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Ab initio molecular orbital study of the conformational energies ($-\Delta G^\circ$ or *A* values) of 4-alkyltetrahydro-2*H*-thiopyrans (tetrahydrothiopyrans, thiacyclohexanes, thianes)†

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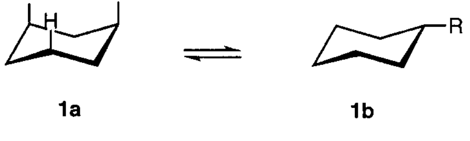
ABSTRACT: *Ab initio* 6–31G* and MP2/6–31G*//6–31G* methods were used to calculate the relative energies of the rotamers in the chair conformations of 4-alkyltetrahydro-2*H*-thiopyrans (tetrahydrothiopyrans, thiacyclohexanes, thianes; CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9, *neo*-C_5H_{11}, $SiMe_3$). The MP2/6–31G*//6–31G* conformational energies ($-\Delta G^\circ$ or *A* values, kcal mol^{-1}) of the 4-alkylthiacyclohexanes (Me =1.94; Et =1.72; *i*-Pr =1.62; *t*-Bu =5.49; *neo*-Pent =1.39; $SiMe_3$ =2.76) are similar to those calculated for the corresponding alkylcyclohexanes. Plots of the calculated conformational energies for the 4-alkylthiacyclohexanes versus the calculated conformational energies for the corresponding alkylcyclohexanes are linear (slope =1.01 and $r = 0.999$ for 6–31G* and slope =1.09 and $r = 0.990$ for MP2/6–31G*//6–31G*). The conformational energies are strongly influenced by the magnitude and number of repulsive nonbonded hydrogen–hydrogen interactions and the *gauche* (synclinal) effects in the conformers. The carbon–sulfur bond lengths are mostly in the narrow range of 1.815–1.818 Å. The C—S—C angles vary from 97.1° to 99.4° and the C(3)—C(4)—C(7) angle in the most stable axial conformer is larger that the corresponding angle in its most stable equatorial conformer. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: conformational energy; tetrahydrothiopyrans; *ab initio* molecular orbital

INTRODUCTION

Substituents on the chair conformation of cyclohexane [(**1**, R = H), Eqn (1)][1–4] or at the 4-position of the half-chair conformation of cyclohexene[4] generally prefer the equatorial position. In monosubstituted cyclohexanes (**1**), the axial substituents may have steric interactions with the synaxial hydrogens at C(3) and C(5) [1, 3-diaxial interactions, Eqn (1)] and with other hydrogens on the ring. The more stable equatorial conformer generally experiences fewer repulsive non-bonded hydrogen–hydrogen interactions. The difference in energy between the most stable axial and its most stable equatorial conformer is called the equatorial preference and designated the conformational energy (ΔG° or *A* value). (The free-energy difference between conformers is referred to as the conformational energy,[5,6] or sometimes as the *A* value.[7] For substituted cyclohexanes it is conventional to specify the value of $-\Delta G^\circ$ for the equilibrium axial ⥂ equatorial. Since $-\Delta G^\circ$ will be negative when the equatorial conformation is more stable than the axial conformation, the value of $-\Delta G^\circ$ is positive for substituents that favor the equatorial position.[6]) The larger the conformational energy, the greater the preference of the substituent for the equatorial position. While much work has been dedicated to the study of conformational energies in carbocycles and in molecules containing first-row elements, much less effort has been devoted to systems containing second-row elements.[8–14]



(1)

This study was undertaken in order to investigate the influence of replacing a methylene group in cyclohexane (**1**, R = H) with a sulfur atom, to give tetrahydro-2*H*-

