Why Doesn't *all-trans*-1,2,3,4,5,6-Hexaspiro(THF)cyclohexane Complex Metal Ions?

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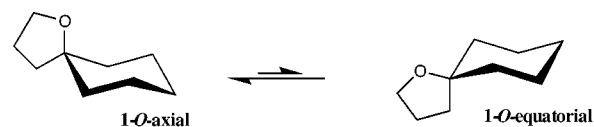Box 351700, Seattle, Washington 98195-1700*

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Despite the inherent preference for placing alkyl substituents, rather than alkoxy substituents, in equatorial positions, *all-trans*-hexaspiro(THF)cyclohexane strongly favors the all-*O*-equatorial conformer. Ab initio and density functional calculations on a series of cyclohexane derivatives containing one, two, or three spiro(THF) units demonstrate that this preference results from at least two important factors. First, when oxygen atoms are attached to adjacent carbons, the gauche effect favors the di-*O*-equatorial arrangement. In *trans*-1,2-dispiro(THF)cyclohexane, the single gauche interaction overcomes the inherent steric preference for projecting the two oxygen atoms axially. Similarly, in the *all-trans*-hexaspiro(THF)cyclohexane the six gauche interactions in the all-*O*-equatorial conformer overpower the inherent conformational biases of the six isolated spiro-(THF) moieties. Nevertheless, the gauche effect only partially accounts for the more than 20 kcal/mol conformational bias calculated for this molecule. There is also another factor, the high energetic cost associated with projecting multiple alkoxy substituents axially on the same face of a cyclohexane scaffold. The calculations find the energetic cost of each 1,3-diaxial interaction is about 2 kcal/mol larger between alkoxy substituents than between alkyl substituents.

The conformational behavior of cyclohexane rings is more thoroughly studied and understood than that of perhaps any other class of organic structure.[1] The preference of substituents to occupy an equatorial, as opposed to an axial, position is described quantitatively by the so-called *A* value. Comparison of the experimental *A* values of ethyl and methoxy reveals that the ethyl group has the stronger preference for equatorial projection, by 1.2 kcal/mol.[2]

This difference is easily understood on steric grounds. In an axial ethyl group, the two hydrogens of the methylene carbon interact with the axial hydrogens at carbons 3 and 5 of the cyclohexane ring. In a methoxy group these two hydrogens are replaced by sterically less demanding oxygen lone pairs.

Simple extrapolation of the behavior of ethyl and methoxy leads to the prediction that, in general, an alkoxy group should occupy an axial position in preference to an alkyl group, whenever one of the two is forced to occupy an axial position. Thus, one would expect the monospiro(THF)cyclohexane **1** to prefer the conformation in which the THF oxygen, not the methylene, occupies the axial position. In fact, experiments have found that the conformational composition of **1** is 68% *O*-axial and

32% *O*-equatorial in solution at 35 °C.[3,4] The preference is not strong, but it certainly operates in the expected direction.

Although the conformational energies of substituents positioned in a 1,4-relationship on a cyclohexane ring are close to additive,[5,6] some breakdown of this additivity occurs for groups located 1,3 to each other, and additivity is entirely lost for most vicinal 1,2 substitution patterns.[7−11] The general cause of these deviations from additivity is the repulsive interaction between the sub-

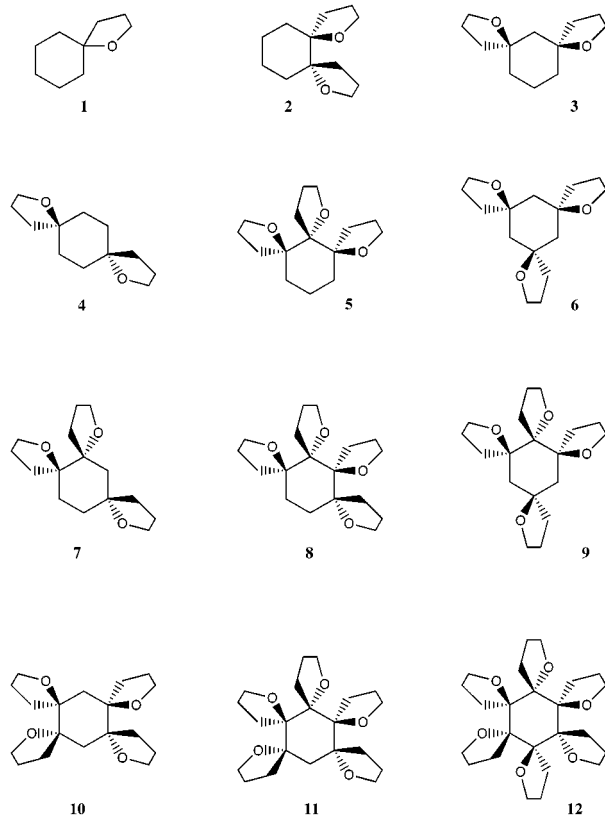† Swarthmore College.
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(1) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, John Wiley and Sons: New York; 1994; pp 686−726. (b) Juaristi, E., Ed. *Conformational Behavior of Six-Membered Rings*; VCH Publishers: New York, 1995.
(2) *A*-value for ethyl = 1.8 kcal/mol (Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1966**, *31*, 804); *A* value for methoxy = 0.6 kcal/mol (Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199).
(3) Picard, P.; Mouline, J. *Tetrahedron Lett.* **1970**, 5133−5136.

