

Conformational pathways of simple six-membered rings

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The conformational equilibria of cyclohexane (as well as its fluoro-, chloro-, methyl-, hydroxy-, and *t*-butyl derivatives), cyclohexanone, piperidine, tetrahydropyran (and its 2-hydroxy derivative) were studied by *ab initio* and DFT procedures. The transition states were calculated at HF/6-31G, B3LYP/6-31+G*, and B3LYP/6-311+G** levels, whereas the intrinsic reaction coordinates (IRCs) were evaluated at the B3LYP/6-31+G* level. The degree of puckering and energy data was nearly not basis set-dependent (using B3LYP) in most of the cases. However, DFT methods gave better agreement with experimental data than HF methods, as expected from electron correlation inclusion. Fluorocyclohexane and 2-hydroxytetrahydropyran showed the largest basis set-energy dependence. It was found that the conversion from chair to skew is direct in some cases, whereas in others it goes through the pseudorotational (skew/boat) pathway. The case of *t*-butylcyclohexane, with a skew form as stable as one of the chairs, is especially interesting. In this compound, as well as in cyclohexanone and 2-hydroxytetrahydropyran, large deviations from the known pseudorotation/inversion scheme are observed. Copyright © 2010 John Wiley & Sons, Ltd.

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Keywords: conformational analysis; cyclohexane; density functional calculations; six-membered rings; transition states

INTRODUCTION

The study of cyclohexane shape is one of the more fascinating subjects of early Organic Chemistry courses. Sachse recognized in 1890 the possibility of having two strain-free puckered shapes, called symmetrical or rigid (nowadays chair) and unsymmetrical or flexible.^[1,2] The idea was then challenged by most of the scientific establishment, who rather believed in a planar cyclohexane.^[3] After some sporadic proofs that Sachse was right,^[1] it took about 50 years to show with spectroscopic studies that the all-staggered chair form was more stable than the partly eclipsed boat form,^[1,4–7] and to estimate the energy difference as 5.6 kcal/mol (23.4 kJ/mol).^[8] The scattered knowledge about cyclohexane conformations was put together in a landmark paper by Barton in 1950.^[9] Most of the modern knowledge of cyclohexane shapes has been settled by a group of papers appearing around 1960: after several diverging results, the energy difference between the chair and the flexible form was determined to be 21–25 kJ/mol both by theoretical and experimental methods (including hand-made models!).^[10–15] At the same time, it was recognized that the boat is not a stable conformer, but that a twisting half-way in passing from one boat to another relieves part of the eclipsing energy giving rise to a stable flexible conformer^[12–15] now called twist-boat, skew-boat or just skew or twist. It was also determined that the transition state between the chair and the skew should not actually be the envelope, with five atoms on the same plane, as previously assumed, but a half-chair in which two contiguous atoms appear above and below the plane formed by the other four.^[11] Its energy was estimated to be 40–50 kJ/mol higher than the chair.^[11,16,17] Later on, the energies of the half-chair and envelope were estimated as 45 and 47 kJ/mol, respectively.^[18,19] The studies were extended to show that for cyclohexanone the flexible form has an energy only 11 kJ/mol higher than that of

the chair.^[10] A great deal of work was carried out in order to determine the energy difference of diverse substituents in axial and equatorial positions.^[1] It has been reported a non-standard trajectory for the chair-skew pathway of cyclohexane,^[20–22] characterized by recrossings and by non-transition state, non-intrinsic reaction coordinate (IRC) dynamics.^[22]

Most of the early theoretical studies of complete puckering surfaces were devoted to pyranosidic carbohydrates,^[23–25] but also included simpler examples as cyclohexane and tetrahydropyran. The conformational pathways of the six-membered rings of carbohydrates were the subject of newer studies as well,^[26–30] especially in view of the evidence that glycosyl hydrolases sometimes bind to flexible (skew or boat) conformations instead to the most stable chair conformation.^[31,32] It has also been shown that during the adiabatic mapping of disaccharide analogs, ring flipping or generation of boat-like structures can occur, in spite of the high-energy barriers.^[33]

Most of the theoretical work on non-carbohydrate cyclohexyl derivatives was devoted to the equilibrium of chairs with axial and equatorial substituents, or their relationship with tetrahydropyran derivatives in relation to the anomeric effect.^[34–37] Only a few studies included the determination of the geometries and energies of the transition states, and even less studied the conformational pathways of substituted rings.^[27,38–42] To the best

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of my knowledge, no systematic ample study has been carried out to compare those pathways in six-membered rings with substituents of different nature. Herein, the potential energy surfaces calculated by DFT for cyclohexane, as well as its fluoro-, chloro-, methyl-, hydroxy- and *t*-butyl derivatives, cyclohexanone, the heterocyclic piperidine, tetrahydropyran and 2-hydroxy-tetrahydropyran are presented. All the transition states were properly identified and characterized, and the IRCs calculated in order to figure out the most probable conformational pathways.

RESULTS AND DISCUSSION

Nine cyclic compounds (Fig. 1) were studied by different quantum mechanics methods, in order to search for all their minima and transition states. The energies of the chair conformers carrying an equatorial or an axial substituent were studied at different levels of the HF, B3LYP, and MP2 methods. The relative energies are shown in Table 1, whereas their absolute values are shown in Table S1 of Supporting Information. The hydroxyl group in cyclohexanol and 2-hydroxytetrahydropyran was left initially at its most stable conformation (H(O) *anti* to C2). The difficulties in finding conformational transition states of six-membered rings due to the continuous mixing of different eigenvectors within flat potential energy surfaces have already been pointed out.^[27] For this reason, finding a few transition states required more elaborate searches (see later).

Axial-equatorial equilibrium

Previous QM determinations of the axial/equatorial equilibrium in fluorocyclohexane showed that it is strongly basis set-dependent.^[34–37] The current work also shows that small basis sets wrongly indicate the axial conformer as the most stable (Table 1), either working with B3LYP or HF. The correlated MP2 method worsens this difference. At least one diffuse function is needed with B3LYP, or even more with HF to get the correct stability. The best match with the gas phase estimated difference (1.0 kJ/mol^[43]) is obtained using B3LYP at the highest level used (6-311+G^{**}). Working at even higher levels, B3LYP increases further the difference to about 1.5 kJ/mol:^[37] at those levels, MP2 seems to give a better match with experimental results.^[37] For chlorocyclohexane, HF results with any basis set give a strong preference for the equatorial conformer (3.1–4.7 kJ/mol, Table 1). The experimental gas-phase difference is estimated as 2.7 kJ/mol.^[44] Our best match is probably given with the MP2/6-311+G^{**} calculations, as the ZPE addition should increase the obtained value (2.4 kJ/mol, Table 1). For cyclohexanol, older

literature indicates a large spread of experimental energy differences (1.2–5.2 kJ/mol^[1]), either in solution or neat. The 5.2 kJ/mol value was estimated in a non-polar solvent.^[45] Cyclohexanol received detailed computational studies,^[37,46] showing marked differences between basis sets and methods. Confirming that data, the current results show that HF gives a low axial-equatorial difference, which is further diminished using MP2. The best results (according to the experimental determinations) are shown with B3LYP at the higher basis set levels, especially after zero-point energy correction.

The equatorial conformer of methylcyclohexane was experimentally estimated to be 7.9 kJ/mol more stable than the axial conformer.^[1] Both B3LYP and HF give larger values with any basis set, as shown earlier.^[37] The difference increases when free energy is calculated. MP2 gives rise to the best results when working with better basis sets (Table 1). It is difficult to measure the energy difference between both chairs of *t*-butylcyclohexane, as one of them hardly appears in the equilibrium. The free energy difference was estimated to be of about 20.5 kJ/mol.^[47] HF results indicate a difference just above 25 kJ/mol, whereas B3LYP reduces it to *ca.* 23 kJ/mol (Table 1). With both methods, the difference is almost independent of the basis set. On the other hand, working with MP2, Wiberg *et al.*^[34] found that the relative energies decreased from 23.4 to 21.3 kJ/mol as they improved the basis set. A similar trend was found in the current work (Table 1). However, it should be mentioned that at the MP2/6-311+G^{**} level (the highest studied) the expected ΔE (20 kJ/mol) value decreased to below 17 kJ/mol when using B3LYP/6-311+G^{**} geometries: the high magnitude of the correlation energy for the axial conformer was responsible for this abnormal result.

For piperidine, the free energy difference between axial and equatorial N-H was estimated as 1.5 kJ/mol.^[48] Both conformers are actually related by two different processes, chair-chair flip and nitrogen inversion (see below). A theoretical study determined a difference of 0.8 kJ/mol between both conformers^[49] using B3LYP/6-31G^{**}. The current work shows that the introduction of diffuse functions increases the difference to *ca.* 3 kJ/mol, but free energy determination lowers that value to 2.5 kJ/mol (Table 1). MP2 shows a similar trend.