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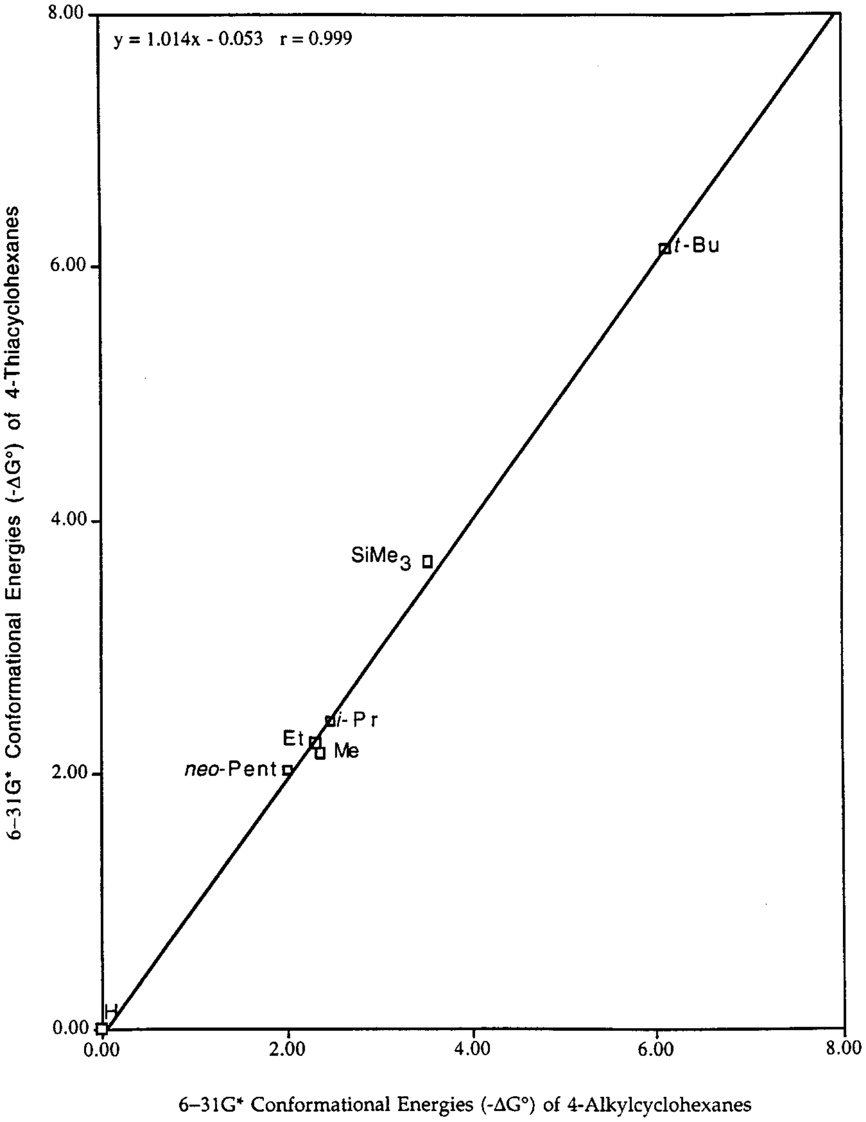


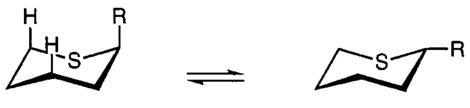
Figure 1. Plot of the 6–31G* conformational energies of 4-alkylthiacyclohexanes versus the conformational energies of the corresponding alkylcyclohexanes

thiopyran (tetrahydrothiopyran, thiacyclohexane, thiane, **2**), by comparing the geometries (6–31G*) and conformational energies (MP2/6–31G*//6–31G* single point energies) of 4-alkylthiacyclohexanes [**3**, R = CH_3,C_2H_5,*i*-C_3H_7,*t*-C_4H_9,*neo*-C_5H_{11},$SiMe_3$,Eqn (2)] with those of the corresponding alkylcyclohexanes [**1**, Eqn (1); Figures 1 and 2) and with selected 2-alkylthiacyclohexanes [**4**, Eqn (3)].[11]

(2)

2 R = H **3a**

2 R = H **3b**



(3)

4a

4b

Theoretical calculations provide energy differences for isolated molecules at 0 K. Therefore, theoretical calculations are not expected, in principle, to reproduce the experimental results quantitatively.[14] Nevertheless, it is possible to carry out *ab initio* calculations at the Hartree–Fock level, from which many properties and structures can be obtained with an accuracy that is competitive with experiment.[8–19] Since the theoretical results are free from intermolecular interferences, they are a valuable tool for

