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Intrinsic Conformational Preferences of Substituted Cyclohexanes and Tetrahydropyrans Evaluated at the CCSD(T) Complete Basis Set Limit: Implications for the Anomeric Effect

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A series of MP2 and CCSD(T) computations have been carried out with correlation consistent basis sets as large as aug-cc-pV5Z to determine the intrinsic equatorial-axial conformational preference of CH_3-, F-, OCH_3-, and OH-substituted cyclohexane and tetrahydropyran rings. The high-accuracy relative electronic energies reported here shed new light on the intrinsic energetics of these cyclic prototypes for the anomeric effect. At the CCSD(T) complete basis set (CBS) limit, the energy of the equatorial conformation relative to the axial position ($\Delta E_{\mathrm{CCSD(T)}}^{\mathrm{CBS}}$) is −1.75, −0.20, −0.21, and −0.56 kcal mol^{-1} in methyl-, fluoro-, methoxy-, and hydroxycyclohexane, respectively, while $\Delta E_{\mathrm{CCSD(T)}}^{\mathrm{CBS}}$ is −2.83, +2.45, +1.27, and +0.86 kcal mol^{-1} for 2-methyl-, 2-fluoro-, 2-methoxy-, and 2-hydroxytetrahydropyran, respectively. Note that the equatorial and axial conformers are nearly electronically isoenergetic in both fluoro- and methoxycyclohexane. For all eight cyclic species, a zero-point vibrational energy correction decreases $\Delta E_{\mathrm{CCSD(T)}}^{\mathrm{CBS}}$ by a few tenths of a kilocalorie per mole. Relative energies obtained with popular methods and basis sets are unreliable, including Hartree−Fock theory, the B3LYP density functional, and the 6-31G and 6-311G families of split-valence basis sets. Even with the massive pentuple-ζ basis sets, the HF and B3LYP methods substantially overestimate the stability of the equatorial conformers (by as much as 0.99 and 0.73 kcal mol^{-1}, respectively, for 2-methoxytetrahydropyran). Only because of a consistent cancellation of errors do these popular approaches sometimes provide reasonable estimates of the anomeric effect.

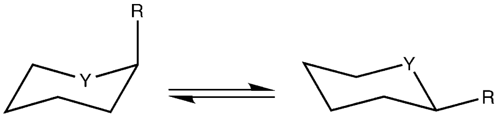
1. Introduction

The anomeric effect[1−4] plays an important role in determining the conformational preferences of a variety of complex biochemical systems including carbohydrates,[1,5] nucleic acids (DNA and RNA),[6] and a large number of natural products that possess oxaspirocyclic backbones.[7−9] It can even control product distribution in chemical reactions.[10] Cyclohexane and tetrahydropyran rings containing simple, electronegative substituents (examples of which are shown in Figure 1) provide a paradigm for the anomeric effect. In cyclohexane, substituents such as CH_3, F, OCH_3, and OH (denoted by 1c−4c, respectively) are expected to adopt an equatorial (nc_{eq}) rather than axial (nc_{ax}) orientation. In heterocycles such as tetrahydropyran (THP), however, stereoelectronic effects can actually induce a preference for the axial position.[11] This phenomenon is known as the anomeric effect, and it generally manifests itself as the propensity of an electronegative substituent at the C(2) position in THP (C(1) position in aldose sugar notation) to assume the axial (no_{ax}) rather than the equatorial (no_{eq}) orientation.[1−4,12] Note that the numbers 1o−4o are used to denote that a particular substituent has been placed at the C(2) position of THP rather than on a cyclohexane ring.

With the notation adopted in Figure 1, the anomeric effect can be quantified in a fairly compact manner. Commonly, this is done by comparing the equatorial-axial free energy difference of the C(2)-substituted THP, $\Delta G(no_{\mathrm{eq}} - no_{\mathrm{ax}})$, to that of the corresponding cyclohexane, $\Delta G(nc_{\mathrm{eq}} - nc_{\mathrm{ax}})$.

$$\Delta\Delta G = \Delta G(no_{\mathrm{eq}} - no_{\mathrm{ax}}) - \Delta G(nc_{\mathrm{eq}} - nc_{\mathrm{ax}}) \tag{1}$$

The last term in eq 1 is simply the negative of the *A*-value for a particular substituent on cyclohexane ($\Delta G(nc_{\mathrm{ax}} - nc_{\mathrm{eq}})$ = *A*-value). Positive ΔG values indicate the axial conformer is more stable than its equatorial counterpart, and $\Delta\Delta G > 0$ indicates that the axial conformer is favored more strongly in THP than in cyclohexane. To avoid entropic contributions, it has also become common to define the enthalpic anomeric effect by an analogous expression involving enthalpy differences.



