J. Org. Chem. **1996,** *61,* 6465−6469

Thermodynamics of the Axial $\rightleftharpoons$ Equatorial Conformational Equilibria of *tert*-Butylcyclohexane and *tert*-Butyl-Substituted Six-Membered Heterocycles. Theoretical Estimation of Non-Zero Entropy Changes

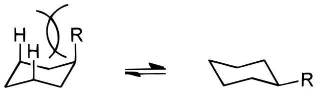
Sandra Antúnez and Eusebio Juaristi*

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apdo. Postal 14-740, 07000 México, D.F., Mexico

Received February 20, 1996

Introduction

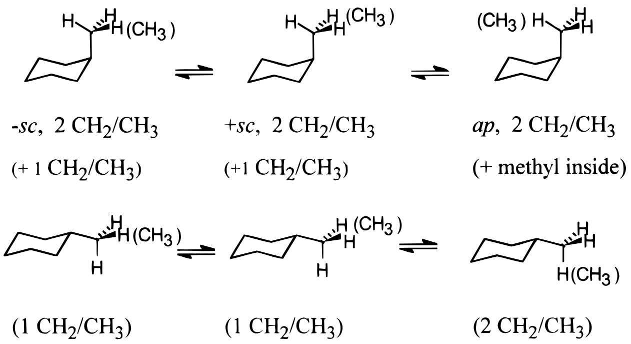
The energy differences between the axial and equatorial conformations of monosubstituted cyclohexanes (*A*-values, eq 1) are of great interest to chemists since they serve as models for more complicated molecules.[1] Alkyl groups prefer equatorial over axial positions in order to avoid the repulsive steric interactions with the methylenes at C(3,5), and it is usually observed that the bulkier the alkyl group the larger the preference for the equatorial form.[2]



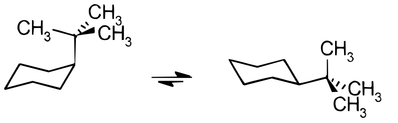
(1)

In this regard, the accepted *A*-values for methyl, ethyl, and isopropyl are 1.74, 1.80, and 2.15, respectively,[2] in line with their increasing size. However, force-field calculations[3] and experimental NMR data[4] indicate that the *enthalpic* contributions to the equatorial preference actually *decrease* along this series: $-\Delta H°(\text{Me}) = 1.75$ kcal/mol, $-\Delta H°(\text{Et}) = 1.6$ kcal/mol, $-\Delta H°(i\text{-Pr}) = 1.52$ kcal/mol.[4,5] Indeed, analysis of the *gauche* interactions present in the axial and equatorial conformers (Scheme 1 illustrates the methyl *versus* ethyl case) indicates that, relative to methyl, enthalpy differences must be *less* for ethyl and isopropyl substituents, because of additional repulsive *gauche* interactions in the equatorial isomers. On the other hand, three populated rotamers in equatorial ethyl- and isopropylcyclohexane *versus* two (ethyl) or one (isopropyl) in the axial form[6] imply that the entropy of mixing makes a substantial contribution to the negative free energy difference (equatorial preference), especially at higher temperatures where the $T\Delta S°$ term becomes more sizable.

Scheme 1

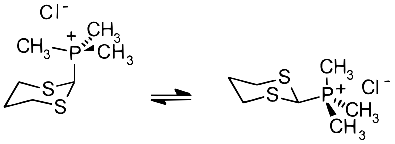


In contrast with methyl-, ethyl-, and isopropylcyclohexane, the axial isomer of *tert*-butylcyclohexane necessarily orients a methyl group inside the ring. Indeed, the conformational preference of *tert*-butyl for the equatorial position in cyclohexane is so large ($-\Delta G° = 4.9$ kcal/mol[7]) that this group is effectively used as an anchoring substituent in many reference compounds.[8] Nevertheless, the extreme onesidedness of equilibrium 1 in *tert*-butylcyclohexane has precluded so far the experimental estimation of the enthalpic and entropic contributions to $-\Delta G°(t\text{-Bu})$.[9] While this situation brings to mind the potential of theoretical calculations as an alternative for determinations not amenable to experiment, apparently only one force-field study[3] has addressed the question of entropy difference in the **1**-ax $\rightleftharpoons$ **1**-eq equilibrium (eq 2).[10] The estimated[3] $\Delta S° = 0$ for this equilibrium seems intuitively plausible by consideration of three isoenergetic staggered conformers both in **1**-ax and in **1**-eq.