(4) The present calculations (Table 1) predict a 0.5−1.1 kcal/mol preference for the *O*-axial conformer, depending on the level of calculation, in at least fair agreement with the experimental findings. The small discrepancy between calculation and experiment could easily be the result of the influence of the solvent, which is neglected in the calculations. The calculated conformational preference also is in good accord with the difference in experimental *A* values between ethyl and methoxy, 1.2 kcal/mol.
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(11) Rockwell, G. D.; Grindley, T. B. *Austr. J. Chem.* **1996**, *49*, 379−390.

Scheme 1

stituents in one, but not both, of the two available chair conformers. Where spiro(THF) appendages are involved, the effects become more subtle because both the alkyl and alkoxy substituents are part of the same five-membered cyclic array. Nevertheless, the initial expectation, based on the preference of **1** for the *O*-axial conformation, is that all-*trans*-hexaspiro(THF)cyclohexane **12** should favor the chair conformer in which the six oxygens are axial. However, it has been found experimentally that the reverse is true - - only the all-*O*-equatorial conformer of **12** is observed. In fact, having the oxygen atoms in the axial positions is so strongly disfavored that this compound fails to coordinate metal ions, as it would have done if the complexation energy were sufficient to overcome the preference of the oxygens for occupying equatorial positions.[12]

To understand the unexpected behavior of **12**, we performed calculations on it and on the model compounds **1**−**11** in Scheme 1. The results of these calculations are reported here. Our calculations mirror the contrasting

conformational preferences of **1** and **12** and provide an explanation for the observation that in **12** the hexa-*O*-equatorial conformer is strongly favored.

Computational Methodology

Both ab initio (HF and MP2) and density functional calculations were carried out with the Gaussian 98 package,[13] using standard Pople basis sets.[14] The density functional calculations employed the B3LYP functional, which consists of Becke's 3-parameter hybrid exchange functional[15] in conjunction with the correlation functional of Lee, Yang, and Parr.[16,17] The stationary points located were identified as minima via calculation of vibrational frequencies. Symmetrical structures that were found to have imaginary frequencies were reoptimized in lower symmetry. Zero-point vibrational energy corrections were scaled by 0.8934 at the HF/6-31G* level,[18] and by 0.97 for the B3LYP calculations.[19] Single-point MP2/6-31G*, B3LYP/6-311+G**, and MP2/6-311+G** energies were calculated at the B3LYP/6-31G* optimized geometries. Energies discussed in the text are B3LYP/6-31G* unless otherwise noted. This level of theory yields energies that are in the middle of the range of values obtained from the various other methods; so the B3LYP/6-31G* energies provide a representative picture. However, the discussion would not be substantially changed if any of the other sets of energies were used instead.

Initial conformational searching was accomplished using the MacroModel software package[20] and the MM2* force field.[20,21] At least 1000 Monte Carlo steps were used for each structure, and the THF rings were permitted full conformational flexibility. The lowest energy structure found in this manner was then used as the starting point for the ab initio geometry optimizations described above. This procedure was used for each conformer (all-*O*-equatorial and all-*O*-axial) of each compound **1**−**12**.