There were numerous theoretical and experimental studies carried out on 2-hydroxytetrahydropyran.^[36,37,40,41] The anomeric effect introduces a preference for the axial conformer, estimated as 3 kJ/mol, but decreasing in the presence of solvent.^[37] Our results show that low-level basis sets overestimate this difference: only when at least a diffuse and a polarization function are used, the energy difference drops below 4 kJ/mol. High-level calculations indicated a CCSD(T) CBS limit value of 3.6 kJ/mol, further reduced to 2.1 after including zero-point energies,^[37] but one high-level calculation increased the free energy difference to

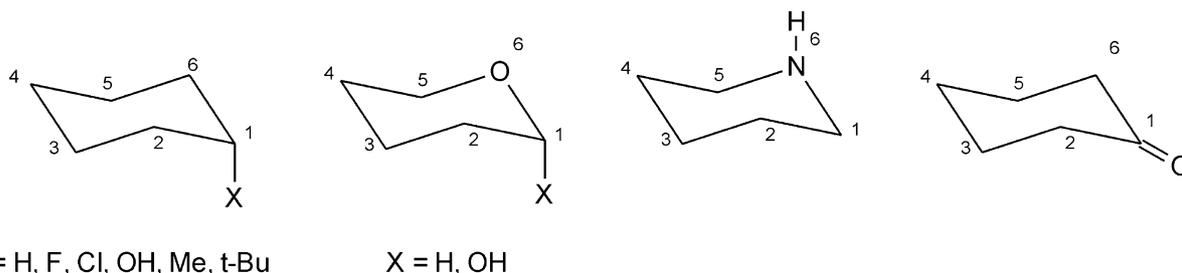


Figure 1. The compounds studied in this work and their numbering conventions. This figure is available in color online at wileyonlinelibrary.com/journal/poc

Table 1. Relative energies ($E_{\text{axial}} - E_{\text{equatorial}}$ in kJ/mol) of several substituted six-membered rings, at different QM levels, and comparison with experimental data

	Fluoro-	Chloro-	Hydroxy-	Methyl-	t-Butyl-		
	Cyclohexane					Piperidine	2-Hydroxy-THP
B3LYP							
6-31G	-0.3	2.7	1.8	8.6	22.9	1.9	-8.8
6-31G*	-0.7	3.6	1.5	9.0	22.3	1.4	-5.1
6-31+G	0.7	3.4	3.5	9.2	23.3	3.6	-7.3
6-31+G*	1.3	4.4	3.7	9.6	22.9	3.4	-3.1
6-311+G**	0.9	3.1	3.3	8.9	22.2	3.1	-2.8
ΔG (6-311+G**)	1.0	3.7	3.8	10.3	25.3	2.5	-1.3
HF							
6-31G	-1.1	3.1	0.7	9.1	26.3	4.1	-9.8
6-31G*	-1.1	4.2	1.0	9.6	25.6	3.4	-5.5
6-31+G	-0.4	3.4	2.1	9.3	26.3	4.3	-8.2
6-31+G*	0.5	4.7	2.8	9.9	25.8	4.0	-3.7
6-311+G**a	0.5	3.7	2.7	9.8	28.0 (25.5) ^d	3.7	-2.5
MP2							
6-31G ^b	-1.3	4.0	0.4	8.3	22.6	2.6	-11.1
6-31+G* ^c	-0.5	4.2	1.8	9.2	22.6	4.1	-5.2
6-311+G**a	0.7	2.4	1.7	7.3	16.7 (19.6) ^d	3.4	-4.1
Experimental ^e	1.0	2.7	1.2–5.2	7.9	≈20.5	1.5	≈-3.0

^a Geometry optimized at the B3LYP/6-311+G** level.
^b Geometry optimized at the HF/6-31G level.
^c Geometry optimized at the HF/6-31+G* level.
^d In parentheses, with the geometry optimized at the level at which the energy was determined.
^e For references, see text.

12 kJ/mol.^[40] Working with the best basis sets, the MP2 method gives results closer to high-level calculations or to experimental results than B3LYP or HF methods, which tend to give lower differences, as shown earlier.^[37]

Minima and transition states. Depiction of geometrical issues

The symmetry in cyclohexane makes both chairs, and all six boats, skews, half-chairs, and envelopes to be equivalent.^[27] It is widely known that the chair is the global minimum (most stable conformer), whereas the skew is a local minimum, the boat is a transition state between skews, and the half-chair is a transition state between chair and skew. The envelope, with five atom rings on the same plane, represents a saddle point of order 2.^[27] It is also known that although the skew represents an energy minimum and the boat an energy maximum, the difference in energy between both is small, and thus a facile pseudorotational circuit is established between boats and skews. A similar pseudorotational pathway is expected to occur between half-chairs and envelopes (though both represent energy maxima), given the small energy difference.^[27] When cyclohexane is substituted, the symmetry is lost partially or totally. The chair conformers, and some boat and envelope conformers of monosubstituted rings like fluoro-, chloro-, methyl-, and *t*-butylcyclohexane still exhibit a symmetry plane which crosses C1 and C4. Other boats and envelopes, as well as all the skews and half-chairs have a

conformational enantiomer (pseudo-enantiomer^[39]). Thus, for all these compounds we expect to have two different chairs, three different skews (plus their pseudo-enantiomers), four different boats (two symmetrical, transitional between pseudo-enantiomeric skews and two non-symmetrical, transitional between pseudo-diastereomeric skews^[39]). Besides, assuming that the half-chairs represent the transition states between chairs and skews, six different half-chairs are expected to appear (plus their pseudo-enantiomers), two for each skew (one in the direction of each chair). Actually (see later), those six transition states are never found, as some pathways appear to be forbidden. Each conformer can be easily identified according to its established nomenclature,^[50] and the potential pathways relating these conformers can be established using Stoddard's diagram.^[19,26] Piperidine exhibits the same symmetry behavior, though the symmetry plane appears across the N and C3. Tetrahydropyran and cyclohexanone exhibit higher symmetry, as both chairs are equivalent. The hydrogen in the hydroxyl group of cyclohexanol is staggered, so that no conformer with this hydrogen *anti* to C2 or C6 can be symmetrical. This conformation has usually less energy than that with this hydrogen *gauche* to both carbons (which can be symmetrical). Thus, strictly speaking, the entire conformational surface should be studied. However, the difference introduced by this hydrogen was found to be small, and thus only half of the surface was studied in the present work. On the other hand, 2-hydroxytetrahydropyran has a chiral carbon, thus lacking symmetry. Six different skews

and boats, and 12 transition states could be expected to appear.

It was early recognized that the conformations of six-membered rings could be conveniently represented by earth-like descriptions, using different formalisms.^[19,26,27,50–53] The most usual is that described by the Cremer–Pople puckering parameters,^[51] though other descriptors have been proposed.^[27,52,53] The puckering coordinates of Cremer and Pople are the radius or magnitude of puckering Q , and the phase angles ϕ (0–360°) and θ (0–180°). Spherical polar coordinates are usually employed for the representation of conformers, considering the conformers to lie on an even external shell of the sphere (of constant radius Q , as this parameter shows less variation). The angle ϕ represents the longitude, whereas θ denotes the latitude.

The chairs appear on the poles ($\theta=0$ and 180° , ϕ irrelevant), whereas the pseudorotational path of skews and boats appears on the equator ($\theta=90^\circ$), each conformer being distinguished by its ϕ value. Perfect envelopes appear at $\theta=54.7$ and 125.3° , whereas the perfect half-chairs come out at $\theta=50.9$ and 129.1° . In order to produce a two-dimensional representation, several approaches have been made, as a rectangular *plate-carrée* projection,^[25] a full representation of the sphere^[27] (both for total depiction) or a hemispheric projection from the north pole^[26] (to show only the pathways between one chair and the boat-skew circuit). Figures 2–4 show the representation of the stationary points and IRCs of the nine compounds under study at the B3LYP/6-31+G* level, using the Cremer–Pople parameters on one hemisphere drawn as an azimuthal orthographic projection