1-ax **1**-eq (2)

From symmetry considerations, a trimethylphosphonium group is similar to a *tert*-butyl group; thus, we were surprised to find that the spectroscopic behavior of 2-(trimethylphosphonio)-1,3-dithiane (**2**) suggested a value for the entropy change in eq 3 equal to $\Delta S° = -1.19$ cal/K·mol.[11]



2-ax **2**-eq (3)

The above considerations, as well as consideration of the fundamental importance of the *tert*-butyl group in

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(1) (a) Barton, D. H. R. *Experientia* **1950**, *6*, 316. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley Interscience: New York, 1965. (c) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991.

(2) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985. (c) Bushweller, C. H. Stereodynamics of Cyclohexane and Substituted Cyclohexanes. Substituent A-Values. In *Conformational Behavior of Six-Membered Rings: Analysis, Dynamics and Stereoelectronic Effects*; Juaristi, E., Ed.; VCH Publishers: New York, 1995; Chapter 2.

(3) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van-Catledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199.

(4) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255.

(5) The benzyl group exhibits similar thermodynamic behavior: $-\Delta H°(\text{CH}_2\text{Ph}) = 1.52 \pm 0.1$ kcal/mol, $\Delta S° = +0.81 \pm 0.3$ cal/K·mol. See: Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* **1991**, 56, 4802.

(6) The methyl-inside rotamers of axial ethyl- or isopropylcyclohexane are nearly 4 kcal/mol higher in energy and can be disregarded.

(7) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267.

(8) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.

(9) Furthermore, an axial *tert*-butyl group usually causes the ring to adopt nonchair conformations: Remijnse, J. D.; Bekkum, H. v.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 93 and references therein.

(10) Other force-field studies focused on the determination of energy minima and structure: (a) Altona, C.; Sundaralingam, M. *Tetrahedron* **1970**, *26*, 925. (b) van der Graaf, B.; Wepster, B. M. *Tetrahedron Lett.* **1975**, 2943. (c) Ōsawa, E.; Collins, J. B.; Schleyer, P. v. R. *Tetrahedron* **1977**, *33*, 2667. (d) van der Graaf, B.; Baas, J. M. A.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 268. (e) Smith, G. D.; Jaffe, R. L.; Yoon, D. Y. *Macromol.* **1994**, *27*, 3166.

(11) Juaristi, E.; Cuevas, G. *J. Am. Chem. Soc.* **1993**, *115*, 1313.

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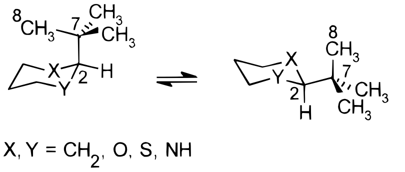
chemistry, motivated the present theoretical reexamination of the enthalpic and entropic contributions to the conformational preference of *tert*-butyl in cyclohexane and in several six-membered heterocycles. The thermodynamics of the trimethylphosphonium group in cyclohexane were also evaluated.

Results and Discussion

Molecular Mechanics Calculations. The MM2[12a] and MM3(92)[12b] force fields were used to evaluate the intramolecular energetics. While the former program has proven quite successful for modeling a large variety of hydrocarbons,[12c] MM3 *does* take into account entropy components to free energy (MM2 refers exclusively to potential energy). Furthermore, with a simple change to the program code,[13] it was possible to get the free energy values and, thus, to estimate ΔG_{pot} for the axial to equatorial equilibrium.