Results and Discussion

Model Systems. The two possible chair conformations of the cyclohexane rings in model compounds **1**−**12** were optimized via HF/6-31G* and B3LYP/6-31G* calculations, followed by single-point energy calculations at somewhat higher levels of theory. The structures involved in these conformational equilibria are shown in Scheme 2, and the corresponding energies appear in Table 1. The number of possible conformations grows rapidly with the number of THF rings; therefore, complete conformational searching via molecular orbital calculations was not feasible. However, we did explore the most likely conformations, including those found to be the most stable via thorough Monte Carlo conformational searching, which was accomplished using the MM2 molecular mechanics force field.[20,21] It seems unlikely that further

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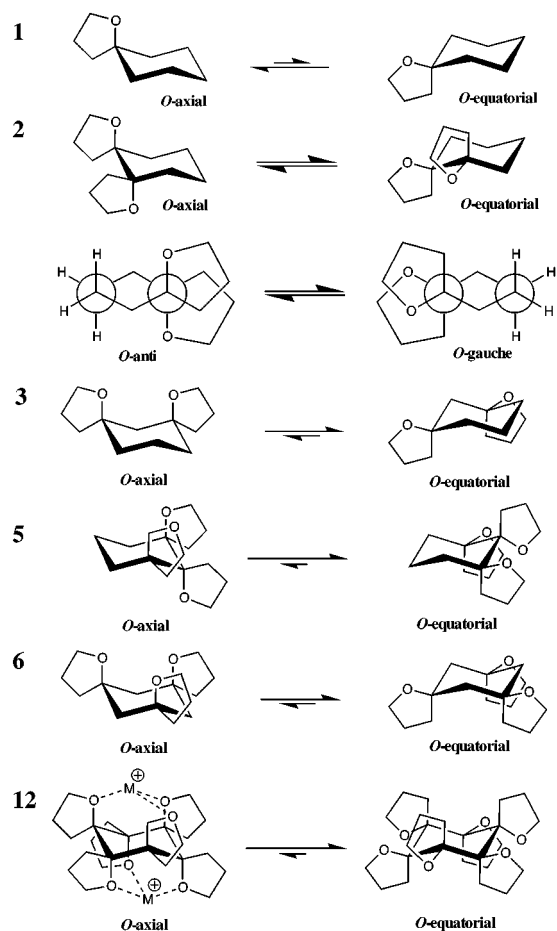
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Scheme 2

searching would have located conformations with significantly lower energies.

Although HF/6-31G* and B3LYP/6-31G* calculations certainly do not represent the highest levels of theory currently available, the fairly large size of **1**−**12** necessitated the use of a relatively inexpensive computational method. Moreover, the conformational behavior of relatively unstrained saturated compounds, consisting of only carbon, oxygen, and hydrogen, is generally well reproduced at modest levels of theory; and even the HF/6-31G* method has proven quite satisfactory in the past.[14,22,23]

As already noted, it is impossible to predict the preferred conformation of hexaspiro(THF)cyclohexane **12** on the basis of that of monospiro(THF)cyclohexane **1**. For example, **1** is calculated to prefer the *O*-axial conformation by 0.7 kcal/mol at the B3LYP/6-31G* level of theory.[24] Based on this result, one can thus estimate that the inherent steric preference for the conformer of **12** in which all the oxygens are axial should be $6 \times 0.7 = 4.2$ kcal/mol. However, **12** is actually calculated to prefer the all-*O*-equatorial conformer, and by 22.0 kcal/mol!

The Gauche Effect. It seemed likely that the so-called gauche effect might provide at least a partial explanation

for the seemingly anomalous behavior of **12**. The gauche effect is known to cause compounds with vicinal electronegative atoms to prefer conformations in which these atoms are in a gauche, rather than an anti, relationship.[23] This phenomenon is generally understood to result from the difference in hyperconjugative donor ability between C−H and C−O bonds that are positioned anti to a C−O bond.[23] Examination of Scheme 2 shows that the all-*O*-equatorial conformer of **12** achieves a gauche arrangement for all pairs of vicinal oxygen atoms; whereas, the all-*O*-axial conformer does so for none of them.[25]

In addition to the electronic factor that favors a gauche relationship between the oxygens in **12**, steric avoidance of gauche interactions between methylene groups may also contribute to the preference for the all-*O*-equatorial conformation in **12**. The all-*O*-axial conformation of **12** places six pairs of methylene groups of the spiro(THF) units in gauche relationships, and the fact that butane prefers an anti conformation over a gauche conformation demonstrates that gauche interactions between alkyl groups are sterically unfavorable. In this paper, wherever the term "gauche effect" is used, both electronic and steric contributions to the preference of trans vicinal THF rings for the *O*-equatorial conformation are implied.