1 R = CH_3
2 R = F
3 R = OCH_3
4 R = OH

Figure 1. Axial and equatorial orientations of several substituted cyclohexane (Y = CH_2) and tetrahydropyran (Y = O) rings. In the text, the numbers 1c−4c are used to denote the former while the numbers 1o−4o denote the latter.

$$\Delta\Delta H = \Delta H(no_{\mathrm{eq}} - no_{\mathrm{ax}}) - \Delta H(nc_{\mathrm{eq}} - nc_{\mathrm{ax}}) \tag{2}$$

Many experiments have been performed to determine these thermodynamic parameters for the compounds in Figure 1.[13−22] (See refs 4 and 23 for additional experimental papers.) However, the equatorial-axial equilibria in cyclohexane and THP are sensitive to the environment. Consequently, those corresponding to thermodynamic quantities in eqs 1 and 2 vary widely with the nature of the solvent (e.g., dielectric constant and capacity for hydrogen bonding). The axial preference of electronegative C(2) substituents in THP (and therefore the magnitude of the anomeric effect) is significantly attenuated as solvent polarity increases. ΔH of 4,6-dimethyl-2-methoxytetrahydropyran, a

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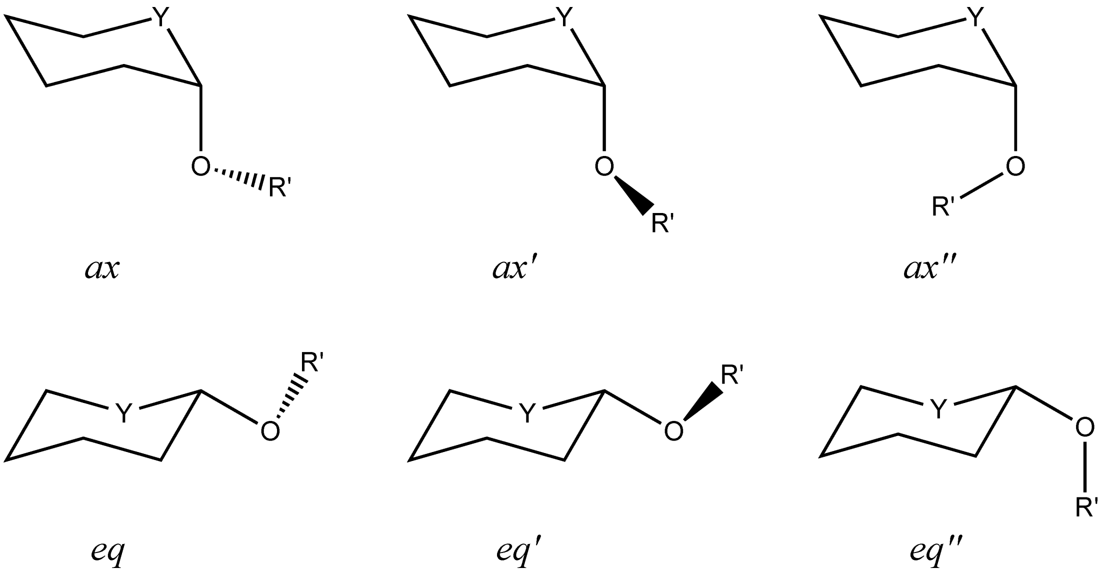

Figure 2. Rotamers of the methoxy ($R' = CH_3$) and hydroxy ($R' = H$) substituents. Note that for cyclohexane ($Y = CH_2$), *ax* and *ax*′ are merely mirror images of each other, as are *eq* and *eq*′.

compound closely related to 3o, can even change sign in highly polar solvents that can form strong hydrogen bonds.[24] Reference 4 provides an excellent review of this topic through 1994.

To fully understand this important and widely studied stereoelectronic effect, it is necessary to distinguish the intrinsic energetics of these systems from solvent, thermal, and entropic effects.[25] This approach has provided much insight into other important chemical phenomena, such as S_N2 reactions, that are highly sensitive to environmental effects.[26−28] Unlike bimolecular substitution reactions, however, there is a paucity of reliable gas-phase energetics for the eight compounds in Figure 1.[19,29−35] One particularly vexing experimental obstacle is that the extinction coefficients of the axial and equatorial conformers of these cyclic prototypes are not necessarily identical,[19,31] an assumption commonly employed when using gas-phase spectra to predict relative energies. Fortunately, electronic structure theory can provide direct insight into the intrinsic energetics of the anomeric effect. The intrinsic magnitude of the anomeric effect (*AE*) can be defined in terms of electronic energy differences (ΔE) between the equatorial and axial conformations of a C(2)-substituted THP and the corresponding cyclohexane.[23]

$$AE = \Delta\Delta E = \Delta E(no_{eq} - no_{ax}) - \Delta E(nc_{eq} - nc_{ax}) \quad (3)$$

Electronic structure calculations can also be used to probe the origin of the anomeric effect through natural bond orbital analysis.[23,25,36−38] However, this work focuses on the reliable characterization of ΔE and $\Delta\Delta E$ for the cyclic prototypes of the anomeric effect shown in Figure 1.

Numerous computational studies have been carried out to determine the relative energies of the equatorial and axial conformers of compounds 1c−4c and 1o−4o.[21,23,39−49] However, only the study by Salzner and Schleyer appears to have combined these electronic energy differences from the same level of theory to directly quantify the anomeric effect via eq 3 for these important cyclic prototypes.[23] A survey of these works and of other computational investigations of closely related systems[5,50,51] reveals rather erratic results. Even for methylcyclohexane, the quantity $\Delta E(1o_{eq} - 1o_{ax})$ can change by more than 0.5 kcal mol^{-1} when a different method or different basis set is used.[21] For fluorocyclohexane (2c)[23,47] and hydroxycyclohexane (4c),[45] the preference for the equatorial versus the axial conformation (i.e., the sign of $\Delta E(nc_{eq} - nc_{ax})$) can actually change with the level of theory. The trends observed in these studies have led to various prescriptions as to which combination of method and basis set provides the best description of the anomeric effect, many of which rely on the cancellation of errors. Definitive values of the intrinsic magnitude of this stereoelectronic effect ($\Delta\Delta E$) and of the equatorial-axial relative energies (ΔE) in these systems are still conspicuously absent.