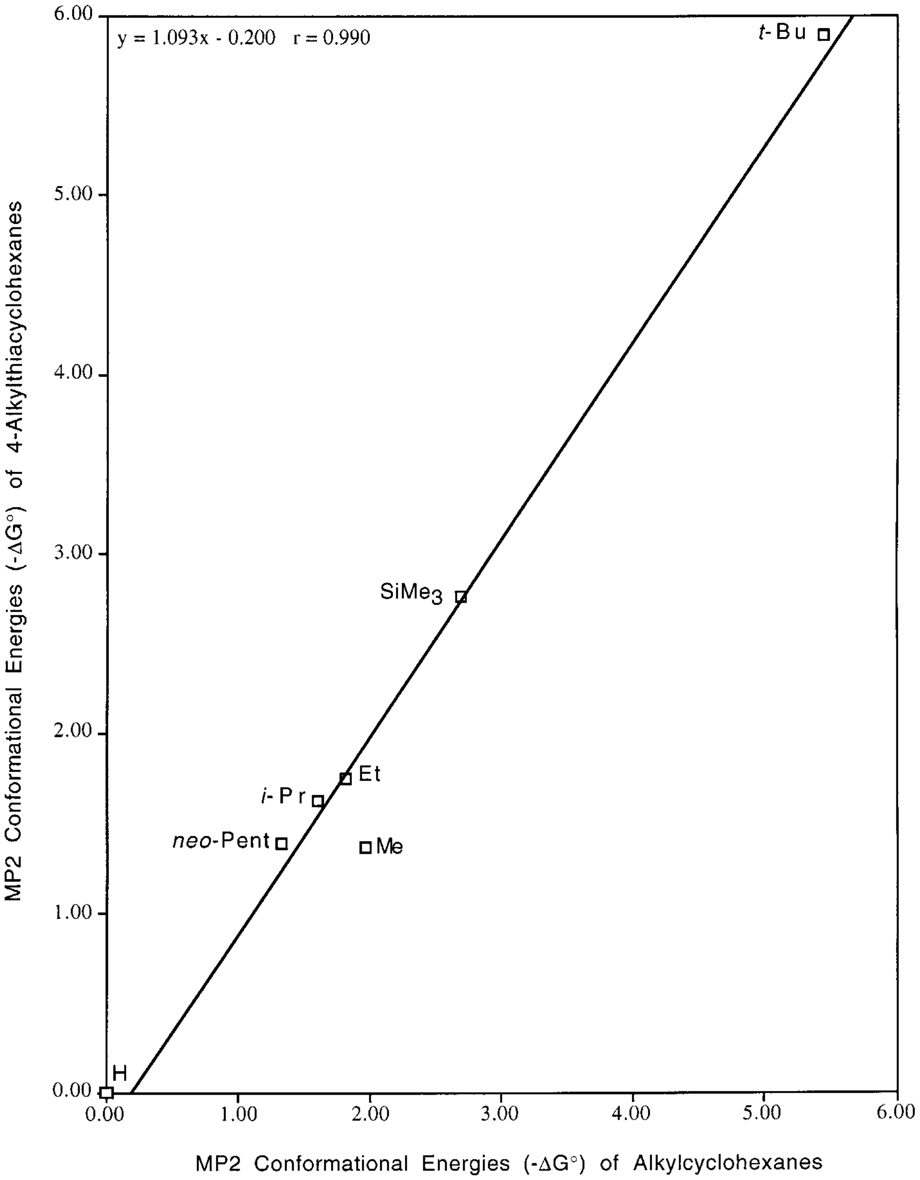


Figure 2. Plot of the MP2/6–31G*//6–31G* conformational energies of 4-alkylthiacylohexanes versus the conformational energies of the corresponding alkylcyclohexanes

a systematic study of substitutent effects in cyclohexanes,[14] tetrahydro-2*H*-pyrans (tetrahydropyrans, oxacyclohexanes, oxanes)[14] and thiacylohexanes (Tables 1 and 2).[8–13]

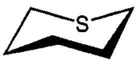
COMPUTATIONAL METHODS

The optimized geometries (6–31G*) and single point energies (MP2/6–31G*//6–31G*) were calculated using the SPARTAN 4.1 computational program.[20–24] The results from MP2/6–31G*//6–31G* calculations are used in the conformational energies[5,6] discussions below.

RESULTS AND DISCUSSION

Although thiacyclohexane (**2**) has a chair structure (Table 1) similar to cyclohexane (**1**, R = H), it is more puckered in order to accomodate the bond angles and bond lengths characteristic of sulfur. Electron diffraction studies in the gas phase reveal a slight flattening of the chair conformation of cyclohexane. The C—C—C—C torsion angles are 55.9°, compared with 60° for the ideal chair conformation.[25] The *gauche* interactions in cyclohexanes and thiacyclohexanes may not be comparable to those of *gauche* butane because the hydrogen–hydrogen interactions are minimized in the cyclic structures.[26–28] The calculational methods used here give some approxima-

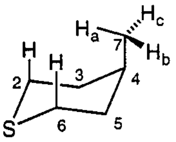
Table 1. Comparison of calculated and experimental bond lengths (Å), bond angles (°) and dihedral angles (°) for thiacyclohexane (**2**)



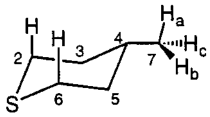
2

Parameter	MM3[12,13]	MM4[12,13]	6–31G*	MW[30]	ED[31]
Bond length					
C—H	1.114	1.113	–	1.095	1.114
C_2—H_{ax}	–	–	1.085	–	–
C_2—H_{eq}	–	–	1.083	–	–
C_2—C_3	1.536	1.531	1.528	1.533	1.528
C_3—C_4	–	–	1.532	1.533	1.528
C_2—S_1	1.813	1.814	1.817	1.832	1.811
Bond angle					
H—C—H	106.4	106.4	–	108.5	105.9
H—C_2—H	–	–	1.074	–	–
H—C_3—H	–	–	1.071	–	–
C_2—C_3—C_4	112.7	112.7	112.8	107.9	112.3
C_3—C_4—C_5	112.6	112.9	113.2	109.2	113.8
C_3—C_2—S_1	111.3	112.8	112.9	114.1	112.7
C_2—S_1—C_6	97.5	97.4	98.5	99.2	97.6
Torsion angle					
C—C—C—C	–	–	59.4	–	58.6
C—C—C—S_1	–	–	60.0	–	60.8
C—C—S_1—C	–	–	53.4	–	55.4

Table 2. Comparison of calculated bond lengths (Å), bond angles (°) and dihedral angles (°) for 4-methylthiacyclohexane (**5**)