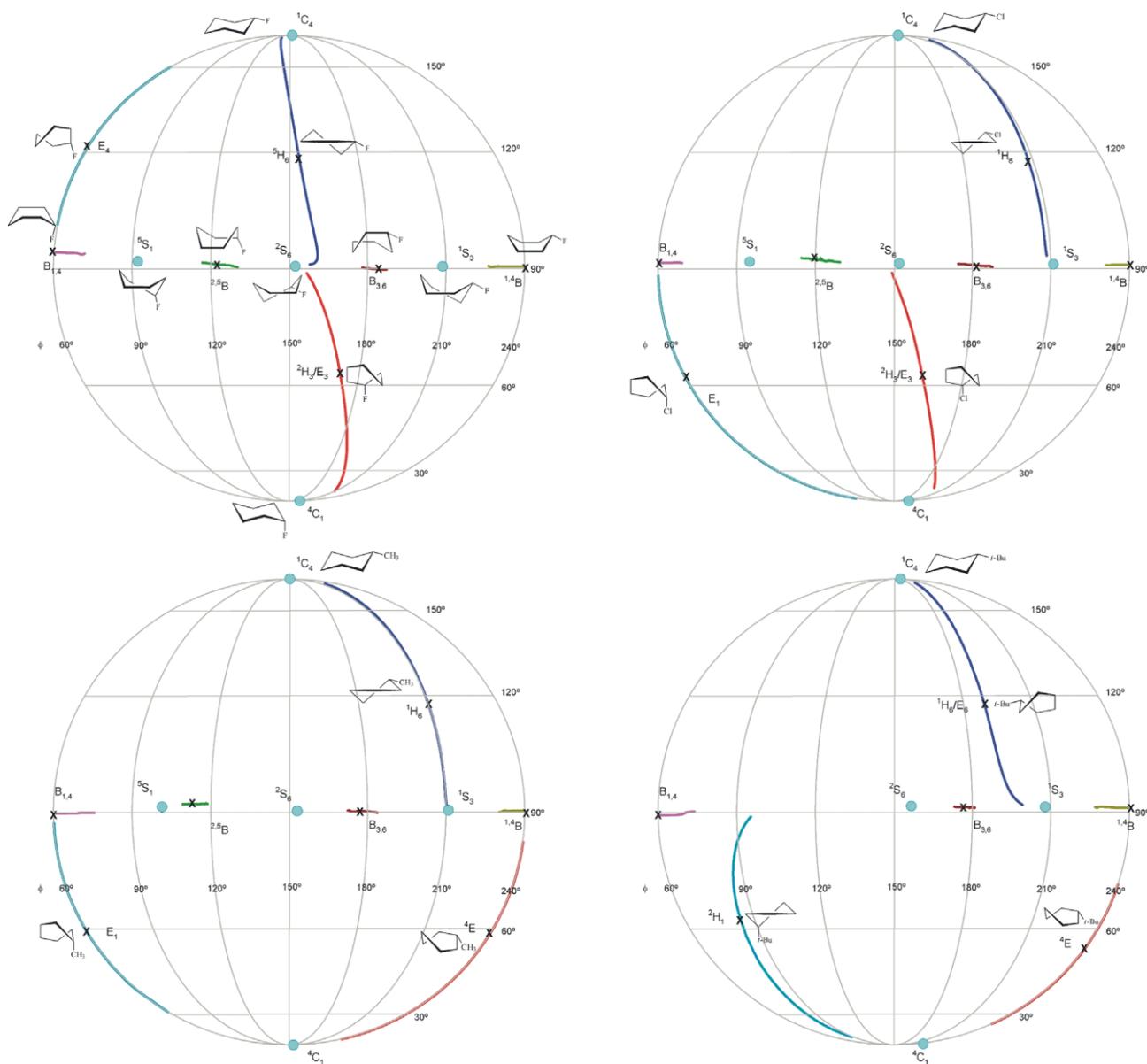


Figure 2. Geometry representations of the Cremer–Pople puckering parameters of minima (blue-sky circles), transition states (crosses), and intrinsic reaction coordinates (IRC, colored lines) in an azimuthal orthogonal projection (centered on the equator) for fluoro-, chloro-, methyl-, and *t*-butylcyclohexane, at the B3LYP/6-31+G* level. The other hemisphere is a mirror image of that drawn. The geometry of all the stationary points is shown only for fluorocyclohexane, whereas some other points are shown for the remaining compounds. This figure is available in color online at wileyonlinelibrary.com/journal/poc

centered in the equator. The other hemisphere can be considered a mirror image of that shown for all the molecules having a symmetry plane; for 2-hydroxytetrahydropyran (Fig. 4), both hemispheres are shown. Table S2 of Supporting Information shows the geometries and energies of all those stationary points at three different levels (HF/6-31G, B3LYP/6-31+G*, and B3LYP/6-311+G**). Neither the geometries nor the energies of these stationary points differ too much with B3LYP at the 6-311+G** and 6-31+G* levels (average differences 0.001 Å in Q , 0.1° in θ , 0.5° in ϕ , and 0.6 kJ/mol in ΔE , maximum differences 0.010 Å in Q , 0.5° in θ , 4.4° in relevant ϕ , and 2.1 kJ/mol in ΔE). The data presented here correspond to the lower level (B3LYP/6-31+G*) because of the high computer requirements for the IRC calculations. It should be considered that, as a convention, the

substituent was facing down (Fig. 1). Thus, the 4C_1 conformer corresponds to that with an axial substituent, whereas the other chair (1C_4) carries an equatorial substituent.

Relative energies of stationary points

The energies and geometries of the stationary points were calculated at the HF/6-31G, B3LYP/6-31+G*, and B3LYP/6-311+G** levels (Table S2 of Supporting Information). It is usually complicated to represent the conformational equilibria in cyclohexanes, because the inversion process has a definite transition state, which links a chair and a pseudorotational wheel of different conformers, usually separated by small energy differences. From some point (or points) in this pseudorotational

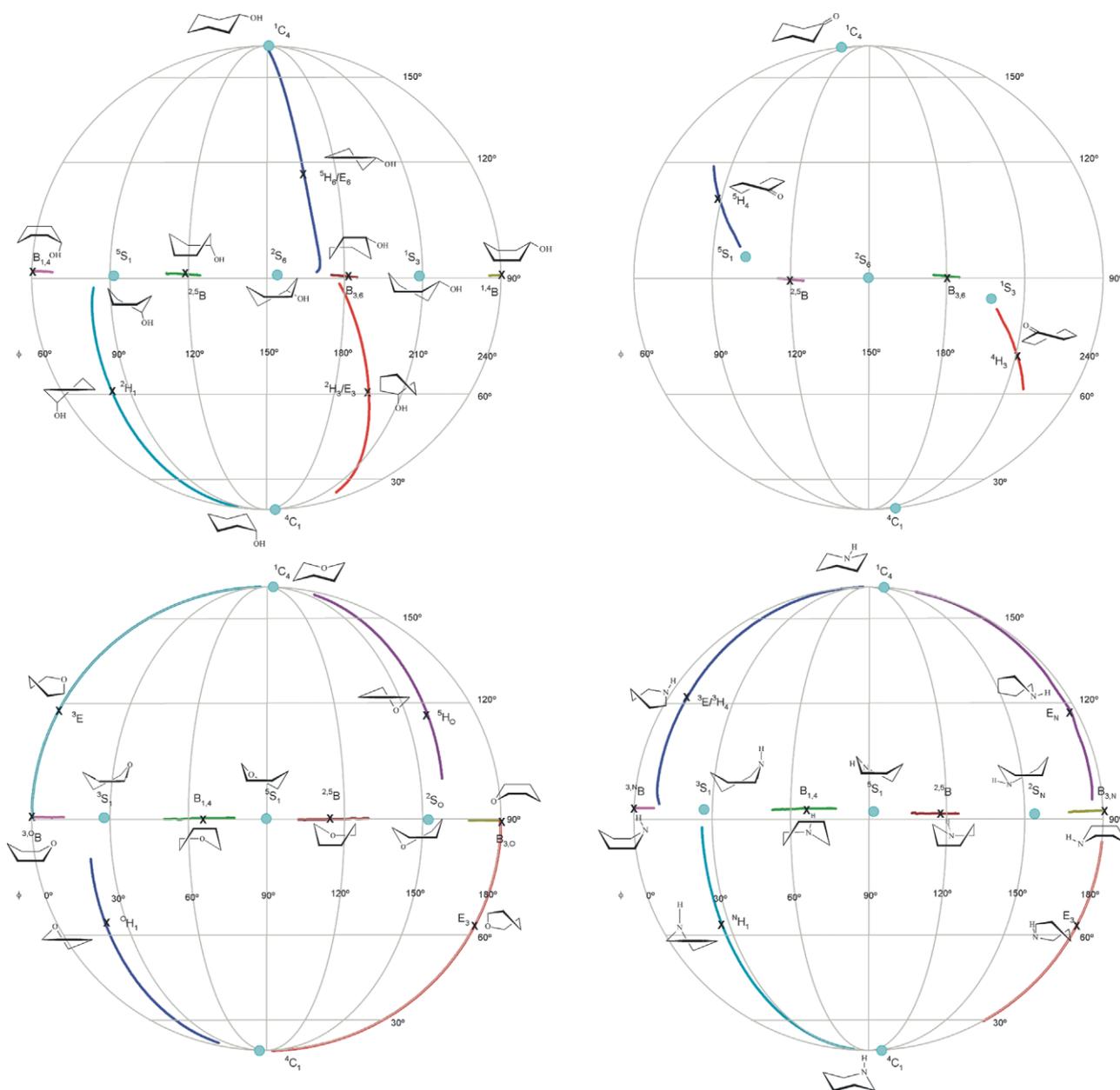


Figure 3. Geometry representations of the Cremer–Pople puckering parameters of minima (blue-sky circles), transition states (crosses), and intrinsic reaction coordinates (IRC, colored lines) in an azimuthal orthogonal projection (centered on the equator) for cyclohexanol, cyclohexanone, tetrahydropyran, and piperidine, at the B3LYP/6-31+G* level. The other hemisphere is a mirror image of that drawn. This figure is available in color online at wileyonlinelibrary.com/journal/poc