To better understand the anomeric effect, it is imperative that its intrinsic magnitude be reliably characterized for these important model systems. The present study provides this information by using basis sets and electronic structure techniques with well-established convergence properties to compute the equatorial-axial energy differences in eq 3. Accurate ab initio data of this type can also be used to develop and validate new force fields and semiempirical methods[52−55] so that more realistic in silico simulations can be carried out on large systems in which the anomeric effect plays a crucial role (e.g., carbohydrates, DNA, RNA).

2. Computational Details

The axial and equatorial conformers of all eight species in Figure 1 were optimized with three popular electronic structure techniques (self-consistent field spin-restricted Hartree−Fock theory (RHF),[56] the B3LYP density functional,[57,58] and second-order Møller−Plesset perturbation theory (MP2)[59]) in conjunction with four different split-valence double- and triple-ζ basis sets: 6-31G(*d*), 6-31++G(*d*), 6-311++G(*d*), and 6-311G-(2*df*,2*pd*).[60] All structures were fully optimized without constraint, including the OH and OCH_3 rotamers shown in Figure 2. Methyl- and fluorocyclohexane (1c and 2c) have C_s symmetry as do the *ax*″ rotamers of methoxycyclohexane (3c) and hydroxycyclohexane (4c) (i.e., $\tau(R'OCH) = 180.0°$). All other compounds belong to the C_1 point group. Although all three rotamers are unique, two rotamers are related by symmetry. Methoxy- and hydroxycyclohexane only have two distinct axial rotamers since *ax* and *ax*′ are merely mirror images of each other. The same holds for the equatorial rotamers (*eq* and *eq*′).

Analytical gradient techniques were used for all geometry optimizations. Harmonic vibrational frequencies were computed using analytical second derivatives for RHF and B3LYP methods with all four split-valence basis sets to ensure that each stationary point was a minimum on the potential energy surface.

For the MP2 method, it was only feasible to compute frequencies with the 6-31G(*d*) basis set.

In addition, RHF, B3LYP, MP2, and CCSD(T) single point energies were computed with Dunning's correlation consistent basis sets: cc-pV*X* Z for H and C and aug-cc-pV*X* Z for O and F (where $X = \mathrm{D}-5$).[61,62] Henceforth, these basis sets will be denoted as aDZ, aTZ, aQZ, and a5Z. B3LYP single point energies were carried out using the B3LYP/6-311G(2*df*,2*pd*) optimized structures [i.e., B3LYP/a*X*Z//B3LYP/6-311G(2*df*,2*pd*)]. All other single point energies (CCSD(T), MP2, and RHF) were obtained with structures from MP2/6-311G(2*df*,2*pd*) optimizations [i.e., CCSD(T)/a*X* Z//MP2/6-311G(2*df*,2*pd*), MP2/a*X*Z//MP2/6-311G(2*df*,2*pd*), and RHF/a*X*Z//MP2/6-311G(2*df*,2*pd*)].

All calculations used spherical harmonic 5*d*, 7*f*, 9*g*, and 11*h* functions rather than their 6*d*, 10*f*, 15*g*, and 21*h* Cartesian counterparts. Electronic energies were converged to at least 1×10^{-7} E_h and Cartesian gradients to 1×10^{-5} E_h bohr^{-1}. The frozen core approximation was used in all MP2 and CCSD(T) calculations. RHF and B3LYP computations were carried out with Gaussian98.[63] MP2 optimizations as well as the RHF, B3LYP, and MP2 single point energies were computed with MPQC.[64−68] CCSD(T) single point energies were computed using PSI3[69] and NWChem.[70,71]

Reliable estimates of the one-particle complete basis set (CBS) limits of the RHF, B3LYP, and MP2 electronic energies were obtained by taking advantage of the systematic nature of the correlation consistent basis sets. The RHF CBS limit was determined by fitting the total RHF electronic energies to a three-parameter function for $X = 3, 4, 5$ where X is the cardinal number of the basis sets.[72,73]

$$E_{\mathrm{RHF}}^{\mathrm{a}X\mathrm{Z}} = E_{\mathrm{RHF}}^{\mathrm{CBS}} + a \exp(-bX) \tag{4}$$

The MP2 CBS limit was determined from a simplified version of Helgaker's two-point extrapolation[74] where only the two most accurate data points are used ($X = 4, 5$).

$$E_{\mathrm{MP2}}^{\mathrm{CBS}} = \frac{125E_{\mathrm{MP2}}^{\mathrm{a5Z}} - 64E_{\mathrm{MP2}}^{\mathrm{aQZ}}}{61} \tag{5}$$

No extrapolation was performed for the B3LYP energies since the relative energies computed with this density functional exhibit very little basis set dependence. The electronic energies computed with the a5Z basis set were used as the CBS limit.