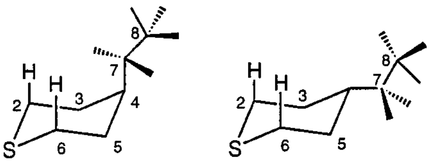
5a



5b

	5a		5b	
Parameter	MM4 (r_g[12,13]	6–31G*	MM4 (r_g[12,13]	6–31G*
Bond length				
C_2—H_{ax}	1.112	1.084	1.112	1.085
C_2—H_{eq}	1.111	1.088	1.112	1.083
C_2—C_3	1.534	1.529	1.535	1.528
C_3—C_4	1.523	1.539	1.529	1.535
S_1—C_2	1.813	1.817	1.812	1.816
S_1—C_6	1.813	1.817	1.812	1.816
Bond angles				
H—C_2—H	105.8	107.1	106.1	107.4
H—C_3—H	106.2	106.9	106.5	107.0
C_2—C_3—C_4	114.3	114.5	113.1	113.5
C_3—C_4—C_5	111.5	111.6	111.6	111.9
S_1—C_2—C_3	112.9	111.6	112.8	112.9
C_2—S_1—C_6	97.5	98.8	97.1	98.2
Torsion angles				
C_2—C_3—C_4—C_5	57.5	57.8	59.2	59.0
S_1—C_2—C_3—C_4	60.7	59.7	61.8	60.5
C_2—S_1—C_6—C_5	54.1	52.6	54.8	53.3

Table 3. Calculated energies (hartree), conformational energies ($-\Delta G°$ or *A* values, kcal mol^{-1})[5–7] and dipole moments (D) of 4-alkylthiacyclohexanes[a–c]



Alkyl group		6–31G*			MP2/6–31G*//6–31G*	
		Energy	$-\Delta G°$	Dipole moment	Energy	$-\Delta G°$
H	**2**[b]	−592.681604	–	2.0	−593.456783	–
CH_{3ax}	**5a**	−631.713486	–	2.1	−632.622890	–
CH_{3eq}	**5b**	−631.717048	2.24	2.0	−632.625992	1.94
C_2H_{5ax}	**7a**	−670.746041	–	2.1	−671.787628	–
C_2H_{5eq}	**7b**	−670.749503	2.17	2.1	−671.790376	1.72
C_2H_{5eq}	**7c**	−670.748147	[1.32]	2.1	−671.789316	[1.06]
i-C_3H_{7ax}	**8a**[b]	−709.776830	–	2.1	−710.953716	–
i-C_3H_{7eq}	**8b**	−709.780663	2.41	2.1	−710.956291	1.62
i-C_3H_{7eq}	**8c**	−709.779648	[1.77]	2.1	−710.955540	[1.14]
t-C_4H_{9ax}	**9a**	−748.800258	–	2.2	−750.114537	–
t-C_4H_{9eq}	**9b**	−748.810048	6.14	2.1	−750.123278	5.49
neo-C_5H_{11ax}	**10a**	−787.843427	–	2.2	−789.287832	–
neo-C_5H_{11eq}	**10b**	−787.846649	2.02	2.1	−789.290046	1.39
$SiMe_{3ax}$	**11a**	−999.886225	–	2.1	−1001.143807	–
$SiMe_{3eq}$	**11b**	−999.892066	3.67	2.1	−1001.148201	2.76

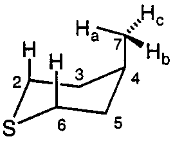
[a] The other values in the $-\Delta G°$ columns are the energy differences (in brackets) between the most stable axial conformer and its other equatorial conformer.
[b] C_1 point group unless specified otherwise.
[c] C_s point group.

Table 4. Calculated torsion angles (°) in 4-alkylthiacyclohexanes

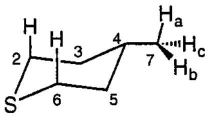
Alkyl group		Torsion angle			
		C_2—C_3—C_4—C_7	C_6—C_5 C_4—C_7	C_3—C_4—C_7—C_8	C_5—C_4 C_7—C_8
CH_{3ax}	**5a**	69.6	69.6	–	–
CH_{3eq}	**5b**	176.9	176.9	–	–
C_2H_{5ax}	**7a**	68.3	69.5	63.8	69.5
C_2H_{5eq}	**7b**	177.6	176.1	64.7	170.7
C_2H_{5eq}	**7c**	172.0	172.0	63.6	63.5
i-C_3H_{7ax}	**8a**	66.9	66.9	178.3 (55.7)	55.7 (178.3)
i-C_3H_{7eq}	**8b**	170.7	172.0	69.6 (164.1)	57.3 (69.0)
i-C_3H_{7eq}	**8c**	177.4	177.4	179.1 (56.0)	56.2 (179.4)
t-C_4H_{9ax}	**9a**	84.2	80.8	50.5 (173.3), 70.0	82.3 (40.5), 157.3
t-C_4H_{9eq}	**9b**	170.6	170.6	63.4 (175.4), 57.8	63.6 (57.8), 175.4
neo-C_5H_{11ax}	**10a**	70.0	69.6	111.5	121.9
neo-C_5H_{11eq}	**10b**	176.3	176.4	106.5	129.3
$SiMe_{3ax}$	**11a**	77.8	78.7	77.2 (162.1), 45.1	56.4 (64.3), 178.7
$SiMe_{3eq}$	**11b**	173.5	173.5	63.6 (175.7), 57.0	63.6 (57.1), 175.8

tion to the equilibrium bond lengths (r_e), whereas the experimental values from electron diffraction (r_g) and microwave (r_s) spectroscopic studies give vibrationally averaged values. These numbers are different physical quantities and have different numerical values. Thus, r_e needs to be converted to r_g and r_s in order to make valid comparisons.[29] Although the chair conformation of **2** was deduced from the microwave spectroscopic investigation, the rotational constants proved insufficient to uniquely specify the molecular conformation.[30, 31] The carbon–sulfur bond (1.817 Å) in **2** is longer than the carbon–carbon bond (1.532 Å) in cyclohexane and the C—S—C bond angle (98.5°) in **2** is smaller than the C—C—C tetrahedral angle (111.5°) in cyclohexane.