Uniform scanning at 5° increments was carried out for the dihedral angle H−C(2)−C(7)−C(8), allowing for complete relaxation of the rest of the atomic coordinates. The conformational energy maps originating from each minimum energy conformation were drawn by means of the Surfer program.[14]



(4)

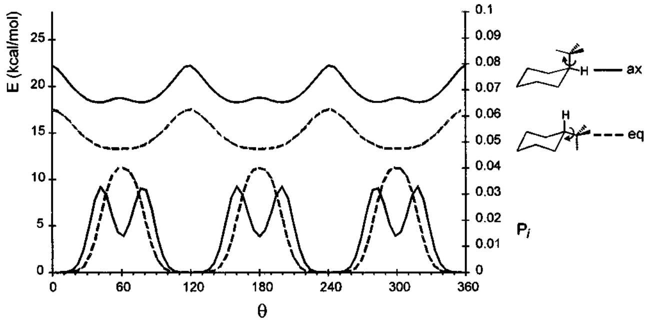
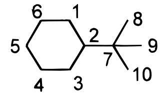


Figure 1. Energy plots (top, left scale) and population plots (bottom, right scale) for *tert*-butyl group rotation in cyclohexane.

Table 1. Calculated Bond Lengths, Bond Angles, and Torsional Angles in Cyclohexane, Staggered−Axial *tert*-Butylcyclohexane, Eclipsed−Axial *tert*-Butylcyclohexane, and Staggered−Equatorial *tert*-Butylcyclohexane



	cyclohexane	staggered-**1**-axial	eclipsed-**1**-axial	staggered-**1**-equatorial
torsional angles[a]				
C(1)−C(2)−C(3)−C(4)	56.34	51.63	56.42	57.51
C(2)−C(3)−C(4)−C(5)	56.34	54.30	56.99	56.64
C(3)−C(4)−C(5)−C(6)	56.34	57.13	56.46	56.55
bond angles[a]				
C(1)−C(2)−C(3)	110.89	111.16	111.91	111.08
C(2)−C(3)−C(4)	110.89	111.93	110.98	110.91
C(3)−C(4)−C(5)	110.89	110.63	109.92	110.04
C(2)−C(1)−C(7)		116.03	118.32	114.27
C(1)−C(7)−C(10)		114.73	114.78	112.72
bond lengths[b]				
C(1)−C(2)	1.54	1.55	1.55	1.54
C(2)−C(3)	1.54	1.54	1.54	1.54
C(3)−C(4)	1.54	1.53	1.53	1.53
C(1)−C(7)		1.56	1.57	1.56
C(7)−C(10)		1.54	1.55	1.54

[a] Degrees. [b] Angstroms (Å).

The free-space intramolecular entropy[15] was calculated according to eq 5 where *R* is the gas constant, *n* is the

$$S° = -R\sum_{i=1}^{n} P_i \ln P_i \qquad (5)$$

number of conformational states sampled, and P_i is the Boltzmann probability of the *i*th conformational state. The P_i, in turn, were computed from the relationship

$$P_i = \frac{e^{-E_i/RT}}{\sum_{i=1}^{n} e^{-E_i/RT}} \qquad (6)$$

where E_i is the intramolecular conformational energy of the *i*th state.

I. MM2 Results. A. *tert*-Butylcyclohexane. Figure 1 presents the MM2 energy profiles for rotation around the $C-C(CH_3)_3$ bond in axial and equatorial *tert*-butylcyclohexane (**1**, eq 4 with X = Y = CH_2), as well as the corresponding population distribution of rotamers.[16] An interesting feature of these plots is the presence of two minima for each staggered arrangement in axial **1** relative to only one for each staggered rotamer in **1**-eq. The conformers of minimum energy in axial *tert*-butylcyclohexane (Table 1) are found at dihedral angles that deviate 19.8° from the perfectly staggered rotamer, which lies 0.50 kcal/mol higher in energy.

The higher energy associated to the perfectly staggered rotamers in **1**-ax originates essentially from nonbonded

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[12] (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405, Program 395. (b) Allinger, N. L.; Yuh, Y. H.; and Lii J.-H.; *J. Am. Chem. Soc.* **1989**, *111*, 8551. (c) Burkert, U.; Allinger, N. L.; *Molecular Mechanics*; ACS Monograph 177, Washington, D.C., 1982. (d) Anet, F. A. L.; Freeberg, D. J.; Storer, J. W.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10969.