An appropriate model for determining the size of the gauche effect in **12** is *trans*-1,2-dispiro(THF)cyclohexane **2**. If the gauche effect controls the conformational behavior of **2**, one would expect a preference for the conformer of **2** that places both oxygens equatorial. As shown in Scheme 2, in this conformation the gauche arrangement of the oxygens is achieved, and the gauche arrangement of the spiro(THF) methylenes is avoided. Indeed, **2** is calculated to prefer the di-*O*-equatorial conformation, by 0.4 kcal/mol.

In **2**, the gauche effect is apparently strong enough to counteract the inherent preference for placing each oxygen axial, which is reflected in the 0.7 kcal/mol preference for the *O*-axial conformation in **1**.[24] The inherent steric preference for the conformer of **2** in which each oxygen is projected axially thus amounts to $2 \times 0.7 = 1.4$ kcal/mol. Based on the net preference of 0.4 kcal/mol for the di-*O*-equatorial conformer, a value of ca. $1.4 + 0.4 = 1.8$ kcal/mol can thus be assigned to the strength of the single gauche interaction in **2**.

The six spiro(THF) moieties in **12** should confer on this cyclohexane a 4.2 kcal/mol inherent steric bias for *O*-axial, but the *six* gauche interactions in the *O*-equatorial conformer favor it by $6 \times 1.8 = 10.8$ kcal/mol. Compared to **2**, the inherent steric preference for *O*-axial is multiplied by three, but the gauche interactions are increased by a factor of 6!

If these were the only two effects that determined the preferred conformation of **12**, the all-*O*-equatorial conformer should be preferred by $10.8 - 4.2 = 6.6$ kcal/mol. However, **12** favors the all-*O*-equatorial conformer, not by 6.6 kcal/mol, but by 22.0 kcal/mol, leaving more than two-thirds of this conformational preference unexplained.

1,3-Diaxial Interactions. The source of the missing 15 kcal/mol can be identified by considering the two possible conformations of *cis*-1,3-dispiro(THF)cyclohexane **3**. Because the spiro(THF) units in **3** do not reside on

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(24) This bias is in qualitative agreement with the 1.2 kcal/mol difference between the experimental *A* values of ethyl and methoxy.

(25) The recent crystal structure analysis of the first sexifuran to be synthesized shows the molecule to populate a conformation in which the oxygens are very predominantly in gauche arrangements with helical consequences: Paquette, L. A.; Ohmori, N.; Lowinger, T. B.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 4303−4308.

Table 1. Conformational Energies of Model Systems

compd	subst. pattern[a]	relative energy[b] (kcal/mol)				
		HF/6-31G*[c]	B3LYP/6-31G*[d]	MP2/6-31G*[e]	B3LYP/6-311+G**[e]	MP2/6-311+G**[e]
1	1	+0.99	+0.69	+1.09	+0.50	+0.53
2	1,2	+0.09	−0.39	−0.53	−0.28	−0.62
3	1,3	−0.62	−0.95	−0.91	−1.57	−1.51
4	1,4	+2.47	+1.82	2.44	1.63	1.47
5	1,2,3	−4.84	−5.25	−5.92	−5.51	−5.78
6	1,3,5	−2.33	−3.10	−2.11	−3.50	−1.76
7	1,2,4	−0.56	−0.88	−1.01	−1.19	−1.34
8	1,2,3,4	−7.98	−8.40	−9.41	−8.72	−9.05
9	1,2,3,5	−4.98	−6.18	−6.76	−6.50	−6.11
10	1,2,4,5	−2.27	−3.75	−4.42	−3.91	−4.14
11	1,2,3,4,5	−11.11	−12.13	−13.37	−12.61	−11.96
12[f]	1,2,3,4,5,6	−21.79	−22.00	−24.79	−22.01	−21.79

[a] Substitution pattern of compound. [b] Energy of all-*O*-equatorial conformer minus that of all-*O*-axial conformer; i.e., positive value means all-*O*-axial is favored, and a negative value indicates that all-*O*-equatorial is favored. [c] Includes HF/6-31G* zero-point vibrational energy (ZPE) scaled by 0.8934. [d] Includes B3LYP/6-31G* zero-point energy (ZPE) scaled by 0.97. [e] Single-point calculation at the B3LYP/6-31G* optimized geometry; includes B3LYP/6-31G* zero-point energy scaled by 0.97. [f] The B3LYP/6-31G* zero-point vibrational energy calculation for the axial conformer, which is of C_1 symmetry, was taken from a similar conformer of C_i symmetry, since a full frequency calculation on the C_1-symmetric structure was not feasible, due to hardware limitations.

adjacent carbons of the cyclohexane ring, there are no gauche interactions between oxygen atoms in this molecule. Since there are no gauche interactions between oxygen atoms in **3**, one might expect the inherent steric preference for placing alkoxy, rather than alkyl, in the axial position to result in a $2 \times 0.7 = 1.4$ kcal/mol preference for the di-*O*-axial conformer.