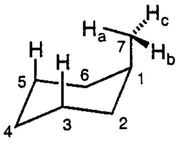
Table 3 shows that the equatorial conformer **5b** [zero *gauche* (synclinal) butane interactions, Table 4] of 4-methylthiacyclohexane (**5**) is more stable ($-\Delta G° =$ 1.94 kcal mol^{-1}) than the axial conformer **5a** [two *gauche* (synclinal) butane interactions, Table 4].[2,12,13,26–28] *Gauche:* In A—B—C—D, ligands A and D are *gauche* if the torsion angle (ABCD) about the B—C bond is near +60° or −60°. Synclinal (*sc*): in X—A—B—Y, ligands X and Y are synclinal if the torsion angle (XABY) about the A—B bond is between +30° and +90° or between −30° and −90°.[1] The MP2/6–31G*//6–31G* calculated conformational energy for **5** ($-\Delta G° = 1.94$ kcal mol^{-1}) is larger than the value ($-\Delta G° = 1.78$ or 1.82 kcal mol^{-1}) obtained by Allinger and co-workers[12,13,32] using molecular mechanics (MM3 and MM4) and the value of 1.80 kcal mol^{-1} obtained from the low-temperature ^{13}C NMR studies of Barbarella *et al.*[33] (in CD_2Cl_2) and of Eliel and Willer[34,35] (in $CDCl_3$). The MP2/6–31G*//6–31G* calculated[11] and the experimental[33–35] conformational energy values for 2-methylthiacyclohexane (**4**) are 1.00 and 1.42 kcal mol^{-1}, respectively. The MP2/6–31G*//6–31G* calculated[14,28,36,37] and the experimental[38,39] conformational energy values for methylcyclohexane (**6**) are 1.96 and 1.74 kcal mol^{-1}, respectively. The similarities and small variations among the conformational energies of alkylcyclohexanes (**1**) and 4-alkylthiacyclohexanes (**3**) are seen in Figs 1 and 2. [It is found experimentally that there is little variation in $-\Delta G°$ between cyclohexane and different heterocycles at the 4-position.[40] For example, axial and equatorial methyl groups at C(4) appear to be 'cyclohexane-like' except for variations in the exact ring shape, as expected.]



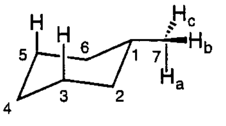
5a



5b



6a



6b

In the axial conformation **5a**, the distances from C(2)—H_{ax} to C(7)—H_a and from C(6)—H_{ax} to C(7)—H_a are 2.388 and 2.388 Å, respectively, which are shorter than the sum (2 × 1.20 = 2.40 Å) of the van der Waals radii for hydrogen. The van der Waals radius, which is determined from interatomic distances in crystals, is the effective size of the atomic cloud around a covalently bonded atom as perceived by another atom. The van der Waals radius is not the distance at which repulsive interactions of the electrons on two atoms outweigh the attractive forces between them. Hydrogen–hydrogen distances greater than 2.500 Å are not included in the discussion. Many sets of van der Waals radii are available.[41–47]) The C(4)—H_{eq} to C(7)—H_b and to C(7)—H_c distances are 2.453 and 2.453 Å , respectively. In the equatorial conformation **5b**, the C(4)—H_{ax} to C(7)—H_b and to C(7)—H_c distances are 2.480 and 2.480 Å , respectively. It is the stronger repulsive non-bonded hydrogen–hydrogen interactions in **5a** which also contribute to its higher energy relative to **5b**. Table 5 shows that the C(2)—C(3)—C(4) and C(3)—C(4)—C(7) angles in the axial conformer **5a** are slightly larger than the corresponding angles in its equatorial conformer **5b**. This suggests that the methyl group in the axial conformer **5a** is tilted away from the interior of the ring in order to minimize the repulsive non-bonded interactions with the synaxial C(2) and C(6) hydrogens. The