The *n*-particle limit was probed by examining the difference between the MP2 and CCSD(T) relative energies.

$$\delta E_{\mathrm{CCSD(T)}}^{\mathrm{a}X\mathrm{Z}} = \Delta E_{\mathrm{CCSD(T)}}^{\mathrm{a}X\mathrm{Z}} - \Delta E_{\mathrm{MP2}}^{\mathrm{a}X\mathrm{Z}} \tag{6}$$

Although the correlation energy may converge rather slowly with respect to the cardinal number of the correlation consistent basis sets (X), this difference ($\delta E_{\mathrm{CCSD(T)}}^{\mathrm{a}X\mathrm{Z}}$) tends to converge rather quickly.[75−77] Thus, the CCSD(T) CBS limit can be reliably estimated by combining the MP2 CBS limit with the $\delta E_{\mathrm{CCSD(T)}}^{\mathrm{a}X\mathrm{Z}}$ values obtained with relatively small basis sets (e.g., for $X = 2$ or 3).

$$\Delta E_{\mathrm{CCSD(T)}}^{\mathrm{CBS}} = \Delta E_{\mathrm{MP2}}^{\mathrm{CBS}} + \delta E_{\mathrm{CCSD(T)}}^{\mathrm{aTZ}} \tag{7}$$

The CCSD(T) computations with the aTZ basis set were only feasible for structures with a plane of symmetry (1c and 2c). Consequently, a modified aTZ basis set was utilized to compute $\delta E_{\mathrm{CCSD(T)}}^{\mathrm{aTZ}}$; the *d*-functions were removed from H and the *f*-functions from C, O, and F. The values for $\delta E_{\mathrm{CCSD(T)}}$ obtained with this modified basis set for structures and differ from the unmodified basis set by no more than 0.01 kcal mol^{-1}.

TABLE 1: Relative Electronic Energies of the Axial and Equatorial Rotamers of Compounds 3c, 4c, 3o, and 4o[a]

rotamer	RHF	B3LYP	MP2	RHF	B3LYP	MP2
	(3o) 2-methoxytetrahydropyran			(4o) 2-hydroxytetrahydropyran		
ax	0.00	0.00	0.00	0.00	0.00	0.00
ax′	3.67	3.68	4.12	3.51	3.56	3.66
ax″	10.29	9.14	10.18	3.62	3.02	3.06
eq	0.00	0.00	0.00	0.00	0.00	0.00
eq′	4.39	4.32	4.50	4.20	4.12	4.16
eq″	3.10	2.93	2.68	0.73	0.00	0.75
	(3c) methoxycyclohexane			(4c) hydroxycyclohexane		
ax	0.00	0.00	0.00	0.00	0.00	0.00
ax″	7.77	6.83	7.57	1.28	0.86	0.94
eq	0.00	0.00	0.00	0.00	0.00	0.00
eq″	2.87	2.51	2.19	0.26	0.08	0.17

[a] All values are in kcal mol^{-1} and have been computed with the 6-311G(2*df*, 2*pd*) basis set.

It is worth noting that relatively small basis sets used in conjunction with correlated methods may not provide reliable energetics for systems similar to those examined here,[78] but they do reliably describe changes between the MP2 and CCSD(T) methods. This additive progression to the *n*-particle limit lies at the heart of several high-accuracy model chemistries (e.g., the G*X* methods of Pople and co-workers,[79−81] the complete basis set (CBS) approaches of Petersson and co-workers,[82−87] Martin's Weizmann-models (W1 and W2),[88] and the focal point analysis developed by Allen et al.[89−91]).

3. Results and Discussion

3.1. Relative Energies (Δ*E*). The relative energies of the methoxy and hydroxy rotamers displayed in Figure 2 are reported in Table 1. The RHF, B3LYP, and MP2 methods indicate that the *ax* rotamer is more stable than either *ax′* or *ax″*. The same holds for the *eq* rotamer relative to its *eq′* or *eq″* counterparts. With the B3LYP functional, however, the energetic separation of the *eq* and *eq″* rotamers is rather small for the OH substituent. Overall, these results are consistent with other ab initio computations[23,40,42,44,45] and experimental observations.[4] Consequently, these lowest energy OH and $\mathrm{OCH_3}$ rotamers (*ax* and *eq*) have been used for determination of the electronic energy differences (Δ*E*) reported in Tables 2−4.

As mentioned in the Introduction, the equatorial-axial relative electronic energies (Δ*E*) reported in the literature for compounds 1c−4c and 1o−4o vary widely as the method and basis change. To illustrate this erratic behavior, Δ*E* has been computed for these cyclic species with three popular methods and four common split-valence basis sets. Table 2 contains the relative energies obtained for all 12 combinations of method and basis set. Even for a simple substituent like $\mathrm{CH_3}$, the magnitude of Δ*E* changes by more than 0.6 kcal mol^{-1} as the different model chemistries are applied to 1c and 1o. The deviations grow as large as 0.8 kcal mol^{-1} for the fluorinated compounds and actually exceed 1.0 kcal mol^{-1} for the $\mathrm{OCH_3}$ and OH substituents. Δ*E* actually changes sign for three of the substituted cyclohexanes. The relative energies for compounds 2c, 3c, and 4c are so inconsistent that it is not even possible to predict which conformer (equatorial or axial) is intrinsically more stable. These equatorial-axial energy differences (Δ*E*) are clearly difficult electronic structure problems, and the erratic results in Table 2 highlight the need for a computational study that systematically improves both the basis set and the treatment of electron correlation.