However, Table 1 shows that **3** is, in fact, calculated to have a 0.9 kcal/mol preference for the di-*O*-equatorial conformation. This finding suggests that there is a penalty of ca. $1.4 + 0.9 = 2.3$ kcal/mol associated with projecting the two oxygens, rather than two THF methylene groups, axially on the same face of the cyclohexane ring.

The same effect is discernible in *all-cis*-1,3,5-trispiro-(THF)cyclohexane **6**. Again, there are no gauche interactions between oxygens, so one might expect the inherent steric preference for placing alkoxy, rather than alkyl, in the axial position to result in a $3 \times 0.7 = 2.1$ kcal/mol preference for the tri-*O*-axial conformer. However, the behavior of **3**, discussed above, indicates that placing the oxygen atoms of two THF units in a 1,3-diaxial arrangement exacts an energetic cost of 2.3 kcal/mol. The *three* 1,3-diaxial interactions in **6**, then, should impart an energetic cost of $3 \times 2.3 = 6.9$ kcal/mol.

Consequently, **6** is in fact expected to prefer the tri-*O*-equatorial conformation, by $6.9 - 2.1 = 4.8$ kcal/mol. As shown in Table 1, the actual size of this preference is computed to be 3.1 kcal/mol, in reasonable agreement with the value based on extrapolating the sizes of the conformational preferences in **1** and **3** to the case of **6**.

Experimentally, it has been found that **6** prefers the all-*O*-equatorial conformer, both in solution and in the solid state.[26] However, the size of this preference is evidently not strong enough to prevent lithium ion complexation from causing **6** to adopt the all-*O*-axial conformation.[26] Nevertheless, in the absence of metal ions, the preferred conformation of **6** is that predicted,

but the opposite of what might have been expected, based only on the preference of **1** for the *O*-axial conformer.[3,4]

What is the origin of the energetic penalty for 1,3-diaxial projection of the oxygen atoms of THF units that are in a cis relationship? Is there, in fact, such a penalty; or is there a stabilizing interaction between the 1,3-diequatorial alkoxy oxygens?

Comparison of the absolute energies (in the Supporting Information) of the di-*O*-equatorial conformations of **3** and **4** reveals that the former is actually higher than the latter at all levels of theory. Therefore, it appears that the stabilization associated with interaction between 1,3-diequatorial alkoxy groups is minimal, if such stabilization exists at all. It then follows that the 2.3 kcal/mol preference for the di-*O*-equatorial conformation in **3** must be due to the fact that the interactions between 1,3-diaxial oxygens are destabilizing.

Of course, it is not surprising, in and of itself, that placing multiple *cis*-cyclohexane substituents in axial positions is unfavorable; for example, 1,3-diaxial interactions are well-known to destabilize the diaxial conformation of *cis*-1,3-dimethylcyclohexane.[1] However, the conformational behavior of **3** and **6** indicates that it is considerably *more* unfavorable to place the oxygen atoms of two *cis*-1,3 THF units in a diaxial relationship than it is to place the methylene groups in a diaxial relationship![24] This result appears to run counter to the finding that axial methylene is sterically more demanding than axial oxygen, as shown by the A-values for ethyl and methoxy and by the preferred conformation of **1**. However, it must also be remembered that the cyclic nature of the THF unit makes the corresponding "alkyl" and "alkoxy" substituents significantly different from free alkyl and alkoxy substituents such as ethyl or methoxy.