[13] In the mm31.for module, beginning in line 1477, two C's (bold, standing for comment) were added to the lines that were meant to bypass the printing of the statistical thermodynamical analysis:

```
C     IF (INORM.EQ.1)THEN

CALL NORMODE (IOUT, ID, ENERGY, LISVEC, LISAMP,
                         1 TEMPER, NOSYM, IPSU, IMIX)

C     END IF
```

[14] *Surfer* Version 4.0, Golden Software, Inc., 809 14th St, P.O. Box 281, Golden, CO 80402-0281.

[15] Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley-Interscience: New York, 1969. See also: López de Compadre, R. L.; Pearlstein, R. A.; Hopfinger, A. J.; Seydel, J. K. *J. Med. Chem.* **1987**, *30*, 900.

[16] The geometry of the cyclohexane ring distorts only slightly as a consequence of an axial *tert*-butyl group (Table 1). See also: (a) Hargrave, K. D.; Eliel, E. L. *Tetrahedron Lett.* **1979**, 1987. (b) Geneste, P.; Kamenka, J.-M.; Roques, R.; Declercq, J. P.; Germain, G. *Tetrahedron Lett.* **1981**, *22*, 949.

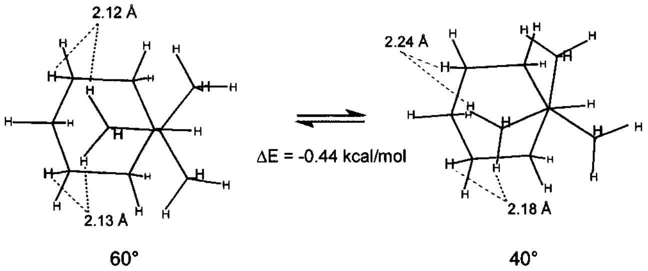


Figure 2. Responsible interactions for the *minor* barrier in axial *tert*-butylcyclohexane.

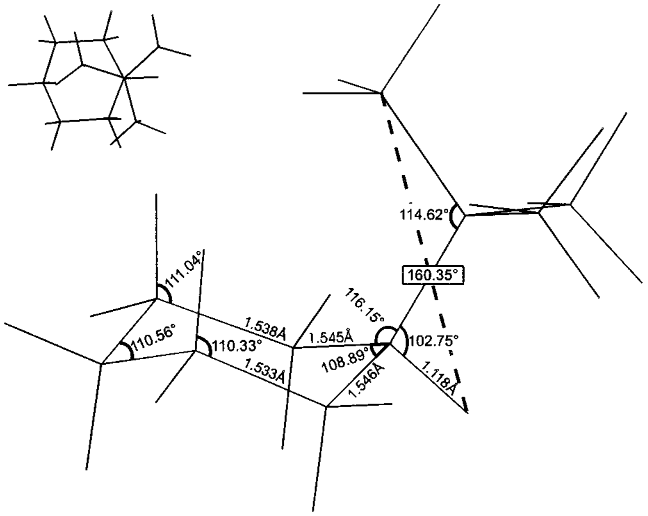
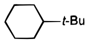
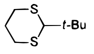
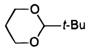
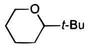
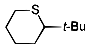
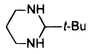
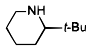
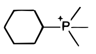
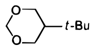


Figure 3. Geometric parameters for the minimum energy conformation in axial *tert*-butylcyclohexane.

Table 2. Deviations from the Perfectly Staggered Arrangements Found for the Minimum Energy Conformations in the Compounds Studied

Entry	axial	equatorial
1, 	19.8°	0.8°
3, 	9.2°	0.6°
4, 	17.7°	0.3°
5, 	21.8°	4.6°
6, 	16.1°	3.3°
7, 	15.9°	3.0°
8, 	19.0°	6.6°
9, 	0.6°	0.5°
10, 	3.4°	2.6°

steric interactions, which are minimized at $\tau = \pm 19.8°$ (Figures 2 and 3). Table 2 presents the deviations found in the minimum energy conformations of all structures studied.