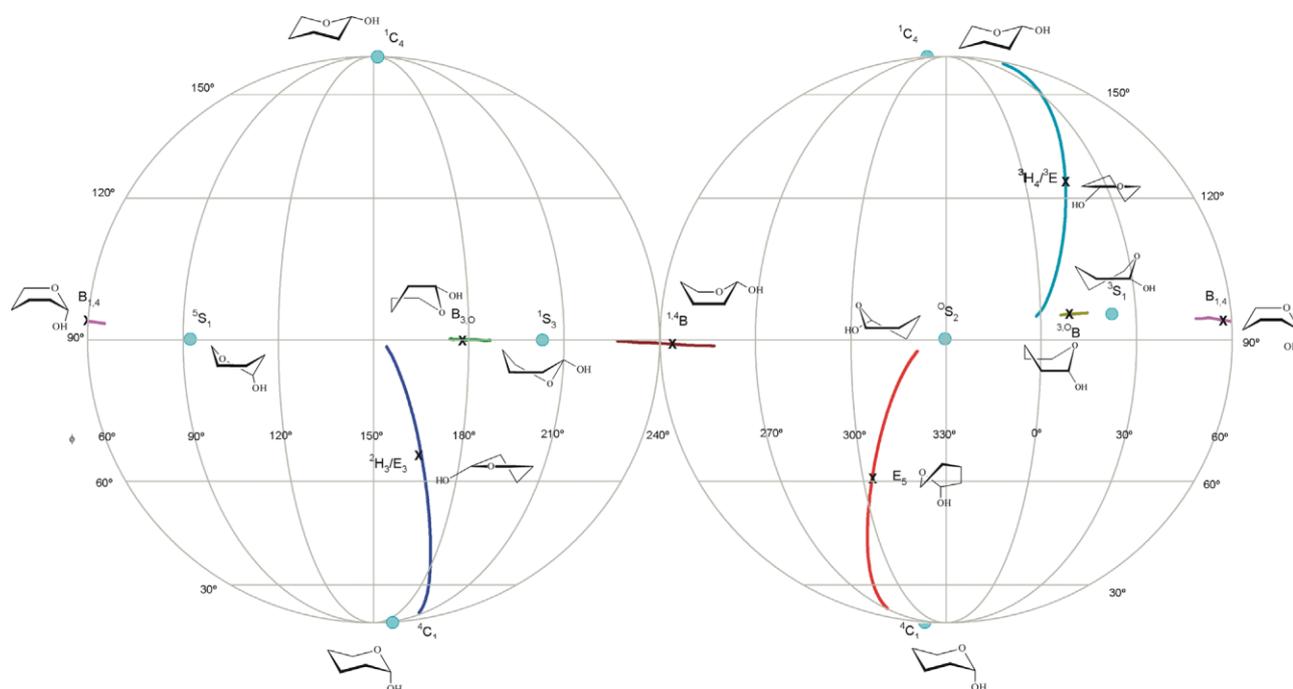


Figure 4. Geometry representations of the Cremer–Pople puckering parameters of minima (blue-sky circles), transition states (crosses), and intrinsic reaction coordinates (IRC, colored lines) in an azimuthal orthogonal projection (centered on the equator) for 2-hydroxytetrahydropyran, at the B3LYP/6-31+G* level. Both hemispheres are shown. This figure is available in color online at wileyonlinelibrary.com/journal/poc

path, a second transition state will lead to the inverted chair. Thus, two different processes appear: an inversion through a half-chair-like transition state, and the boat-skew exchange (pseudorotational circuit). The representation of the combined processes is difficult to handle in a usual ‘reaction coordinate’ plot. Thus, a 3D representation with the energies on a circle view from a side was proposed for the pseudorotational process, with attachment of the chair inversion process.^[39] Although those plots represent better the process, in order to compare energies, a classical plot is more illustrative. Figures 5–7 point up the energies involved in the conformational pathways of the nine compounds under study, calculated using B3LYP/6-311+G**. It has to be borne in mind that the pseudorotational circuit shown represents only half of the true circle (as occurs with the spheres shown in Figs 2 and 3). Besides, each chair was made to appear on either side just to avoid as much overlapping of lines as possible. Thus, the plots do not have a ‘geometry logic’, but attempt to depict the energy shifts involved in the conformational pathways. The magnitude of the imaginary frequencies involved in the transition states also appears in Table S2 of Supporting Information. Usually half-chair/envelope transition states exhibit imaginary frequency values of ca. 200 cm⁻¹, whereas boat-like transition states show much lower values (typically around 60 cm⁻¹). Following, an analysis of the geometries and energies (at the B3LYP/6-311+G** level, except when indicated in contrary) of the process involved for each of the compounds under study is made.

Cyclohexane

At the best level studied, the skew is 26.6 kJ/mol less stable than the chair. Further free energy calculations lower this value to 24.7 kJ/mol. The boat form is 4–5 kJ/mol less stable. The half-chair transition state is easily found using HF/6-31G, but in order to

obtain it using B3LYP, less tight termination parameters (as in Jaguar) are needed to find a conformer with just one imaginary frequency, right on the meridian ($\phi = 60 \times n + 30^\circ$, with n integer). Only by starting with this geometry, the optimizer in Gaussian can ‘find’ the transition state with the tight termination conditions. Other attempts finished in conformers having two imaginary frequencies, because of the half-chair–envelope equilibrium. In the transition state, this movement has a very low frequency (25–28 cm⁻¹ by B3LYP, 45 cm⁻¹ by HF). The energy of the half-chair falls from almost 50 kJ/mol by HF/6-31G to 46.6 by B3LYP/6-311+G**, and even less (43.7 kJ/mol) when free energy is calculated by the last method. The experimental value is 45.2 kJ/mol,^[18,19] close to our calculations. The difficulties in finding the half-chair transition state might be related to the reported non-transition state dynamics occurring for cyclohexane.^[22] A negligible energy difference between half-chair and envelopes (actually of every conformer with the same θ and different ϕ) might complicate further the pseudorotational movement around the equator of the Cremer–Pople sphere. A flat ridge surface characterizes better the transition state region (θ ca. 60 or 120°) than that with separate, well-defined barriers. Pseudorotation appears to be constant throughout the entire surface: the adiabatic energy surface of Dowd *et al.*^[25] is consistent with this assertion. Thus, cyclohexane might have a more complex conformational equilibrium^[20–22] than its substituted counterparts.

Fluorocyclohexane

The small fluorine atom has a small tendency to prefer the equatorial position.^[34–37,43] Thus, as expected, the six different skews (three on each hemisphere) have low-energy differences (23–27 kJ/mol above the most stable chair, Fig. 5), and the same