TABLE 2: Relative Electronic Energies (ΔE) of the Equatorial Conformers with Respect to Their Axial Counterparts Can Change Substantially as Method and Basis Set Are Varied for Substituted Cyclohexanes and Tetrahydropyrans (Compounds 1c−4c and 1o−4o, Respectively)[a]

basis set	ΔE_{RHF}	$\Delta E_{\mathrm{B3LYP}}$	ΔE_{MP2}	ΔE_{RHF}	$\Delta E_{\mathrm{B3LYP}}$	ΔE_{MP2}
	(1c) methylcyclohexane			(1o) 2-methyltetrahydropyran		
6-31G(*d*)	−2.31	−2.13	−1.90	−3.33	−3.09	−3.11
6-31++G(*d*)	−2.36	−2.27	−2.09	−3.45	−3.33	−3.27
6-311++G(*d*)	−2.43	−2.19	−1.82	−3.53	−3.34	−3.15
6-311G(2*df*,2*pd*)	−2.38	−2.16	−1.68	−3.45	−3.29	−2.91
	(2c) fluorocyclohexane			(2o) 2-fluorotetrahydropyran		
6-31G(*d*)	+0.19	+0.18	+0.59	+2.96	+2.85	+3.40
6-31++G(*d*)	−0.12	−0.25	+0.01	+2.86	+2.96	+3.38
6-311++G(*d*)	−0.16	−0.20	−0.13	+2.65	+2.90	+2.89
6-311G(2*df*,2*pd*)	+0.03	+0.21	+0.28	+2.54	+2.82	+2.85
	(3c) methoxycyclohexane			(3o) 2-methoxytetrahydropyran		
6-31G(*d*)	−0.27	−0.27	+0.57	+1.38	+1.18	+2.12
6-31++G(*d*)	−0.57	−0.70	+0.04	+1.07	+0.80	+1.82
6-311++G(*d*)	−0.60	−0.61	+0.12	+0.93	+0.78	+1.59
6-311G(2*df*,2*pd*)	−0.35	−0.20	+0.59	+0.99	+0.99	+1.82
	(4c) hydroxycyclohexane			(4o) 2-hydroxytetrahydropyran		
6-31G(*d*)	−0.31	−0.40	+0.21	+1.22	+1.15	+1.79
6-31++G(*d*)	−0.62	−0.85	−0.38	+0.90	+0.76	+1.33
6-311++G(*d*)	−0.64	−0.80	−0.38	+0.80	+0.75	+1.19
6-311G(2*df*,2*pd*)	−0.40	−0.33	+0.14	+0.93	+1.07	+1.52

[a] All values are in kcal mol^{-1}.

Table 3 contains a similar set of RHF, B3LYP, and MP2 relative energies. However, these values have been computed with the a*XZ* family of correlation consistent basis sets. ΔE converges very rapidly as the cardinal number of the basis increases. For a particular method, the relative energies computed with the aQZ and a5Z basis sets never differ by more than 0.03 kcal mol^{-1}. Even the RHF, B3LYP, and MP2 calculations with the aTZ basis provide relative energies within 0.15 kcal mol^{-1} of the corresponding CBS limit. In stark contrast, however, is the aDZ basis set, which is generally inadequate and can even predict the wrong sign for ΔE_{MP2} for 2c and 3c.

Also included in Table 3 are the differences between the MP2 and CCSD(T) relative energies as defined by eq 6. As expected, the quantity $\delta E_{\mathrm{CCSD(T)}}$ shows very little basis set dependence. The aDZ and aTZ values lie within 0.02 kcal mol^{-1} of each other for all eight compounds. The magnitude of $\delta E_{\mathrm{CCSD(T)}}$ also tends to be quite small. In most cases, the MP2 relative energies are well within 0.1 kcal mol^{-1} of the CCSD(T) values computed with the same basis set. The difference between the two methods approaches but does not exceed 0.2 kcal mol^{-1} for methoxycyclohexane (3c). These results suggest that MP2 adequately recovers the contribution to ΔE from electron correlation. Only for the OCH_3 substituent do higher-order correlation effects contribute more than 0.1 kcal mol^{-1} to the relative energies.

The CCSD(T) CBS limit of the relative energies ($\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ in Table 4) have been determined via eq 7 by combining the MP2 and CCSD(T) results from Table 3. As expected, the equatorial conformation is more stable ($\Delta E < 0$) for compounds 1c−4c and 1o, while the anomeric effect induces an axial preference ($\Delta E > 0$) in 2o, 3o, and 4o. However, the magnitude of ΔE at the CCSD(T) CBS limit suggests that the intrinsic

TABLE 4: Comparison of Theoretical and Available Experimental Energetics[a]

	$\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$	$\Delta E^{\circ\,\mathrm{CBS}}_{\mathrm{CCSD(T)}}$	ΔE°[b]	ΔG[c]	ΔH[d]
1c	−1.75	−1.98 ± 0.05		−1.80 to −1.74	−1.92 to −1.75
2c	−0.20	−0.28 ± 0.04	−0.26	−0.50 to −0.10	−0.47 to −0.22
3c	−0.21	−0.38 ± 0.06		−0.75 to −0.40	−0.71
4c	−0.56	−0.68 ± 0.03	−0.59	−1.5 to −0.30	−1.24
1o	−2.83	−3.04 ± 0.01		−2.86	
2o	+2.45	+2.21 ± 0.03			
3o	+1.27	+1.01 ± 0.02		+0.48 to +0.78	+0.03 to +0.61
4o	+0.86	+0.50 ± 0.02		+0.12 to +0.75	−0.63

[a] All data are in kcal mol^{-1}. [b] References 33 and 34. [c] References 14−17, 19−21, and 23. [d] References 13 and 18−23.