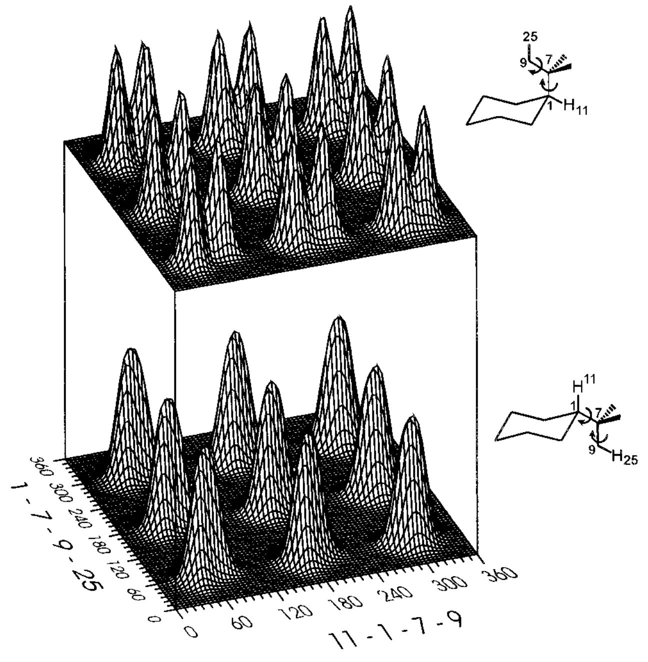
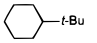
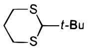
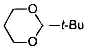
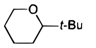
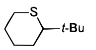
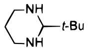
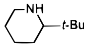


Figure 4. Population surfaces for axial (top) and equatorial (bottom) *tert*-butyl rotation in tert-butylcyclohexane.

Table 3. Thermodynamic Parameters Calculated (MM2) for the Axial *versus* Equatorial Conformations of *tert*-Butylcyclohexane and Heterocyclic Analogues

Entry	$\Delta H^{\ne}_{rot}$(ax)	$\Delta H^{\ne}_{rot}$(eq)	$\Delta\Delta H^{\ne}_{ax/eq}$	$\Delta H^{\circ}_{ax/eq}$	$\Delta S^{\circ}_{ax/eq}$
 (**1**)	3.993	4.216	0.223	-5.00	-0.44
 (**3**)	3.533	5.666	2.133	-4.42	-0.96
 (**4**)	3.952	4.934	0.982	-9.50	-0.90
 (**5**)	4.751	4.586	-0.165	-6.41	0.05
 (**6**)	3.847	5.036	1.189	-4.32	-0.72
 (**7**)	5.831	6.966	1.135	-7.53	-0.71
 (**8**)	4.970	5.591	0.621	-6.40	-0.74

While deviation from perfectly staggered conformations in axial *tert*-butylcyclohexane has been observed before by van der Graaf *et al.*,[10d,17] possible consequences on entropy content were not discussed. Nevertheless, Figure 4 clearly shows that the *libration* phenomenon results in twice as many conformational states available to axial *tert*-butylcyclohexane relative to the equatorial isomer. This is reflected in increased entropy content for **1**-ax, as confirmed in the calculated $S^{\circ}_{ax} - S^{\circ}_{eq} = \Delta S^{\circ}_{ax/eq} = -0.44$ cal/K·mol.

Also in line with a negative entropy change associated to the axial → equatorial conformational change in *tert*-butylcyclohexane is the calculated barrier for rotation in **1**-ax, which is lower than that in **1**-eq (Table 3). It can be argued[11] that a lower barrier in **1**-ax should result in greater conformational mobility (faster rotation) in this isomer relative to the equatorial one.

Finally, Table 3 includes also the calculated difference in energy (enthalpy) between axial and equatorial **1**:

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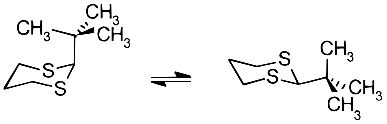
[17] These researchers[10d] localized the energy minima for **1**-ax at ±20.9° angles, relative to perfect staggering.