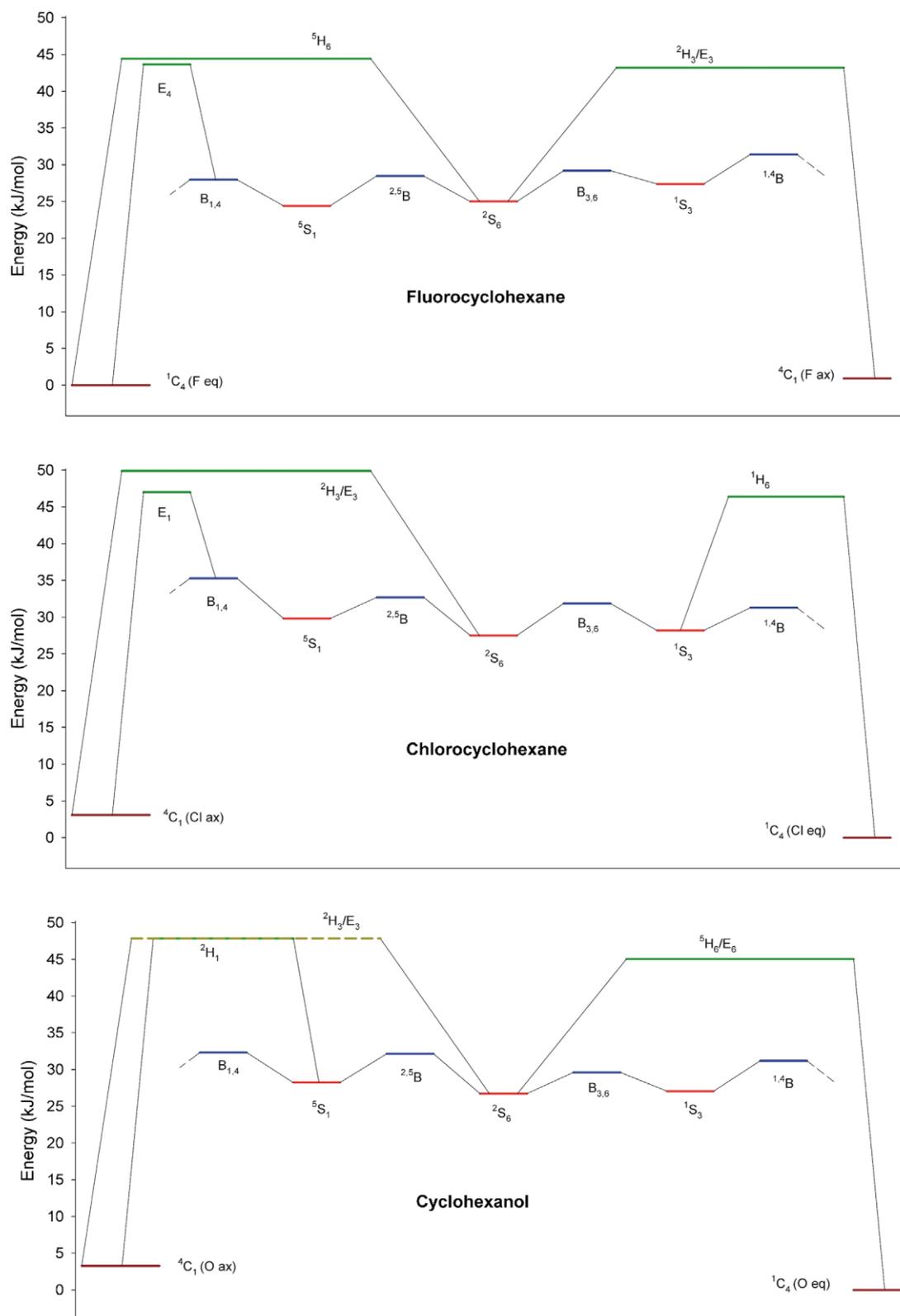


Figure 5. Conformational pathways for fluoro-, chloro-, and hydroxy-cyclohexane with energies and geometries calculated at the B3LYP/6-311+G** level. Only one hemisphere is shown. Chair conformers are denoted in brown, skews in red, boats in blue, and half-chair/envelopes in green. This figure is available in color online at wileyonlinelibrary.com/journal/poc

occurs with the boats (28–31 kJ/mol), all of them within the same energy range as those occurring in cyclohexane. However, it is surprising that although the chair with equatorial fluorine is better stabilized, the skews and boats having a pseudoequatorial F atom (to the right in Figs 2 and 5) tend to have higher energies than those having a pseudoaxial F atom (to the left in Figs 2 and 5). Their geometries are close to those of cyclohexane (Fig. 2). It might have been expected to find one transition state for the path between each chair and each skew. On the hemisphere shown, this makes six paths, three from the north pole to the equator and three from the south pole to the equator. First attempts with the coarse HF/6-31G method indicated such three paths from the 1C_4 F equatorial-bearing conformer, but only one from the 4C_1 axial conformer. Attempts to find other transition states failed, as shown previously for other substituted cyclohexanes.^[39] The 'southern' transition state linked the 4C_1 and the 2S_6 conformers (Fig. 2) through a 2H_3 geometry. From the chair with the equatorial F atom, two half-chairs (5H_6 and 1H_6) led to the 2S_6 and 1S_3 skews. The third transition state, however, occurred through an envelope (the symmetric E_4), by flattening C1 (the atom bearing the F). A new flip of C1 originates the $B_{1,4}$ conformer, and from there elsewhere, through the pseudorotational circuit. When these four transition states were recalculated by B3LYP (with either 6-31+G* or 6-311+G** basis sets), the transition states E_4 and 5H_6 remained mostly unaltered, but the 1H_6 disappeared (optimizes to 5H_6), whereas the half-chair 2H_3 shifted to E_3 (Fig. 2), yielding a non-symmetric coordinate leading to 2S_6 . The relative energies of the three transition states are very similar (Fig. 5): 43–44 kJ/mol (free energies 40–41 kJ/mol). Those values are ca. 3 kJ/mol lower than those determined for cyclohexane.

Chlorocyclohexane

Chlorine has a stronger bias toward equatoriality than fluorine (see above), because of its larger size. Thus, it is not surprising that the energy of the boats increases from right to left in Fig. 5 (i.e., from equatorial chlorine to pseudoequatorial, to pseudoaxial, to flagpole), and the skews follow a similar trend. All of the skews have higher relative energies ($\Delta E = 27.5$ – 29.8 kJ/mol, $\Delta G = 26.0$ – 28.4 kJ/mol) than those of cyclohexane (26.6 and 24.7 kJ/mol, respectively), and so do the boats ($\Delta E = 31.3$ – 35.3 kJ/mol, $\Delta G = 31.4$ – 35.8 kJ/mol against 30 kJ/mol for cyclohexane). The three calculation methods indicate three different transition states for the hemisphere shown. One occurs with 1H_6 geometry, linking the equatorial chlorine-bearing conformer 1C_4 with the flexible pseudorotational path through conformer 1S_3 , with an IRC going over the $\phi = 210^\circ$ meridian (Fig. 2). The other chair shows two different ways of inversion: through a ${}^2H_3/E_3$ conformer toward 2S_6 , very similar to that occurring for fluorocyclohexane (Fig. 2), or after symmetric flipping of C4 to give the E_1 envelope (with a pseudoaxial chlorine atom). The ΔG^\ddagger s for the inversion process are similar to those observed in cyclohexane (Fig. 5), or even lower in the case of that occurring through the E_1 conformer (which goes from the higher energy 4C_1 chair).

Cyclohexanol

Although the bias for equatoriality is slightly higher for a OH substituent than for a Cl (Table 1), the presence of the former substituent has less effect on the geometries and energies of the

flexible conformers: the energies of the skews ($\Delta E = 26.7$ – 28.3 kJ/mol, $\Delta G = 25.0$ – 27.4 kJ/mol) and boats ($\Delta E = 29.6$ – 32.3 kJ/mol, $\Delta G = 30.2$ – 33.2 kJ/mol) are similar to those of cyclohexane, giving a simple pseudorotational path (Fig. 5). The higher energy values, however, were found for those conformers bearing an axial or pseudoaxial hydroxyl group (Figs 3 and 5). Smith found similar results using another method.^[41] As occurred with Cl- and F-substituted cyclohexane, three transition states were found on the hemisphere (Fig. 3): one linking the 1C_4 and the 2S_6 conformers through a 5H_6 geometry (as occurred with fluorocyclohexane), another one linking the same skew with the 4C_1 conformer (as occurred with the two halocyclohexanes), but the third one links the same higher energy chair with the 5S_1 conformer through a half-chair with 2H_1 geometry. The three barriers are similar (41–45 kJ/mol above the chair from which they depart) among themselves, and to that showed by cyclohexane. Working with HF/6-31G two of the three transition states appear severely shifted: the ${}^5H_6/E_6$ ($\phi = 166^\circ$) appears as 1H_6 ($\phi = 200^\circ$), and ${}^2H_3/E_3$ ($\phi = 191^\circ$) as 4H_3 ($\phi = 154^\circ$).

Methylcyclohexane

The presence of a large substituent, with a stronger tendency to stay equatorial alters sharply the simple pseudorotational circuit. As expected, the energy of the skews ($\Delta E = 26.5$ – 34.7 kJ/mol, $\Delta G = 25.5$ – 33.6 kJ/mol) climbs from right to left (Fig. 6) from the base value of cyclohexane up to the effect of an axial methyl group (ca. 9 kJ/mol, Table 1). The boats ($\Delta E = 30.1$ – 44.3 kJ/mol, $\Delta G = 30.5$ – 45.2 kJ/mol) show the same trend, although they get to a larger effect in $B_{1,4}$, where the flagpole position of the methyl group introduces an additional destabilizing steric factor. Furthermore, conformers 5S_1 and 2S_6 are very deformed, with geometries (Fig. 2) and energies very close to each other (only 0.5 kJ/mol), indicating a very flat region which implies an easy fall from $B_{1,4}$ to 2S_6 . Furthermore, it is questionable to call the boat-skew circuit as pseudorotational in this case. It is indeed pseudorotational on the way from 5S_1 to its pseudo-enantiomer 3S_1 through 1A_B (Fig. 6), but the passage through $B_{1,4}$ requires 10–12 kJ/mol (similar values were found by Fernández-Alonso *et al.*^[39]), an energy difference surmountable, but certainly not pseudorotational. Furthermore, the energy of activation for converting this boat to the 4C_1 conformer (6–9 kJ/mol, Fig. 6) is lower than that needed to originate this boat. Besides, it shows a larger imaginary frequency magnitude (-110 – 127 cm^{-1}) than those usually found in regular boats. As found by different calculations with methylcyclohexane,^[39] three transition states appear linking the chairs with the 'flexible' region. The more stable chair (1C_4) is converted to the more stable skew (1S_3) through a 1H_6 -like conformation (Figs 2 and 6). Fernández-Alonso *et al.*^[39] indicated for this transition state a 1E conformation. The energy of this transition state ($\Delta E = 46$ kJ/mol, $\Delta G = 42$ kJ/mol) is similar to that found for cyclohexane. On the other hand, the chair with the axial methyl group (4C_1) might experience flipping either on C1 or on C4, getting to the 1A_B and $B_{1,4}$ boats through 4E and E_1 transition states, respectively, as already found earlier.^[39] The difference in energy between both transition states is only 3 kJ/mol (E_1 higher). Previously both states were considered isoenergetic (as the difference varied with the method),^[39] in spite of the higher 1,3-diaxial repulsive interactions present in E_1 and absent in 4E . Possibly these interactions are counterbalanced in 4E by the torsional strain originated in the eclipsing interactions of the methyl group and the neighboring hydrogen atoms. The