One effect that contributes to disfavoring *cis*-1,3-diaxial oxygens relative to *cis*-1,3-diaxial methylene groups is that the oxygens have larger partial charges on them than the methylene groups do. The negatively charged oxygen atoms have a larger Coulombic repulsion energy when they are both *cis*-diaxial, rather than *cis*-diequatorial. Another possible contributor to *cis*-1,3-diaxial oxygens being disfavored is that in this conformation the lone pairs on the oxygen atoms approach each other closely enough to undergo antibonding four-electron interactions.[27]

(26) (a) Paquette, L. A.; Tae, J. S.; Hickey, E. R.; Rogers, R. D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1409−1411. Once several spiro-(THF) rings are installed on a cyclohexane scaffold, the tendency to project as many C−O bonds as possible in the equatorial plane is quite evident: Paquette, L. A.; Stepanian, M.; Branan, B. M.; Edmondson, S. D.; Bauer, C. B.; Rogers, R. D. *J. Am. Chem. Soc.* **1996**, *118*, 4504−4505. (b) Paquette, L. A.; Tae, J.; Branan, B. M.; Bolin, D. G.; Eisenberg, S. W. E. *J. Org. Chem.* **2000**, *65*, 9172−9179.

Table 2. Energy Components Contributing to the Preference of Hexaspiro(THF)cyclohexane 5 for the *O*-Equatorial Conformation

component	source[a]	energy[b,c] (kcal/mol)				
		HF/6-31G*	B3LYP/6-31G*	MP2/6-31G*	B3LYP/6-311+G**	MP2/6-311+G**
A: spiro(THF) substituent	**1**	+1.0	+0.7	+1.1	+0.5	+0.5
G: gauche *O-O* interaction	**2**	−1.9	−1.8	−2.7	−1.3	−1.7
D: 1,3-diaxial *O-O* interaction[d]	**3**	−2.6	−2.3	−3.1	−2.6	−2.6

[a] Model compound from which the size of this energy is estimated. [b] A positive value means *O*-axial is favored; a negative value indicates *O*-equatorial is favored. [c] HF energies include zero-point energy (ZPE) scaled by 0.8934; B3LYP and MP2 energies include B3LYP/6-31G* ZPE scaled by 0.97. [d] *Differential* cost of placing two *cis*-1,3 spiro(THF) substituents in a di-*O*-axial orientation *instead of* a di-*O*-equatorial orientation. The *absolute* cost of the 1,3-diaxial *O-O* interaction is presumably greater.

Conformational Analysis of Polyspiro(THF)cyclohexane Systems. The 22.0 kcal/mol preference of **12** for the *O*-axial conformation can be explained semiquantitatively on the basis of three effects, revealed by our calculations on **1**−**3**. These effects are: (1) the intrinsic steric preference for placing alkoxy, instead of alkyl, in the axial position in **1**, (2) the stabilizing gauche interaction found in **2**, and (3) the energetic cost in **3** of projecting *cis*-1,3 oxygens axially. The size of each of these contributions is shown in Table 2. Since there are six contributions of each type in **12**, they sum to 6 × (0.7 − 1.8 − 2.3) = −20.4 kcal/mol, where the negative sign indicates the lower energy of the *O*-equatorial conformer. The 20.4 kcal/mol lower energy of the *O*-equatorial conformer of **12**, predicted on the basis of B3LYP/6-31G* calculations on **1**−**3**, is very close to the value of 22.0 kcal/mol that is actually computed at the B3LYP/6-31G* level for **12** (Figure 1).

The same approach can be applied to the other polyspiro(THF)cyclohexane systems shown in Scheme 1 and Table 1. In Table 3, predictions of the equatorial-axial energy difference are made for each of the compounds **1**−**12**, using the three parameters in Table 2. In general, the predictions are fairly reliable, with an RMS error of ±1.2 kcal/mol. The maximum error, 1.7 kcal/mol, occurs in the cases of **6** and **10**. Obviously, factors other than the three we have identified affect the quantitative energy difference between the *O*-axial and *O*-equatorial conformations of **1**−**12**. However, the three discussed here are adequate for semiquantitatively duplicating the results of our calculations.[28]

(27) A *large* repulsion between axial *oxygens* can rationalize the observation that the energetic cost of each 1,3-diaxial interaction is 2.3 kcal/mol larger between alkoxy substituents than between alkyl substituents in **3** (and **5**). However, an unexpectedly *small* interaction between axial *alkyl groups* could explain this observation equally well. It would not be unreasonable to suppose that distortion of the axial C−C bonds away from the center of the cyclohexane ring is less costly for the methylene groups of spiro(THF) units than for acyclic alkyl substituents. However, the same effect would, of course, also serve to diminish the repulsive interactions between 1,3-diaxial oxygens.