Table 5. Calculated bond angles (°) in 4-alkylthiacyclohexanes

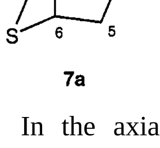
Alkyl group		Bond angle				
		C_2—S_1—C_6	C_2—C_3—C_4	C_3—C_4—C_5	C_3—C_4—C_7	C_5—C_4—C_7
–	**2**	98.5	112.8	112.9	–	–
CH_{3ax}	**5a**	98.8	114.5	111.6	112.5	112.5
CH_{3eq}	**5b**	98.2	113.5	111.9	110.8	110.8
C_2H_{5ax}	**7a**	99.0	114.5	110.7	114.1	111.9
C_2H_{5eq}	**7b**	97.9	113.6	111.4	112.2	109.9
C_2H_{5eq}	**7c**	98.4	113.0	111.6	112.5	112.5
i-C_3H_{7ax}	**8a**	99.4	114.4	109.0	114.0	114.0
i-C_3H_{7eq}	**8b**	98.2	113.2	111.1	111.8	114.0
i-C_3H_{7eq}	**8c**	97.1	114.3	110.7	111.7	111.7
t-C_4H_{9ax}	**9a**	98.3	117.4	109.8	115.9	117.6
t-C_4H_{9eq}	**9b**	97.6	113.4	109.9	113.7	113.7
neo-C_5H_{11ax}	**10a**	98.2	114.7	111.0	112.9	112.6
neo-C_5H_{11eq}	**10b**	98.1	113.6	111.1	111.3	110.9
$SiMe_{3ax}$	**11a**	98.7	114.6	110.9	116.5	116.2
$SiMe_{3eq}$	**11b**	98.1	113.6	111.5	112.7	112.7

Table 6. Calculated (6–31G*) bond distances (Å) of 4-alkylthiacyclohexanes

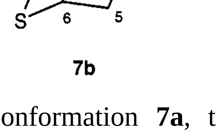
		Bond distance			
Alkyl group		C_4—C_7	C_4—C_5	C_2—S_1	C_6—S_1
–	**2**	–	1.532	1.817	1.817
CH_{3ax}	**5a**	1.534	1.539	1.817	1.817
CH_{3eq}	**5b**	1.530	1.535	1.816	1.816
C_2H_{5ax}	**7a**	1.540	1.540	1.818	1.817
C_2H_{5eq}	**7b**	1.537	1.537	1.815	1.815
C_2H_{5eq}	**7c**	1.539	1.536	1.816	1.816
i-C_3H_{7ax}	**8a**	1.551	1.542	1.818	1.818
i-C_3H_{7eq}	**8b**	1.549	1.538	1.815	1.815
i-C_3H_{7eq}	**8c**	1.551	1.540	1.812	1.812
t-C_4H_{9ax}	**9a**	1.571	1.542	1.815	1.815
t-C_4H_{9eq}	**9b**	1.565	1.542	1.813	1.813
neo-C_5H_{11ax}	**10a**	1.553	1.540	1.816	1.816
neo-C_5H_{11eq}	**10b**	1.550	1.537	1.815	1.815
$SiMe_{3ax}$	**11a**	1.922	1.545	1.816	1.817
$SiMe_{3eq}$	**11b**	1.913	1.543	1.815	1.815

carbon–sulfur bond distances in **5a** and **5b** are the same (1.817 Å, Table 6).

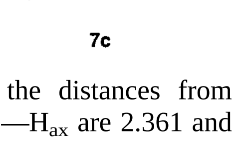
Table 3 shows that the equatorial conformer **7b** of 4-ethylthiacyclohexane (**7**) is more stable than its axial conformer **7a** ($-\Delta G° = 1.72$ kcal mol^{-1}). This value is larger than the calculated ($-\Delta G° = 1.16$ kcal mol^{-1}) value for 2-ethylthiacyclohexane (**4**)[11] and is similar to the calculated ($-\Delta G° = 1.80$ kcal mol^{-1})[36] and experimental values ($-\Delta G° = 1.79$ kcal mol^{-1}) for ethylcyclohexane (in solution, the entropy and enthalpic terms must be considered.[38,39,48,49]). The axial conformer has three rotamers: **7a** (two *gauche* butane interactions)[1,26–28] and its mirror image, and a high-energy rotamer (very low population) with the methyl group pointing toward the ring. The equatorial conformer **7b** also has three populated rotamers: conformer **7b** (one *gauche* butane interaction) and its mirror image, and conformer **7c** (two *gauche* butane interactions).[1,26–28] Interestingly, the 6–31G* and MP2/6–31G* //6–31G* calculated energy difference between the equatorial conformers **7b** and **7c** are 0.85 and 0.66 kcal mol,$^{-1}$ respectively, either of which is approximately one *gauche* butane interaction.[1,26–28]