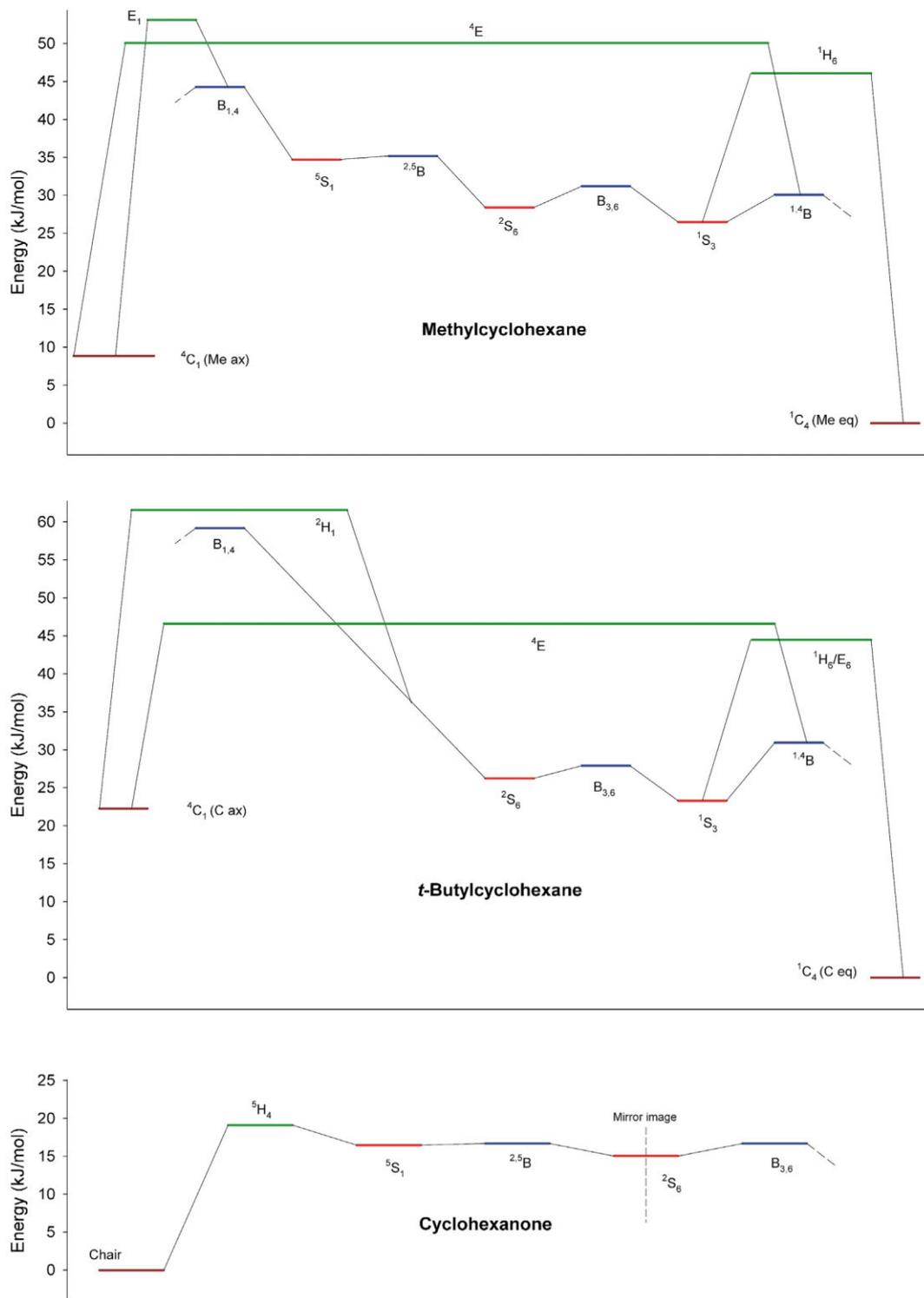


Figure 6. Conformational pathways for methyl- and *t*-butylcyclohexane, and cyclohexanone with energies and geometries calculated at the B3LYP/6-311+G** level (B3LYP/6-311+G**//B3LYP/6-31+G* for *t*-butylcyclohexane). One hemisphere is shown for the first two compounds, only part of the hemisphere for cyclohexanone. Chair conformers are denoted in brown, skews in red, boats in blue, and half-chair/envelopes in green.

energies of these transition states, although in absolute terms higher than that of the ${}^1\text{H}_6$ transition state, turn actually to lower barriers, when considering that they originate in the ${}^4\text{C}_1$ conformer: the calculated ΔG^\ddagger is of only 38 kJ/mol, lower than that found for cyclohexane. This can be explained by the high energy of the 'ground' axial conformer, with 1,3-diaxial interactions partially released as the methyl group becomes synclinal in ${}^4\text{E}$. This is partially counterweighed (as mentioned earlier) by the eclipsing of the methyl group (against the Hs in cyclohexane), but the relief of the axial condition appears to be more important in the balance.

t-Butylcyclohexane

The trend shown with methylcyclohexane peaks with this compound, sometimes considered to be 'fixed' in the equatorial position, meaning that the equilibrium highly favors this conformation.^[1] The ${}^5\text{S}_1$ conformer was not found (*cf.* methylcyclohexane, where a flat surface was found in that region), and thus the high-energy $\text{B}_{1,4}$ conformation links two pseudo-enantiomeric skews (${}^2\text{S}_6$ and ${}^6\text{S}_2$). The other link of these skews is truly pseudorotational, passing through the more stable skews (${}^1\text{S}_3$ and ${}^1\text{S}_5$, *ca.* 23 kJ/mol above ${}^1\text{C}_4$). The other boats have relative energies (28–32 kJ/mol) in the order of that of cyclohexane (Figs 2 and 6). It is worth noting that a skew form (${}^1\text{S}_3$) and a chair form (${}^4\text{C}_1$) have very similar energies, explaining why *t*-butyl disubstituted compounds might adopt a skew conformation.^[34] The energy of activation from the skews to $\text{B}_{1,4}$ is 33–35 kJ/mol, clearly not pseudorotational (the imaginary frequency is -140 cm^{-1}), and more like the barrier for a chair inversion. Three transition states for the chair inversion were found. They are similar (but not equal) to those found for methylcyclohexane: one linking the most stable chair and the most stable skew, through an E_6 -like transition state, with an energy of 44.5 kJ/mol. From the less stable chair two transition states are found, one through flattening of C1 (E_4), identical to that of methylcyclohexane, but only 22–23 kJ/mol above the chair and 16–17 kJ/mol above the boat which are linked by this transition state. It is worth noting that this E_4 transition state is more stable than that of methylcyclohexane even when compared with the 'ground state' with an equatorial substituent. It is also more stable than the $\text{B}_{1,4}$ conformer. The other transition state is shifted from the E_1 conformation, with an axial arrangement of the *t*-butyl group, to a ${}^2\text{H}_1$ conformation, where it becomes pseudoaxial. Although it has a relatively high energy, it is only slightly higher than that of the $\text{B}_{1,4}$ conformer (2–4 kJ/mol), and about 40 kJ/mol above ${}^4\text{C}_1$ (the chair associated with this transition state).

Cyclohexanone

It has already been estimated a long time ago that the skew form of cyclohexanone is only 11 kJ/mol less stable than the chair.^[10] Previous modeling studies found just one skew form, 14.4 kJ/mol above the only chair.^[41] This work shows the presence of two different skews, the most stable one (${}^2\text{S}_6$, $\Delta E = 15.1$ kJ/mol, $\Delta G = 12.6$ kJ/mol, Figs 3 and 6) with the carbonyl group on the main plane, between the atoms above and below the plane, and another one with slightly higher energy (*ca.* 1.5 kJ/mol) with the carbonyl group out of the main plane. However, this skew (${}^5\text{S}_1$, and their symmetry equivalents) has an energy only 0.2 kJ/mol lower than a closer boat (${}^2\text{S}_6$), indicating a flat region. It is thus

feasible that using other methods^[41] it is not encountered. However, free energy measurements favor the skew over the boat by more than 3 kJ/mol, suggesting that the skew really exists as a minimum. The conformational pathway of cyclohexanone is completely different from the others mentioned before, as the skews ${}^5\text{S}_1$ and its equivalent ${}^3\text{S}_1$ are not linked through the $\text{B}_{1,4}$ conformer, but directly through the half-chair ${}^5\text{H}_4$ (with an activation energy of 2–4 kJ/mol) to the chair. Thus, cyclohexanone exhibits a pseudorotational itinerary for an arc of the equatorial circle, but the pathway mixes up with the chair inversion process, with very low-activation energies. This compound has a higher symmetry, and thus some of the reported skews, boats, and half-chairs appear in quadruplicate.