$\Delta H^\circ_{ax/eq} = 5.0$ kcal/mol. This value agrees quite well with the value estimated by Wepster *et al.*,[10d] 4.8 kcal/mol, and with the experimental value determined by Eliel, $\Delta G^\circ_{ax/eq} = 4.9$ kcal/mol.[7]

B. 2-*tert*-Butyl Substituted Heterocycles. 2-*tert*-Butyl-1,3-dithiane. Steric congestion in the axial isomer of 2-*tert*-butyl-1,3-dithiane (**3**-ax, eq 7) gives rise to different rotameric arrangements in which, although the total energy does not drop substantially, it does not increase significantly either. In other words, the *minimum energy valley is quite broad* (Figure 5, supporting information). The relatively ample range of torsional angles accessible to each staggered arrangement is understood by the fact that libration in **3**-ax does not significantly reduce the van der Waals repulsion that is present in the perfectly staggered rotamer; i.e., interatomic distances remain essentially unchanged (Figure 6, supporting information).

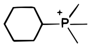
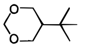
In contrast with the behavior exhibited by **3**-ax, relatively unhindered staggered arrangements are attained in **3**-eq. A graphic consequence of this enthalpic behavior is that sharp, narrow population curves are produced (Figure 7, supporting information), which imply less intramolecular movement and therefore reduced entropy. That is, the *lower degree of confinement* in the staggered axial rotamers relative to those in **3**-eq results in higher entropy for the former. Indeed, the estimated $\Delta S^\circ_{ax/eq}$ for **3**-ax → **3**-eq is a substantial $\Delta S^\circ_{ax/eq} = -0.96$ cal/K·mol.



3-ax **3**-eq (7)

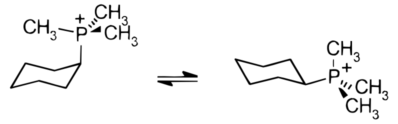
Additional *tert*-Butyl-Substituted Heterocycles. Figures 8–12 (supporting information) present the energy profiles and population plots for rotation of the $C-C(CH_3)_3$ bond in 2-*tert*-butyl-1,3-dioxane (**4**), 2-*tert*-butyltetrahydropyran (**5**), 2-*tert*-butylthiacyclohexane (**6**), 2-*tert*-butyl-1,3-diazacyclohexane (**7**), and 2-*tert*-butylazacyclohexane (**8**), respectively. These heterocycles present again in the axial isomers a distortion from the perfectly staggered rotamers to give two energy minima separated by a small energy barrier, worth between 0.18 kcal/mol in the 1,3-dioxane and 1.01 kcal/mol in the case of the tetrahydropyran ring (Table 3). A most interesting finding, however, was the good relationship observed between the width of the population curves L[18] and the entropy content $S°$ associated to both isomers (Figures 13 and 14, supporting information). Thus, the magnitude of the $S°$ term depends on L, so that maximum entropy is observed for increased L values. Furthermore, the good correlation between the ratio L_{ax}/L_{eq} and $\Delta S^\circ_{ax/eq}$ for the compounds studied (Figure 15, supporting information) confirms the determinant effect that libration phenomena have over the thermodynamic components in the axial ⇌ equatorial equilibria of the systems of interest. Indeed, the wider the energy valley for each staggered conformer the higher its entropy content.

Table 4. Calculated (MM2) Thermodynamic Parameters for the Axial *versus* Equatorial Conformations of (trimethylphosphonio)cyclohexane (9) and 5-*tert*-Butyl-1,3-dioxane (10)

Entry	$\Delta H^{\neq}_{rot}$(ax)	$\Delta H^{\neq}_{rot}$(eq)	$\Delta\Delta H^{\neq}_{ax/eq}$	$\Delta H^\circ_{ax/eq}$	$\Delta S^\circ_{ax/eq}$
	4.56	5.22	0.66	-3.25	-0.48
	3.94	4.15	0.21	-2.40	-0.28

Nevertheless, it should be emphasized that with the exception of 2-*tert*-butyltetrahydropyran, all barriers for rotation of the $C-C(CH_3)_3$ bond in the axial isomers are smaller than those for the equatorial isomers (Table 3). Presumably, steric congestion in the former raises the energy of the ground state (staggered or nearly staggered) reducing the difference in energy relative to the transition state for rotation (eclipsed rotamers) and allowing for faster rotation and thus increased entropy in the axial isomers.[11]