7a



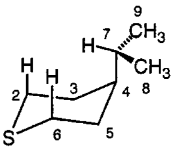
7b



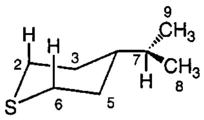
7c

In the axial conformation **7a**, the distances from C(7)—H_a to C(2)—H_{ax} and to C(6)—H_{ax} are 2.361 and 2.381 Å, respectively. The C(4)—H_{eq} to C(7)—H_b distance is 2.468 Å and C(3)—H_{eq} is 2.294 Å from one C(8)—H. In the chiral equatorial conformer **7b**, the C(4)—H_{ax} to C(7)—H_b, the C(5)—H_{eq} to C(7)—H_b and the C(3)—H_{eq} to C(8)—H distances are 2.493, 2.364, and 2.276 Å, respectively. The six repulsive nonbonded hydrogen–hydrogen distances in the symmetrical equatorial conformer **7c** for C(3)—H_{ax} to C(8)—H_b, C(3)—H_{eq} to C(7)—H_b, C(4)—H_{ax} to C(7)—H_a, C(4)—H_{ax} to C(7)—H_b, C(5)—H_{eq} to C(7)—H_a and C(5)—H_{ax} to C(8)—H_a are 2.367, 2.490, 2.396, 2.396, 2.490, and 2.367 Å, respectively. Thus, the additional non-bonded interactions and the additional *gauche* butane interaction help to make the equatorial conformer **7c** of higher energy that **7b**. The similarity of the calculated conformational energies for **5** and **7**, is consistent with rotation about the C(4)—C(7) bond in **7** in such a way that the ethyl group adopts conformations which minimize the effects of the additional methyl group (*cf.* **5a**, **6a** and **7a**).[40]

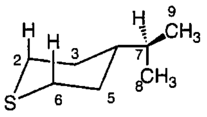
Table 3 shows that the equatorial conformers **8b** ($-\Delta G° = 1.62$ kcal mol^{-1}) and **8c** of isopropylthiacyclohexane (**8**) are more stable than the axial conformer **8a**. Interestingly, the conformational energy ($-\Delta G° = 1.62$ kcal mol^{-1}) of **8** is close to the calculated value for isopropylcyclohexane ($-\Delta G° = 1.59$ kcal mol^{-1}, Fig. 1 and 2).[36,40] The axial conformer **8a** (four *gauche* butane interactions)[26–28] exists as a single rotamer and the equatorial conformer has three rotamers (**8b** and **8c** and its enantiomer). The more stable equatorial conformer **8b** has two *gauche* butane interactions and the less stable conformer **8c** and its mirror image each has three *gauche* butane interactions. The difference in energy between the equatorial conformers **8b** and **8c** is 0.48 kcal mol^{-1} (Table 2).



8a



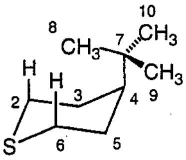
8b



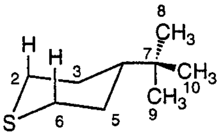
8c

In the axial conformer **8a**, the distances from C(7)—H to C(2)—H_{ax} and to C(6)—H_{ax} are 2.353 and 2.353 Å, respectively, which are shorter than the sum of the van der Waals radii for hydrogen.[41–47] The C(3)—H_{eq} to C(9)—H and the C(5)—H_{eq} to C(8)—H distances in **8a** are is 2.176 and 2.176 Å, respectively. In the equatorial conformer **8b**, the C(3)—H_{eq} to C(9)—H and the C(5)—H_{eq} to C(8)—H distances are is 2.129 and 2.127 Å, respectively. In the equatorial conformer **8c**, the C(3)—H_{ax} to C(8)—H_b distance is 2.399 Å, the C(5)—H_{ax} to C(8)—H_a distance is 2.308 Å and the C(7)—H to C(5)—H_{eq} distance is 2.337 Å. In addition, in **8c**, the C(3)—H_{eq} to C(9)—H_b distance is 2.283 Å and the C(4)—H_{ax} to C(9)—H_a distance is 2.403 Å.

An axial *tert*-butyl group cannot avoid the stringent steric repulsion of the 1,3-diaxial interactions with the methyl group. The equatorial conformer **9b** (four *gauche* butane interactions) of 4-*tert*-butylthiacyclohexane (**9**) is more stable than its axial conformer **9a** (six *gauche* butane interactions, $-\Delta G° = 5.49$ kcal mol^{-1}). In **9a**, the distances from C(2)—H$_{ax}$ to C(8)—H$_b$ and from C(6)—H$_{ax}$ to C(8)—H$_a$ are 2.174 and 2.194 Å, respectively. The distance from C(5)—H$_{eq}$ to C(9)—H is 2.440 Å. Also in **9a**, the C(3)—H$_{eq}$ and C(4)—H$_{eq}$ distances to C(10)—H$_a$ and C(10)—H$_b$ are 2.157 and 2.394 Å, respectively. In **9b**, the C(3)—H$_{eq}$ to C(8)—H distance is 2.118 Å and the C(4)—H$_{ax}$ to C(10)—H$_b$ and the C(5)—H$_{eq}$ to C(10)—H$_a$ distances are 2.444 and 2.117 Å, respectively. The C(3)—H$_{ax}$ to C(9)—H$_b$ and the C(5)—H$_{ax}$ to C(9)—H$_a$ distances are 2.325 and 2.325 Å, respectively. The much larger conformational energy value for **9** compared with methyl (**5**), ethyl (**7**) and isopropyl (**8**) is a consequence of requiring a methyl group to reside over the interior of the thiacyclohexane ring in the axial conformation (**9a**) of **9**.