Tetrahydropyran

Modeling of this compound with high symmetry received more attention in the literature.^[25,27,38,39,41] There is just one chair, two different skews, and two different boats. One boat is symmetrical (${}^3\text{O}_B$), with the oxygen atom out of the main plane, and the other is non-symmetrical, with the oxygen atom on the main plane ($\text{B}_{1,4}$ and three equivalent shapes). There are also two skews, the higher energy ${}^5\text{S}_1$ (and its equivalent ${}^1\text{S}_5$) linking topomeric boats, and the lower energy ${}^3\text{S}_1$ (and three equivalents), linking different boats (Figs 3 and 7). Our calculations indicate that ${}^3\text{S}_1$ is 24.6 kJ/mol less stable than the chair ($\Delta G = 22.3$ kJ/mol). The other skew is 3 kJ/mol less stable. Older MM calculations yield similar values (23.2 and 25.9 kJ/mol),^[25] whereas other QM calculations indicated an energy of 23.6–24.2 kJ/mol for the most stable skew,^[27,38,39,41] and 25.9–28.5 kJ/mol for the less stable one^[38,39,41] (Ionescu *et al.*^[27] mention only one skew). The topomeric boats with pathways linked by the ${}^5\text{S}_1$ skew have an energy barely higher (1.7 kJ/mol in our calculations and others^[39]), suggesting an easy pseudorotational pathway (Fig. 7), whereas the other boat has even lower energy (27 kJ/mol). Two pathways of chair inversion have already been postulated for tetrahydropyran.^[27,38,39] Roughly, one involves flattening of the O (through a ${}^3\text{E}$ or E_3 transition state), and the other involves the flattening of C3. The former was found by our three procedures to occur exactly over the meridian toward ${}^3\text{O}_B$ (Fig. 3) with a ΔE of 42.7 kJ/mol and a ΔG of 38.1 kJ/mol. The other transition state is shifted, and occurs with a ${}^{\text{O}}\text{H}_1$ (= ${}^5\text{H}_0$) geometry with similar B3LYP energy, but higher free energy. This transition state cannot be obtained by HF/6-31G calculations (it finishes in E_3). Lambert *et al.*^[54] indicated an experimental activation energy of 43 kJ/mol for tetrahydropyran, and suggested a ${}^3\text{H}_4$ -like transition state as the most stable on grounds of torsional strain. Other authors found values of 39–44 kJ/mol for these transition states.^[27,38,39] These results indicate that the most stable skew, boat, and half-chair/envelope forms of tetrahydropyran have only slightly less relative energy (*ca.* 3 kJ/mol) than those of cyclohexane, although larger differences have been predicted, at least for the boat.^[1]

Piperidine

The trivalent nitrogen carries one hydrogen atom, which can be either axial or equatorial, breaking part of the symmetry present in tetrahydropyran. The geometries and energies involved in the conformational pathways of piperidine (Figs 3 and 7) are very similar to those of monosubstituted cyclohexanes. However, possibly the ring inversion process seldom occurs, as other

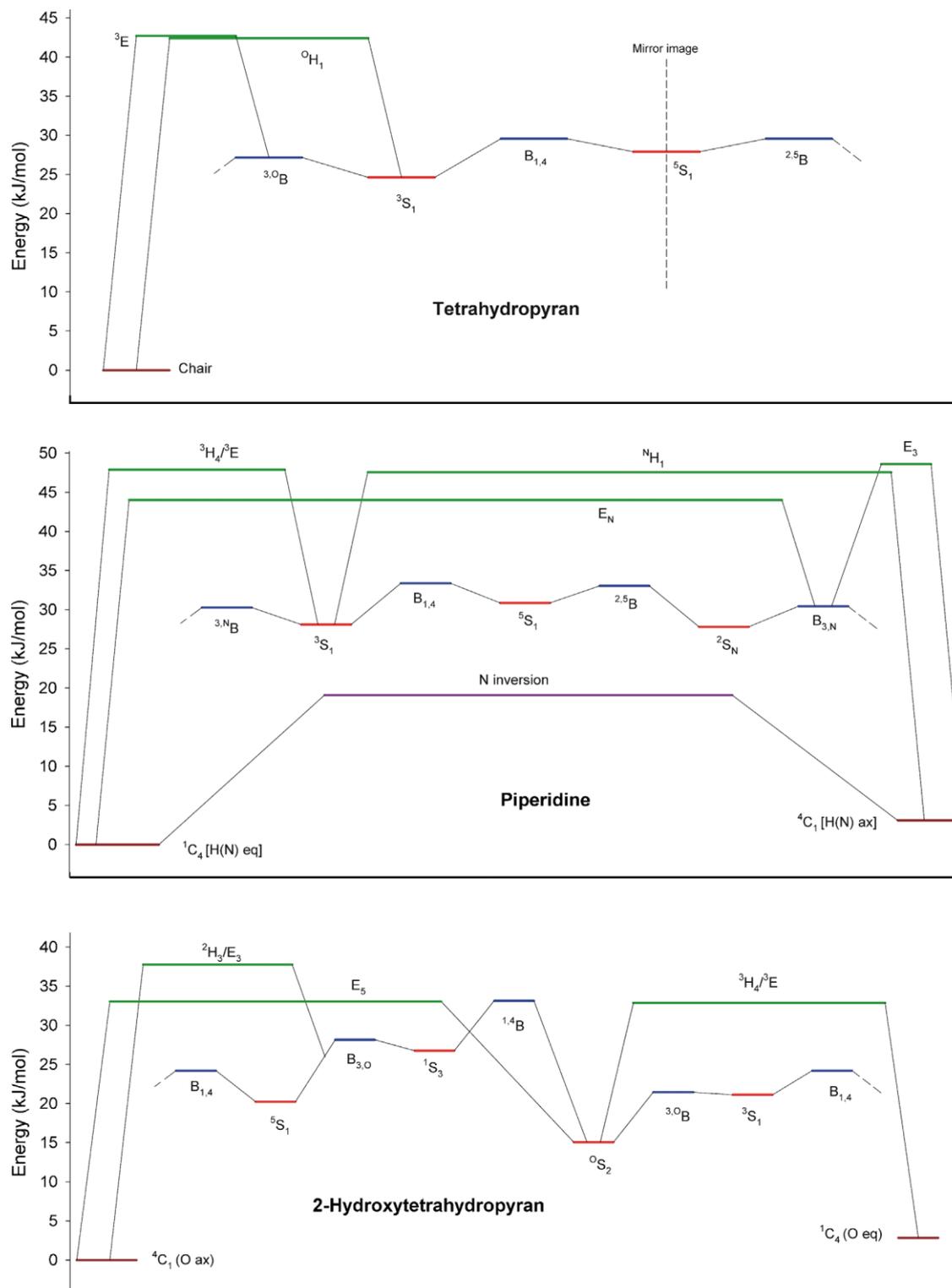


Figure 7. Conformational pathways for tetrahydropyran, piperidine and 2-hydroxytetrahydropyran with energies and geometries calculated at the B3LYP/6-311+G** level. Part of the hemisphere is shown for the first compound, the whole hemisphere for the second, and both hemispheres (full pathway) for the third. Chair conformers are denoted in brown, skews in red, boats in blue, and half-chair/envelopes in green.

process, nitrogen umbrella inversion^[49] also converts a chair bearing an equatorial H(N) into the other, with a lower activation energy. The inversion proceeds through a transition state with a sp^2 N atom, with a ΔE^\ddagger of 19 kJ/mol and a ΔG^\ddagger of 15 kJ/mol;

previous works^[49] indicated a calculation of 18 kJ/mol and an experimental barrier of 25 kJ/mol.^[48] For the skews, the inversion is also possible: the process exchanging 5S_1 and 1S_5 shows a ΔE^\ddagger of 12 kJ/mol and a ΔG^\ddagger of 8 kJ/mol, whereas that exchanging 2S_N

and ${}^N\text{S}_2$ (the last one pseudo-enantiomeric with ${}^3\text{S}_1$) through N inversion shows a ΔE^\ddagger of 15 kJ/mol and a ΔG^\ddagger of 11 kJ/mol. These processes should not be important, as pseudorotation interconverts those skews with much lower activation energies. It has to be remembered that we used the convention (Fig. 1) of keeping the hydrogen on the nitrogen facing up, when looking at the ring numbered clockwise seen from above. This explains why ${}^N\text{S}_2$ is pseudo-enantiomeric with ${}^3\text{S}_1$ (as the latter could have been called ${}^N\text{S}_4$). The pseudorotational pathway involves one hemisphere (Figs 3 and 7) three skews with $\Delta E = 27.8\text{--}30.9$ kJ/mol, $\Delta G = 25.3\text{--}28.2$ kJ/mol, and four boats with $\Delta E = 30.3\text{--}33.4$ kJ/mol, $\Delta G = 29.7\text{--}32.3$ kJ/mol, with respect to the most stable chair, i.e., around but slightly above the values for cyclohexane. As occurred with tetrahydropyran, the symmetric boats are more stable than the non-symmetric ones (Fig. 7), and the conversion of the flexible forms into chairs can happen through flattening of N or C3. However, as two different chairs appear for piperidine, four different transition states are possible: E_N and ${}^3\text{E}$ for the chair with equatorial H, ${}^N\text{H}_1$, and E_3 for the chair with axial H. E_N has the lowest B3LYP energy ($\Delta E = 44.0$ kJ/mol, $\Delta G = 42.4$ kJ/mol), but ${}^3\text{E}$ has a lower free energy ($\Delta E = 47.9$ kJ/mol, $\Delta G = 41.8$ kJ/mol), as occurred with tetrahydropyran. The other two transition states have very similar energies ($\Delta E = 44.5\text{--}45.5$ kJ/mol, $\Delta G = 39.9\text{--}42.0$ kJ/mol above the ${}^4\text{C}_1$ conformer). An experimental energy of 43.5 kJ/mol has been estimated for the chair reversion.^[48]