C. (Trimethylphosphonio)cyclohexane (9). Figure 16 (supporting information) presents the energy profiles for rotation around the C–P bond in axial and equatorial **9** (eq 8), as well as the corresponding population distribution of rotamers. As expected (see the Introduction), several features of these plots point to the similarity between the conformational behavior of (trimethylphosphonio)cyclohexane and *tert*-butylcyclohexane; for example, the energy minima for the axial staggered rotamers are wider than those for the equatorial ones (cf. Figures 1 and 16 (supporting information)). Nevertheless, the longer $C-{}^+P(CH_3)_3$ bond relative to the $C-C(CH_3)_3$ bond (1.87 Å *versus* 1.56 Å, respectively) results in a decreased conformational preference of the trimethylphosphonio group ($\Delta H^\circ_{ax/eq} = -3.25$ kcal/mol[19]) relative to that of the *tert*-butyl group ($\Delta H^\circ_{ax/eq} = -5.0$ kcal/mol, this work) for the equatorial position. Furthermore, the reduced steric hindrance between the inside $P-CH_3$ group and the methylenes at C(3,5) in **9**-ax makes the perfectly staggered rotamers true energy minima (Figure 16, supporting information).



9-ax **9**-eq (8)

The population and energy plots depicted in Figure 16 (supporting information) are wider in the axial isomer, suggesting a negative entropy change for the **9**-ax → **9**-eq process. Indeed, the calculated value is $\Delta S^\circ_{ax/eq} = -0.48$ cal/K·mol (Table 4).

D. 5-*tert*-Butyl-1,3-dioxane (10). In agreement with literature precedent,[20] substitution of the C(3,5) methylenes in *tert*-butylcyclohexane by oxygen (**1** → **10**) is

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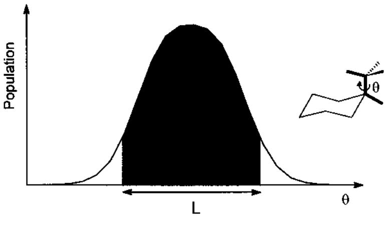
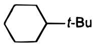
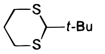
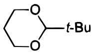
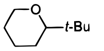
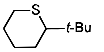
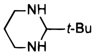
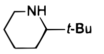
[18] The width L is taken as the projection on X's axis when 90% of the area under the curve is considered.



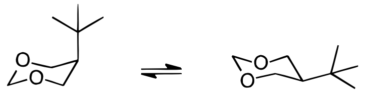
[19] Experimentally, $-\Delta G^\circ_{(PMe_3^+)}$ in cyclohexane was measured as larger than 3.0 kcal/mol: Gordon, M. D.; Quin, L. D. *J. Org. Chem.* **1976**, *41*, 1690.

[20] Cf. Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444.

Table 5. Calculated Thermodynamic Parameters (MM3) for the Axial *versus* Equatorial Conformations of *tert*-Butylcyclohexane and Heterocyclic Analogues

Item	$\Delta H^{\neq}_{rot}$(ax)	$\Delta H^{\neq}_{rot}$(eq)	$\Delta\Delta H^{\neq}_{ax/eq}$	$\Delta H^{o}_{ax/eq}$	$\Delta S^{o}_{ax/eq}$	$\Delta G^{o}_{ax/eq}$
 (**1**)	5.44	6.29	0.86	-6.14	-0.62	-6.14
 (**3**)	4.98	7.17	2.19	-6.69	-0.88	-6.69
 (**4**)	3.98	5.19	1.21	-12.64	-1.02	-12.42
 (**5**)	5.52	5.77	0.25	-7.73	-0.16	-7.73
 (**6**)	5.42	6.90	1.48	-5.51	-0.63	-5.51
 (**7**)	5.35	6.69	1.35	-7.81	-0.69	-7.81
 (**8**)	5.65	6.60	0.95	-6.35	-0.39	-6.36

estimated to reduce the amount of steric hindrance in the axial conformer (eq 9). The calculated enthalpy



10-ax **10**-eq (9)

difference, $\Delta H^{o}_{ax/eq}$(**10**) = -2.40 kcal/mol, is much less than those calculated for *tert*-butylcyclohexane [$\Delta H^{o}_{ax/eq}$(**1**) = -5.0 kcall/mol] or 2-*tert*-butyl-1,3-dioxane [$\Delta H^{o}_{ax/eq}$(**4**) = -9.5 kcal/mol].