TABLE 3: Relative Electronic Energies (ΔE) of the Equatorial Conformers with Respect to Their Axial Counterparts Computed with the a*XZ* Basis Sets[a]

	ΔE_{RHF}	$\Delta E_{\mathrm{B3LYP}}$	ΔE_{MP2}	$\delta E_{\mathrm{CCSD(T)}}$	ΔE_{RHF}	$\Delta E_{\mathrm{B3LYP}}$	ΔE_{MP2}	$\delta E_{\mathrm{CCSD(T)}}$
		(1c) methylcyclohexane				(1o) 2-methyltetrahydropyran		
aDZ	−2.58	−2.34	−1.79	−0.04	−3.60	−3.33	−3.13	+0.06
aTZ	−2.60	−2.30	−1.70	−0.02	−3.64	−3.27	−2.92	+0.08
aQZ	−2.62	−2.30	−1.73		−3.65	−3.29	−2.91	
a5Z	−2.62	−2.31	−1.73		−3.66	−3.30	−2.91	
CBS	−2.62	[−2.31]	−1.73	[−0.02]	−3.66	[−3.30]	−2.90	[+0.8]
		(2c) fluorocyclohexane				(2o) 2-fluorotetrahydropyran		
aDZ	−0.12	−0.18	+0.27	+0.02	+2.62	+2.82	+3.13	+0.05
aTZ	−0.38	−0.35	−0.10	+0.03	+2.17	+2.53	+2.59	+0.00
aQZ	−0.42	−0.35	−0.17		+2.10	+2.47	+2.51	
a5Z	−0.43	−0.37	−0.20		+2.08	+2.44	+2.48	
CBS	−0.44	[−0.37]	−0.23	[+0.03]	+2.07	[+2.44]	+2.45	[+0.00]
		(3c) methoxycyclohexane				(3o) 2-methoxytetrahydropyran		
aDZ	−0.93	−0.65	+0.40	−0.17	+0.65	+0.79	+1.80	−0.09
aTZ	−1.12	−0.75	+0.12	−0.18	+0.35	+0.60	+1.51	−0.10
aQZ	−1.17	−0.74	+0.01		+0.29	+0.55	+1.40	
a5Z	−1.17	−0.75	−0.01		+0.28	+0.54	+1.39	
CBS	−1.18	[−0.75]	−0.03	[−0.18]	+0.28	[+0.54]	+1.37	[−0.10]
		(4c) hydroxycyclohexane				(4o) 2-hydroxytetrahydropyran		
aDZ	−0.81	−0.84	−0.08	−0.04	+0.54	+0.62	+1.32	−0.00
aTZ	−1.01	−0.92	−0.38	−0.04	+0.31	+0.51	+1.03	−0.02
aQZ	−1.04	−0.91	−0.49		+0.26	+0.48	+0.92	
a5Z	−1.04	−0.92	−0.50		+0.26	+0.46	+0.90	
CBS	−1.05	[−0.92]	−0.52	[−0.04]	+0.25	[+0.46]	+0.88	[−0.02]

[a] For the smaller basis sets, the deviations between the MP2 and CCSD(T) values ($\delta E_{\mathrm{CCSD(T)}}$) are also reported. CBS values in square brackets are assumed. (See eq 7 and surrounding text.) All data are in kcal mol^{-1}.

energetics for most of these cyclic prototypes are significantly different than previous studies would suggest. For example, the equatorial and axial conformers are nearly electronically isoenergetic in both fluorocyclohexane (2c) and methoxycyclohexane (3c) ($\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}} = -0.20$ and -0.21 kcal mol^{-1}, respectively).

The benchmark relative energies indicate that the RHF and B3LYP methods cannot provide accurate relative energies for most of these systems. The RHF and B3LYP CBS limits reported in Table 3 are quite different than $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ in Table 4. Even with the massive a5Z basis sets, the RHF and B3LYP methods have a tendency to substantially overestimate the stability of the equatorial conformers relative to their axial counterparts. In other words, for the CH_3, OCH_3, and OH substituents, $\Delta E^{\mathrm{a5Z}}_{\mathrm{RHF}}$ and $\Delta E^{\mathrm{a5Z}}_{\mathrm{B3LYP}}$ are significantly more negative than $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ (by an average of roughly 0.7 kcal mol^{-1} for RHF and 0.4 kcal mol^{-1} for B3LYP).

Despite the erratic relative energies obtained with the split valence basis sets (Table 2), the zero-point vibrational energy (ZPVE) corrections to ΔE from the unscaled harmonic vibrational frequencies are remarkably consistent. As can be seen from the data in Table 4, these ZPVE corrections increase the stability of the equatorial conformers relative to their axial counterparts by a few tenths of kcal mol^{-1}. In other words, the ZPVE corrected energy difference (ΔE°) is more negative than ΔE for all eight cyclic compounds. The ZPVE corrected CCSD(T) CBS limits ($\Delta E^{\circ\mathrm{CBS}}_{\mathrm{CCSD(T)}}$) in Table 4 are reported as the average ZPVE corrected energy difference plus or minus the maximum deviation of the ZPVE corrections from the average. A table of the ZPVE corrections can be found in the Supporting Information.