2-Hydroxytetrahydropyran

As a model compound for sugars, the pathways of this compound have also been studied thoroughly.^[25,27,40,41] Although it has the combined characteristics of cyclohexanol and tetrahydropyran (both with pathway energies and geometries similar to that of cyclohexane), the conformational pathway of 2-hydroxytetrahydropyran is quite different, given the stereoelectronic effects of the combined action of the ring oxygen and a neighboring polar atom (anomeric effect).^[40] Thus, the energies of some skews, boats, and all of the half-chair/envelopes are well below those of the cyclohexane and derivatives (Fig. 7). Using any of three methods, we were able to find only four of the six potential skews (Fig. 4), but Smith has found all six,^[41] and Ionescu *et al.*^[27] found five, working with different methods. One of them (${}^O\text{S}_2$) is very stable (15.1, 13.2 kJ/mol free energy), probably for having the hydroxyl group *anti*-periplanar to an orbital of the oxygen ring atom.^[40] Other two skews (${}^5\text{S}_1$ and ${}^3\text{S}_1$, Figs 4 and 7) also have low energies ($\Delta E = 20\text{--}21$ kJ/mol, $\Delta G = 18$ kJ/mol), whereas the fourth (${}^1\text{S}_3$), with a pseudoequatorial hydroxyl group, has the energy of the cyclohexane skew ($\Delta E = 27$ kJ/mol, $\Delta G = 23$ kJ/mol). Early MM calculations found only three of those minima, as ${}^3\text{S}_1$ was missed. This makes sense when looking at Figs 4 and 7, showing that the geometries and energies of ${}^3\text{S}_1$ and ${}^{3,0}\text{B}$ are quite close, and thus, a slightly different potential function can easily lead directly from $\text{B}_{1,4}$ to ${}^O\text{S}_2$. The values determined in the literature are for ${}^O\text{S}_2$ a ΔG of 18 kJ/mol^[27] and a ΔH_{298} of 14 kJ/mol,^[39] for ${}^3\text{S}_1$ and ${}^5\text{S}_1$, energy values between 18 and 22 kJ/mol,^[40,41] and for ${}^1\text{S}_3$ values around 26 kJ/mol.^[27,41] Two boats ($\text{B}_{1,4}$ and ${}^{3,0}\text{B}$) with an axial or pseudoaxial hydroxyl group have quite low energies (22–24 kJ/mol, Figs 4 and 7). $\text{B}_{3,0}$, with a pseudoequatorial hydroxyl group, has a relative energy slightly lower than that of cyclohexane (*ca.* 28 kJ/mol), whereas ${}^1\text{A}_B$, with equatorial hydroxyl group, has the highest energy (31–33 kJ/mol), slightly above that observed

for cyclohexane. Similar values were reported in the literature.^[27] The low-energy ${}^O\text{S}_2$ conformer is the intermediate for chair inversion. Figures 4 and 7 show that this skew can convert to the ${}^1\text{C}_4$ and to the ${}^4\text{C}_1$ chairs through ${}^3\text{H}_4/{}^3\text{E}$ and E_5 transition states, respectively. Both are isoenergetic (*ca.* 18 kJ/mol above the skew, 33 kJ/mol above the ${}^4\text{C}_1$ conformer), though the free energy of the latter is slightly higher. Ionescu *et al.*^[27] calculated a ΔG^\ddagger (from the skew) of 18 kJ/mol for the transition to ${}^1\text{C}_4$ (${}^3\text{E}$), and about 3 kJ/mol less for the other transition. The data of Smith^[40] indicate that the ${}^3\text{E}$ transition state is 43 kJ/mol (36 kJ/mol of free energy) above the most stable chair. A third inversion process appears (Figs 4 and 7), through a ${}^2\text{H}_3/\text{E}_3$ conformer, leading to the place where the ${}^2\text{S}_0$ conformer should appear. Although we did not find such skew conformation, other authors were able to find it.^[27,41] In any case, it might enter into the pseudorotational pathway to go on its way to other skews, boats, or chair inversion. This process requires a higher activation energy (*ca.* 5 kJ/mol).

COMPUTATIONAL METHODS AND NOMENCLATURE

Quantum mechanical calculations were performed using Gaussian 03W (version 6, revision B0.3)^[55] and Jaguar 6.0107,^[56] both with standard basis sets and default minimization methods and termination conditions. The energies and geometries of the stationary points reported in this paper come from Gaussian optimizations. All minima and transition states had zero or one imaginary frequency, respectively, as appropriate. For the transition states, it was verified that this frequency corresponded to the conformational pathway searched for. The transition states were obtained either by the traditional Berny algorithm, or by using the QST2 procedure. In some cases, the Gaussian transition state optimization did not converge, after jumping back and forth between two close conformations with no improvement in the displacement indicators. Usually this was solved by submitting the Jaguar-optimized geometry to the Gaussian optimization process. A pre-optimization by Jaguar was used several times. Free energies were calculated at 298 K as reported in the Gaussian output file, without scaling. The IRC pathways were obtained by the standard methods of either of the two programs. The step size and number of points were raised in order to cover as much of the path as possible. In some cases, more than one run had to be done in order to find the right step size. The progress of optimization of the transition states was followed in terms of the Cremer–Pople parameters, in order to check for the appearance or disappearance of half-chair/envelope transition states with the different methods. The numbering and conventions regarding the compounds under study are shown in Fig. 1. For substituted cyclohexanes, the IUPAC numbering scheme was used, with the substituent facing down when numbering clockwise observed from above. The heterocycles were numbered following the usual carbohydrate convention, with C1 clockwise to the heteroatom (which is equivalent to atom 6). The names of the different conformers follow the usual conventions.^[50] The hydrogen of the hydroxyl group of cyclohexanol and 2-hydroxytetrahydropyran was initially oriented *anti* to C2, which corresponds to the minimum-energy arrangement.

CONCLUSIONS

The conformational pathways of several substituted cyclohexanes and six-membered heterocyclic rings were studied by quantum mechanics at different levels. Although detailed geometry and energy issues differ for the distinct calculation methods, the main features are common to all of them. For most of the compounds, the pseudorotational pathway and the chair inversion are independent but connected processes, as in some cases it is not possible to achieve complete chair inversion without a walk within the pseudorotatory itinerary. The relative energies of the skews for cyclohexane rings carrying substituents which do not have a large effect on the axial-equatorial preference (F, Cl, OH) are in the same order ($\Delta E = 24\text{--}30$ kJ/mol, $\Delta G = 23\text{--}28$ kJ/mol) of the skew form of cyclohexane itself ($\Delta E = 27$ kJ/mol, $\Delta G = 25$ kJ/mol). The same happens with the boat forms, which act as transition states for the interconversion of skews: compare an energy span of 28–36 kJ/mol versus 30 kJ/mol for cyclohexane. For compounds having a 'heavy' substituent (Me, *t*-Bu), the low-energy skews and boats have the same relative energy as those of cyclohexane, but the others carry considerably more energy. The heterocycles tetrahydropyran and piperidine also show boats and skews with similar relative energies to those of cyclohexane. On the other hand, in 2-hydroxytetrahydropyran some skews and boats carry considerably less energy (6–8 kJ/mol) than those of cyclohexane, but one (1S_3) reaches the same values. In regard to the activation energies involved in inversion, it was found that for most of the compounds, both ΔE^\ddagger and ΔG^\ddagger are lower than or at most equal to those of cyclohexane. Only two paths (one for chlorocyclohexane and one for piperidine) showed higher activation energy values, with a surplus lower than 2 kJ/mol. Not every theoretically possible chair-skew pathway appears, usually only half are found, and the remaining conversion occurs through pseudorotation. Taking into account the nine compounds analyzed in the current study, fluorocyclohexane, chlorocyclohexane, cyclohexanol, piperidine, and tetrahydropyran exhibit a simple pseudorotatory circuit, similar to that of cyclohexane. Methylcyclohexane has one step in the pseudorotational itinerary which takes about 10–12 kJ/mol, thus hindering true pseudorotation. This effect is maximized in *t*-butylcyclohexane, where this step would take 33–35 kJ/mol, an energy in the order of those of chair inversion. Furthermore, chair inversion processes in *t*-butylcyclohexane involve sometimes lower energies; thus both processes appear interspersed. The pyranose model 2-hydroxytetrahydropyran also shows a complex circuit, where one boat and a couple of envelopes have the same energy, thus leading to 'pseudorotational' and inversion circuits equally probable, and thus mixed up, at least in part. Cyclohexanone represents a special case: the pseudorotational circuit cannot be completed, as the direct interconversion of two skews requires chair inversion through the half-chair. In any case, the whole circuit progresses easily, as the energies involved are less than half those observed for cyclohexane.

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