(28) Another effect one might consider is the contribution from 1, 4 interactions. The calculations on **4** indicate that a 1,4-interaction favors the di-*O*-axial conformation by 1.8 − 1.4 = 0.4 kcal/mol. The larger than expected preference of **12** for the all-*O*-equatorial conformation can be rationalized by introducing a fifth effect into the three-parameter model. In the model system **3** used to determine the strength of 1,3-diaxial interactions, the cyclohexane ring is able to distort so as to relieve some of the 1,3-diaxial strain. In fact, in both **3** and **6**, the axial oxygens are visibly splayed outwards. However, in **12**, distortion of this sort must either worsen the strain on the opposite face of the cyclohexane ring, or else result in partial eclipsing strain around the six-membered ring. Consequently, this type of distortion, which relieves the repulsions between 1,3-diaxial oxygens, occurs to a lesser extent in **12** than in **6**. The B3LYP/6-31G* optimized O−O distances between the axial oxygen are 2.97 Å in **6**, but only 2.90 à in **12**. Obviously, a five-parameter model would bring the estimates of the conformational preferences of **1**−**12** into better quantitative agreement with the B3LYP/6-31G* computational results. However, the much simpler three-parameter model is capable of predicting the preferred conformations of **1**−**12** correctly, albeit with slightly less quantitative accuracy.
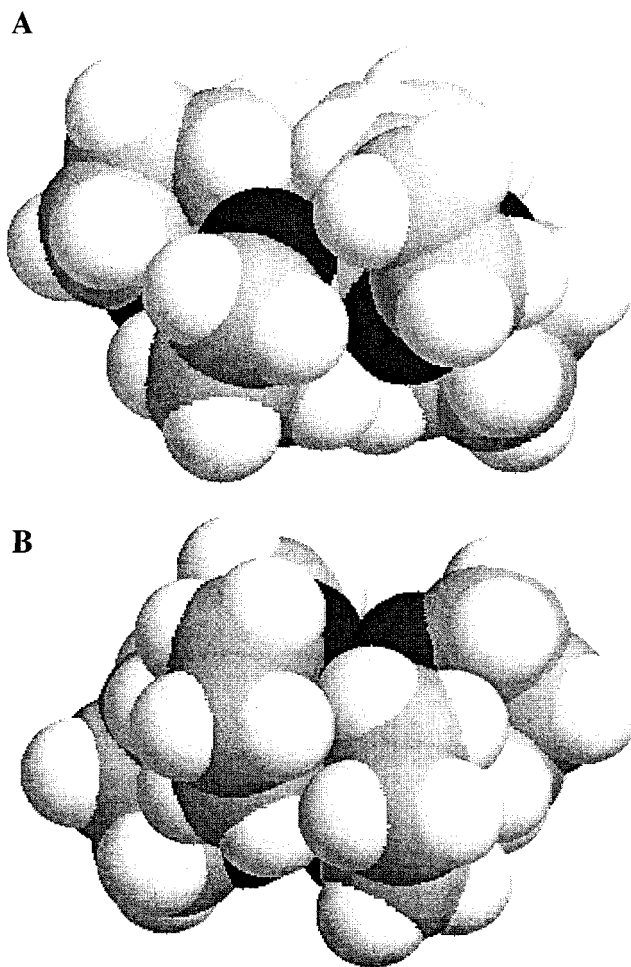
A

B

Figure 1. Space-filling representations of the B3LYP/6-31G*-optimized geometries of *all-trans*-hexaspiro(THF)cyclohexane **12**: (A) all-*O*-equatorial conformation; (B) all-*O*-axial conformation.

Summary

Single alkoxy substituents show a weaker preference for equatorial over axial projection than do single alkyl substituents. When an oxygen competes with a methylene carbon for an equatorial position in spiro(THF)-cyclohexane **1**, B3LYP/6-31G* calculations show a ca. 0.7 kcal/mol preference for the conformer that places the alkoxy substituent in the axial position. However, when multiple alkoxy and alkyl substituents are installed on a single cyclohexane ring, two factors operate to counteract the natural tendency of the alkoxy substituents to occupy the axial positions. First, when alkoxy substituents are located on adjacent carbons, as in **2**, the gauche effect favors the diequatorial conformation. The gauche effect in this context can be considered to have both an