It is particularly interesting to note that the equatorial and axial conformations of methoxycyclohexane (3c) are electronically isoenergetic at the MP2 CBS limit (Table 3). Only after considering higher-order correlation effects at the CCSD(T) level does the equatorial conformation of 3c become more stable (0.21 kcal mol^{-1}) than its axial counterpart. The equatorial and axial configurations of fluorocyclohexane (2c) are also nearly isoenergetic. At the CCSD(T) CBS limit, they are only separated by 0.20 kcal mol^{-1}. Inclusion of the zero-point vibrational energy slightly increases the energetic separation in both. $\Delta E^{\circ\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ is -0.28 ± 0.04 for 2c and -0.38 ± 0.06 for 3c.

3.2. Comparison to Experiment. *Gas-Phase Energetics.* The CCSD(T) CBS limits reported here are in very good agreement with the available gas-phase relative energies (ΔE° in Table 4). The relative intensities of rotational transitions in the microwave spectrum of fluorocyclohexane (2c)[34] have been used to determine an equatorial-axial energy difference of 0.26 kcal mol^{-1}, while for hydroxycyclohexane (4c)[33] a value of 0.59 kcal mol^{-1} was determined from IR intensities. In both cases, the calculated $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ is in spectacular agreement with the experimental value. For 2c, the CCSD(T) CBS limit ranges from -0.20 kcal mol^{-1} (no ZPVE correction) to -0.32 kcal mol^{-1} when the largest ZPVE correction is included. For 4c, $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}} = -0.56$ kcal mol^{-1} is almost identical to the experimental energy difference. The ZPVE correction makes ΔE slightly more negative, but the computed energy difference still lies within ~0.1 kcal mol^{-1} of the experimental value.

Despite the excellent agreement between the relative energies evaluated at the CCSD(T) CBS limit and those obtained experimentally in the gas phase, certain caveats should be kept in mind. For example, the computed relative energies for the methoxy and hydroxy compounds do not account for statistical sampling of other rotamers. Also, the IR intensities from the frequency calculations indicate that the vibrational modes of the axial and equatorial conformers tend to have very different IR intensities which strongly supports concerns that have been expressed regarding the inequality of extinction coefficients for the two isomers as mentioned in the Introduction.[19,31]

TABLE 5: Magnitude of the Anomeric Effect ($\Delta\Delta E$) in Four Cyclic Prototypes Evaluated at RHF, B3LYP, MP2, and CCSD(T) CBS Limits[a]

substituent	$\Delta\Delta E^{\mathrm{CBS}}_{\mathrm{RHF}}$	$\Delta\Delta E^{\mathrm{CBS}}_{\mathrm{B3LYP}}$	$\Delta\Delta E^{\mathrm{CBS}}_{\mathrm{MP2}}$	$\Delta\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$
CH_3	−1.04	−0.99	−1.17	−1.08
F	+2.52	+2.81	+2.67	+2.65
OCH_3	+1.45	+1.28	+1.40	+1.48
OH	+1.30	+1.38	+1.40	+1.42

[a] All data are in kcal mol^{-1}.

Thermodynamic Parameters. Many experimental free energy differences and enthalpy differences are available for these systems from temperature-dependent NMR studies in the neat liquid and a variety of solvents. 2-Fluorotetrahydropyran (2o) is the only compound for which no experimental data is available. Although the computed electronic energy differences certainly cannot be compared to the experimental ΔG's and ΔH's listed in Table 4, some trends are worth discussing.

For all but 2-methoxytetrahydropyran (3o), there is semiquantitative agreement between the electronic and free energy differences; $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ and/or $\Delta E^{\circ\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ lie within or just outside the range of experimental ΔGs for 1c−4c, 1o, and 4o. ΔH also happens to be in fair agreement with ΔG and ΔE for all four cyclohexanes (1c−4c). In contrast, ΔH is substantially different from ΔG and ΔE for the 2-hydroxytetrahydropyran (4o) which may be indicative of this substituent's propensity for hydrogen bonding. Finally, although there is some agreement between ΔG and ΔH for 2-methoxytetrahydropyran (3o), ΔE deviates substantially from these two quantities. Other computational studies of 2-methoxytetrahydropyran[42] and a closely related compound (4,6-dimethyl-2-methoxytetrahydropyran)[24,51] attribute this difference to solvent effects.

3.3. Anomeric Effect ($\Delta\Delta E$). The RHF, B3LYP, MP2, and CCSD(T) CBS limits of the anomeric effect listed in Table 5 have been determined according to eq 3 for all four substituents. The RHF and B3LYP data in Table 5 are in far better agreement with the MP2 and CCSD(T) results than in Table 3 because the equatorial stability is overestimated in both cyclohexane and THP. Consequently, the errors in ΔE cancel when calculating $\Delta\Delta E$. The contributions from higher-order correlation effects also have a tendency to cancel. Although $\delta E_{\mathrm{CCSD(T)}}$ approaches 0.2 kcal mol^{-1} for methoxycyclohexane, the MP2 CBS limit of $\Delta\Delta E$ deviates from the CCSD(T) value by no more than 0.1 kcal mol^{-1}.