Reduction of the *syn*-diaxial repulsive steric interaction in **10**-ax relative to **1**-ax also results in flatter energy profiles for the staggered arrangements (Figure 17, supporting information), so that the barrier for interconversion of the lowest energy rotamers in axial **10** (localized at ±3.4° relative to the perfectly staggered arrangements) is only 0.07 kcal/mol (Table 4). Nevertheless, wider energy and population profiles in the rotamer analysis for **10**-ax relative to **10**-eq results in negative entropy change for the **10**-ax → **10**-eq process, $\Delta S^{o}_{ax/eq} = -0.28$ cal/K·mol.

II. MM3 Calculations. Equation 5 calculates the entropy solely on the basis of population distribution of rotamers, neglecting rotational and vibrational contributions that might have a significant effect on entropy content. Moreover, it has been suggested that for dynamic molecular systems at room temperature, probability functions rather than point distributions should be used in order to estimate Boltzmann distributions.[21,22] These points are taken into account in Allinger's more recent force field program MM3,[12b] so it was deemed necessary to reexamine the conformational behavior of **1** and **3**–**8** with this program.

The resulting energy and population plots for *tert*-butyl group rotation (Figures 18–24, supporting information) are quite similar to those obtained with MM2. Furthermore, the thermodynamic parameters calculated for the corresponding axial to equatorial conformational processes (Table 5) confirm the lower entropy content associated to the latter isomers. This finding, namely the similar values for ΔS^{o}_{mixing} (derived from MM2 calculations) and ΔS^{o}_{total} ($S^{o}_{total} = S^{o}_{trans} + S^{o}_{rot} + S^{o}_{vibr} + S^{o}_{mix}$ obtained from MM3 calculations), suggests that the entropy of mixing is the dominant contributing entropy term in these six-membered ring systems.

Conclusions

Theoretical examination of the rotameric distribution of the axial and the equatorial conformers of *tert*-butylcyclohexane, (trimethylphosphonio)cyclohexane, and eight more *tert*-butyl substituted, *N*-, *O*-, and *S*-containing heterocycles was carried out by means of Allinger's MM2 and MM3(92) programs. With only one exception (2-*tert*-butyltetrahydropyran), all systems were found to have greater entropy in the axial relative to the equatorial isomers.

Examination of the energy profiles for C$-$C(CH$_3$)$_3$ or C$-^{+}$P(CH$_3$)$_3$ bond rotation, as well as consideration of the corresponding rotamer distribution plots, indicates that the substantial steric repulsion present in the staggered arrangements of the axial isomers gives way to a libration phenomenon, which is responsible for their increased entropy. By contrast, the staggered rotamers in the equatorial isomers are well-defined global minima, which effectively confine these conformers to a reduced number of rotameric states and thus to a lower entropy content.

Acknowledgment. We are grateful to CONACYT, Mexico, for financial support and to Profs. N. L. Allinger and E. Lissi for useful comments.

Supporting Information Available: Energy profiles and population plots obtained with MM2 for 2-*tert*-butyl-1,3-dithiane, 2-*tert*-butyl-1,3-dioxane, 2-*tert*-butyltetrahydropyran, 2-*tert*-butyltetrahydrothiopyran, 2-*tert*-butyl-1,3-diazacyclohexane, and 2-*tert*-butylazacyclohexane and energy profiles and population plots obtained with MM3(92) for *tert*-butylcyclohexane, 2-*tert*-butyl-1,3-dithiane, 2-*tert*-butyl-1,3-dioxane, 2-*tert*-butyltetrahydropyran, 2-*tert*-butylthiacyclohexane, 2-*tert*-butyl-1,3-diazacyclohexane, and 2-*tert*-butylazacyclohexane (Figures 5–24) (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[21] See, for example: Baginski, M.; Piela, L. *J. Comput. Chem.* **1993**, *14*, 478.

[22] See also: Senderowitz, H.; Guarnieri, F.; and Still, W. C. *J. Am. Chem. Soc.* **1995**, *117*, 8211.