Table 3. Comparison of ab Initio Calculated Conformational Energies with Predictions of the Simple Additive Model

compd	subst. pattern[a]	model energy components[b]	relative energy[c,d] (kcal/mol)									
			HF/6-31G*		B3LYP/6-31G*		MP2/6-31G*[f]		B3LYP/6-311+G**[f]		MP2/6-311+G**[f]	
			model[e]	diff.[f]	model[e]	diff.[f]	model[e]	diff.[f]	model[e]	diff.[f]	model[e]	diff.[f]
1	1	A	+1.0	0.0	+0.7	0.0	+1.1	0.0	+0.5	0.0	+0.5	0.0
2	1,2	2A + G	+0.1	0.0	−0.4	0.0	−0.5	0.0	−0.3	0.0	−0.7	−0.1
3	1,3	2A + D	−0.6	0.0	−0.9	0.0	−0.9	0.0	−1.6	0.0	−1.6	−0.1
4	1,4	2A	+2.0	−0.5	+1.4	−0.4	+2.2	−0.2	+1.0	−0.6	+1.0	−0.5
5	1,2,3	3A + 2G + D	−3.4	+1.4	−3.8	+1.5	−4.4	+1.5	−3.7	+1.8	−4.5	+1.3
6	1,3,5	3A + 3D	−4.8	−2.5	−4.8	−1.7	−6.0	−3.9	−6.3	−2.8	−6.3	−4.5
7	1,2,4	3A + G + D	−1.5	−0.9	−2.0	−1.1	−2.5	−1.5	−2.4	−1.2	−2.8	−1.5
8	1,2,3,4	4A + 3G + 2D	−6.9	+1.1	−7.2	+1.2	−9.9	−0.5	−7.1	+1.6	−8.3	+0.8
9	1,2,3,5	4A + 2G + 3D	−7.6	−2.6	−7.7	−1.5	−10.3	−3.5	−8.4	−1.9	−9.2	−3.1
10	1,2,4,5	4A + 2G + 2D	−5.0	−2.7	−5.4	−1.7	−7.2	−2.8	−5.8	−1.9	−6.6	−2.5
11	1,2,3,4,5	5A + 4G + 4D	−13.0	−1.9	−12.9	−0.8	−17.7	−4.3	−13.1	−0.5	−14.7	−2.7
12	1,2,3,4,5,6	6A + 6B + 6C	−21.0	+0.8	−20.4	+1.6	−28.2	−3.4	−20.4	+1.6	−22.8	−1.4
RMS[g]				1.5		1.2		2.4		1.5		2.0

[a] Substitution pattern of compound. [b] Components of simple additive model listed in Table 2 required to describe compound. [c] A positive value means *O*-axial is favored; a negative value indicates *O*-equatorial is favored. [d] HF energies include zero-point energy (ZPE) scaled by 0.8934; B3LYP and MP2 energies include B3LYP/6-31G* ZPE scaled by 0.97. [e] Conformational energy difference predicted from additive model described in Table 2. [f] Difference between prediction of additive model (previous column) and the corresponding ab initio or DFT calculation (Table 1). [g] RMS (root-mean-square) deviations between the predictions of the additive model and the ab initio or DFT calculations.

electronic component, which favors a gauche relationship between the oxygens, and also a steric component, which resists the alternative gauche relationship between methylene groups. The competition between the gauche effect and the intrinsic steric preference for placing methylene groups equatorial and oxygens axial, results in a modest preference for the di-*O*-equatorial conformer in 1,2-dispiro(THF)cyclohexane **2**, computed to be 0.4 kcal/mol at the B3LYP/6-31G* level.

The second effect which favors conformations that place *O*-equatorial is the high energetic cost of interactions between *cis*-1,3-diaxial oxygens of THF units. Based on the results of B3LYP/6-31G* calculations on **3**, the energetic cost of a 1,3-diaxial interaction between THF oxygens is about 2.3 kcal/mol larger than that between THF methylene groups. This destabilizing interaction between 1,3-diaxial oxygens probably results from a combination of electrostatic repulsion between the partial negative charges on the oxygens and four-electron, antibonding interactions between the oxygen lone pairs.

The combination of the six gauche and the six O−O 1,3-diaxial interactions in **12** overwhelm the intrinsic

preference for having each of the six oxygens axial. This results in the all-*O*-axial conformation being so disfavored for **12** that even the energy lowering associated with metal complexation is unable to drive **12** to adopt this conformation.

Supporting Information Available: Cartesian coordinates of B3LYP/6-31G*-optimized structures corresponding to the energies in Table 1; calculated energies in Hartrees. This material is available free of charge via the Internet at http://pubs.acs.org.

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