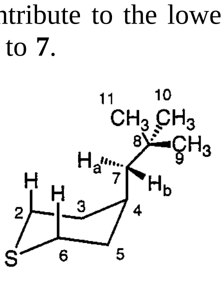


9a

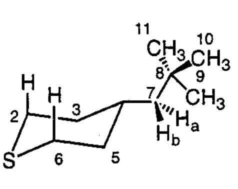


9b

Table 3 shows that the equatorial conformer **10b** (two *gauche* butane interactions) of 4-neopentylthiacyclohexane (**10**) is more stable than the axial conformer **10a** (four *gauche* butane interactions, $-\Delta G° = 1.39$ kcal mol^{-1}). The similarity of the conformational energy for of **10** and 4-ethylthiacyclohexane (**7**, $-\Delta G° = 1.72$ kcal mol^{-1}) again reflects the ability of the methyl group (in **7**) and the *tert*-butyl group (in **10**) in the axial conformer to rotate away from the ring in order to minimize repulsive non-bonded interactions. In the axial conformation **10a**, there are four repulsive nonbonded hydrogen–hydrogen interactions. The distances from C(2)—H$_{ax}$ to C(7)—H$_a$ and from C(6)—H$_{ax}$ to C(7)—H$_b$ are 2.285 and 2.364 Å, respectively. Also in **10a**, the distance from C(4)—H$_{eq}$ to C(9)—H is 2.209 Å and the distance from C(4)—H$_{eq}$ to C(10)—H is 2.266 Å. In the equatorial conformer **10b**, the C(3)—H$_{ax}$ to C(7)—H$_a$ and the C(5)—H$_{ax}$ to C(7)—H$_b$ distances are 2.418 and 2.362 Å, respectively. The C(4)—H$_{ax}$ to C(10)—H and C(11)—H distances in **10b** are 2.342 and 2.215 Å, respectively. These repulsive nonbonding interactions in the equatorial conformer **10b** may also contribute to the lower equatorial preference in **10** relative to **7**.

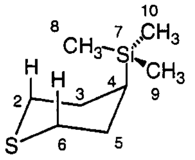


10a

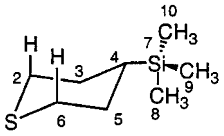


10b

Table 3 shows that the equatorial conformer **11b** (four *gauche* butane interactions) of 4-trimethylsilylthiacyclohexane (**11**) is more stable than the axial conformer **11a** (six synclinal interactions, $-\Delta G° = 2.76$ kcal mol^{-1}). In the axial conformer **11a**, there are two repulsive nonbonded hydrogen–hydrogen interactions: C(2)—H$_{ax}$ to C(8)—H$_a$ = 2.416 Å and C(6)—H$_{ax}$ to C(8)—H$_b$ = 2.357 Å. There are no non-bonded hydrogen–hydrogen interactions (<2.500 Å) in the equatorial conformer **11b**. The smaller conformational energy of the trimethylsilyl group relative to the *tert*-butyl group (**9**, $-\Delta G° = 5.49$ kcal mol^{-1}) is due to the longer carbon–silicon bond which moves the methyl groups farther from the ring. The carbon–silicon bond lengths in **11a** and **11b** are 1.922 and 1.913 Å, respectively.



11a



11b

CONCLUSIONS

Table 3 shows that conformational energy is not solely a function of substituent size. Perusal of the conformational energies indicates that an alkyl group in either the axial or equatorial position can orient itself in such a way as to minimize repulsive non-bonded interactions with the ring. The number of *gauche* interactions in a population of conformers when the alkyl groups are in the axial or equatorial position and the non-bonded repulsive interactions in all conformers must be considered in evaluating conformational energies.[26–28,38,39,48,49] The carbon–sulfur bond lengths (Table 6) in the 4-substituted thiacyclohexanes are mostly in the narrow range of 1.815–1.818 Å for the 14 axial and equatorial conformers studied. The C—S—C angles vary from 97.1° to 99.4° and the C(3)—C(4)—C(7) angle in the most stable axial conformer is larger that the corresponding angles in its most stable equatorial conformer (Table 5).

It is recognized that the conformational energies of groups in heterocycles generally cannot be directly equated with cyclohexane $\Delta G°$ values owing to differences in bond angles and bond lengths. However, if it is assumed that there are no stereoelectronic effects, it should be possible to derive a proportionality constant that relates cyclohexane to thiacyclohexane by comparing conformational energies of simple alkyl groups and other nonpolar carbon functions.[14,50,51] [Although steric effects are considered to be responsible for equatorial preferences in cyclohexanes,natural bond orbital analysis (NBO)[14] suggests that bond–anti-bond interactions of the exocylic C(1)—C(7) bond in methylcyclohexane (**6**) with $^{*}{}_{C—C}$ and $\sigma^{*}{}_{C—H}$ bonds are mainly responsible for the equatorial preference.] Plots (Figs 1 and 2) of the calculated conformational energies ($-\Delta G°$) for the 4-alkylthiacyclohexanes versus the calculated $-\Delta G°$ values for the corresponding alkylcyclohexanes are linear (slope = 1.01 and $r = 0.999$ for 6–31G*; slope = 1.09 and $r = 0.990$ for MP2/6–31G*//6–31G*).[40] Thus, although the thiacyclohexane ring may be more puckered that than the cyclohexane ring, the conformational energies in the heterocycles are influenced similarly by factors (*gauche* effects, non-bonded interactions, steric effects, stereoelectronic effects) which are observed in the corresponding alkylclohexanes.

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