These cancellations are rather consistent and can even lead to fairly accurate results with the split valence basis sets. For example, the RHF, B3LYP, and MP2 relative energies obtained with the 6-31G(*d*) basis set (Table 2) give $\Delta\Delta E$'s that lie within 0.2 kcal mol^{-1} of the CCSD(T) CBS values for the four substituents examined in this study despite the fact that the errors in ΔE can exceed 0.9 kcal mol^{-1}. However, computational procedures employing split valence basis sets are not recommended because this cancellation does fail occasionally, which can lead to errors in $\Delta\Delta E$ as large as 0.7 kcal mol^{-1}.

ZPVE corrections tend to have only a small effect on $\Delta\Delta E$. For CH_3, the ZPVE corrections to the equatorial-axial relative energies are nearly identical in 1c and 1o. Consequently, the ZPVE has almost no effect (≤ 0.06 kcal mol^{-1}) on the magnitude of $\Delta\Delta E$ for the CH_3 substituent. For F, OCH_3, and OH, however, the ZPVE correction tends to be larger for the THP compounds

(2o−4o) than for the cyclohexanes (2c−4c), which leads to a small decrease in the magnitude of the anomeric effect (0.12−0.19 kcal mol^{-1} for F, 0.06−0.14 kcal mol^{-1} for OCH_3 and 0.22−0.25 kcal mol^{-1} for OH).

Before concluding, a brief discussion of other means to quantify the anomeric effect is presented. Equations 1−3 do not address the bond length contraction of the ring framework that occurs when a methylene unit in cyclohexane is replaced by an O atom in THP. One manifestation of this phenomenon is the 1 kcal mol^{-1} increase in the equatorial preference of the CH_3 group in THP (1o) relative to cyclohexane (1c). Because a similar effect should occur for other substituents (e.g., F, OCH_3, OH), eqs 1−3 may underestimate the magnitude of the anomeric effect in THP systems. (The reverse can occur in thio-analogues due to bond length expansion in the ring framework.) Attempts have been made to account for the difference between the C−O bond lengths in THP and the corresponding C−C bond lengths in cyclohexane.[92,93] However, these approaches have certain drawbacks. For example, some schemes require that the energy or enthalpy differences in eqs 1−3 be decomposed into steric and electronic components in order to obtain a correction for the different steric environments in THP and cyclohexane. (See pages 11−13 of Reference 4 for additional details and references.) The decomposition process can be problematic as a result of the intimate connection between electronic and steric effects. Additionally, the magnitude of this stereoelectronic phenomenon becomes highly dependent upon the method(s) used to evaluate the steric component.[11] Consequently, these approaches to evaluating the anomeric effect have not been used here.

4. Conclusions

By evaluating the equatorial-axial relative energies at the CCSD(T) CBS limit, this work provides the first definitive intrinsic conformational energetics of these four substituted cyclohexanes (1c−4c) and four C(2)-substituted tetrahydropyrans (1o−4o). Particularly noteworthy are the magnitudes of $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ for fluoro- and methoxycyclohexane. Electronically, the equatorial conformations of these compounds are only 0.2 kcal mol^{-1} more stable than the axial configurations. For all eight compounds, $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ becomes more negative by a few tenths of a kilocalorie per mole when the ZPVE correction is included. Generally, the MP2 relative energies are in excellent agreement with the CCSD(T) values computed with the same basis set. The difference between the two is typically less than 0.1 kcal mol^{-1} and never exceeds 0.2 kcal mol^{-1}.

The relative energies evaluated at the CCSD(T) CBS limit are in excellent agreement with two available gas-phase experimental values. There is also semiquantitative agreement between the computed relative electronic energies and experimental free energy differences. Only for 2-methoxytetrahydropyran (3o) is there a substantial discrepancy between ΔE and ΔG. In contrast, all but one of the available experimental ΔH values are substantially different than the computed ΔE's. These trends are consistent with the interpretation that environmental effects play a large role in the equatorial-axial energetics of these species (ΔE and ΔH tend to be very different), but these extrinsic effects are canceled out by entropic contributions (ΔE and ΔG tend to be very similar). However, it is too early to draw definitive conclusions from these trends since the semiquantitative agreement between ΔE and ΔG frequently stems from the fact that the former lies somewhere within the wide range of values reported for the latter.

Relative energies obtained with split valence basis sets [6-31G(*d*), 6-31++G(*d*), 6-311++G(*d*), and 6-311G(2*df*,2*pd*)] are unreliable regardless of the theoretical method employed (RHF, B3LYP, MP2). However, despite rather erratic results for ΔE, these split valence basis sets can frequently provide more accurate estimates of the intrinsic magnitude of the anomeric effect ($\Delta\Delta E$) due to a fairly consistent cancellation of errors in both cyclohexane and THP. Nevertheless, the cancellation does fail on several occasions, and these basis sets should be used judiciously.

The RHF and B3LYP methods do not reliably describe the energetics of these systems. Even with massive correlation consistent basis sets, these two popular methods tend to overestimate the stability of the equatorial conformers. $\Delta E^{\mathrm{CBS}}_{\mathrm{RHF}}$ and $\Delta E^{\mathrm{CBS}}_{\mathrm{B3LYP}}$ are significantly more negative than $\Delta E^{\mathrm{CBS}}_{\mathrm{CCSD(T)}}$ for all but the fluorinated compounds.

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Supporting Information Available: Cartesian coordinates of all of the optimized structures used for the single point energy calculations. ZPVE corrections to the relative energies reported in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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