dd, J = 12, 3 Hz, 1 H, H6); 4.95 (d, J = 3 Hz, 1 H, H2).[1] The coupling of 3 Hz for the anomeric proton (H2) is inconsistent with the chair form; but it is consistent with the twist-boat form (see the Newman projection in Figure 4). The current study suggests that the TB conformation is also one of the stable forms for 2-methoxy-4-THPNs, such as compounds **I–III**. A footnote in the original paper states "It is assumed that in each case, reduction is indeed occurring through the ground state conformation. While the strong conformational definition of the systems would tend to support this formulation, it is not proven".[1] We were not able to find definite ^{1}H NMR data given in the reference to support a chair form with equatorial phenyl group. Our study shows that the ground state conformation of the THPNs is not very well defined; the conformation of a 4-*tert*-butylcyclohexanone is locked, but the conformation of a THPN is not fixed by a 2-phenyl group. Since the ground-state conformational preferences of the 4-THPNs are relatively small and the barrier for ring inversion is low, the results from the reduction of the THPNs, in our opinion, do not serve as solid evidence to support the Cieplak theory.

In conclusion, MM2 calculations show that the *syn*-(2-methoxy-6-phenyl)-*anti*-(5-methyl)-THPN (**I**) prefers the conformation in which the phenyl group and the methoxy group are axially oriented. The 4-THPN ring can distort at little energy cost to allow the phenyl and methoxy groups to bend outward and reduce the 1,3-diaxial interaction in the AC form. The α-methyl group in a 4-THPN ring favors the equatorial orientation to a greater extent than it would in a cyclohexane system because of the α-alkyl ketone effect.[17] Both MM2 and ab initio calculations show that the 2-hydroxyl group in a 4-THPN favors the axial orientation by ~1.4 kcal/mol. The conformational inversion barrier in a 2-hydroxyl-4-THPN is relatively small (6.4 kcal/mol) according to calculations at the 6-31G* level. Although it does not disprove the suggested transition structure, this study supports the notion that the reductions of 4-THPNs by L-selectride occur through the normal equatorial attack. Steric approach holds true for bulky hydrides even in these 4-THPNs, but their conformational flexibility leads to seemingly abnormal results. It should be stressed that the conclusion of this study does not negate the excellent contributions made by Danishefsky and Langer in tetrahydropyran chemistry. Neither does this study attempt to disprove the Cieplak hypothesis. Experiments designed to test the importance of this model are currently taking place in our laboratories, and the results will be reported in due course.

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Supplementary Material Available: The MM2 Cartesian coordinates for compounds **I–III** and conformations **1–10**, and the Z-matrix for conformations **1–5** (6-31G*) and TSa and TSe (12 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.