Conformational Analysis of Poly(spirotetrahydrofuranyl)cyclohexyl Systems. The Preference of Multiple C−O Bonds for Equatorial Occupancy

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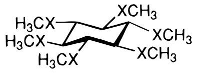
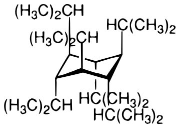
Recognition of the chair conformation of cyclohexane rings[3] and the spatial projection of their substituents[4] has played a central role in the development of modern conformational analysis.[5] $\Delta G°$ differences between axial and equatorial conformations in monosubstituted cyclohexanes (*A* values[6]) are widely accepted as a measure of the effective steric bulk of the R group (for CH_2CH_3 =1.79 kcal/mol; for OCH_3 =0.55−0.75 kcal/mol).[7] The decided preference for the equatorial position, which stems from the lessening of 1,3-diaxial interactions, can carry over to vicinally substituted examples. For example, the all-trans hexaethyl (**1a**)[8] and hexamethoxy (**1b**) derivatives[9] are recognized on experimental and theoretical grounds (MM3), respectively, to adopt an all-equatorial arrangement, with each methyl group staggered either antiperiplanar to (**1a**) or eclipsing (**1b**) its proximal axial hydrogen.



1a, X = CH_2
b, X = O



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A well-known exception is **2**,[8b,10] where the excessive steric strain can best be accommodated by axial occupancy and directed orientation of the isopropyl methine hydrogens toward the cyclohexane core. However, such extreme degrees of substitution mask a more general pattern, viz., that *geminal and vicinal conformational free energies fail to display additivity.*[11−14] In their study of 1-methylcyclohexanols, for example, Allinger[12] and Uebel[13] uncovered surprisingly little preference for axial OH over geminal axial methyl. These research groups did not speculate on the origin of the leveling effect. On the other hand, Eliel has suggested alteration in rotameric populations, buttressing effects, and changes in local solvation as possible causes.[11]

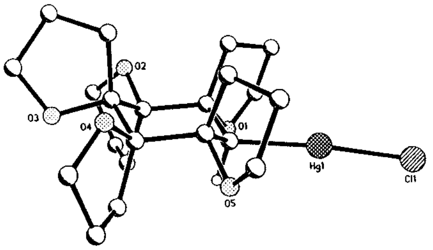
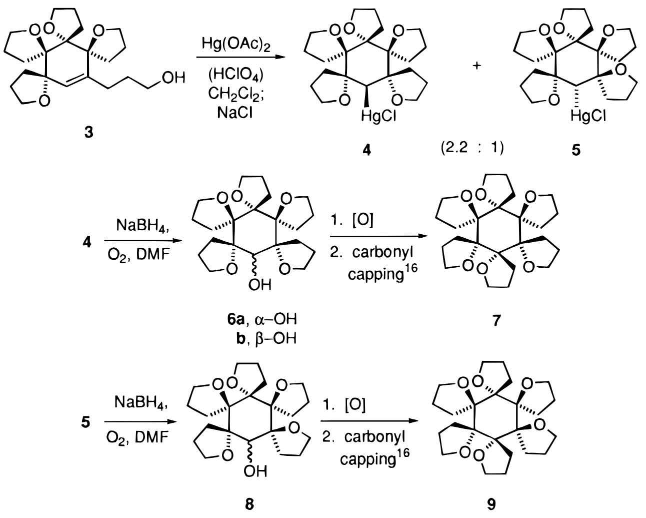


Figure 1. Computer-generated perspective drawing of the final X-ray model of **4**.

Scheme 1



In the course of our exploratory synthetic studies aimed at the stereocontrolled synthesis of poly(spirotetrahydrofuranyl)cyclohexane ionophores,[15] several key crystalline intermediates have recently been produced and examined by X-ray crystallographic analysis. Quite unexpectedly, the solid-state experimental data have revealed a uniformly strong bias for axial disposition of the methylene carbons rather than the oxygen atoms of the pendant heterocyclic rings. Several examples of this unprecedented apparent reversal in steric control are documented here, along with MM3 calculations for the pair of hexaspiro systems where entirely parallel conformational biases are seen to persist in the gas phase.

The synthetic protocol developed to access **4**−**9** is outlined in Scheme 1 without comment. The diastereomeric mercuric chlorides **4** and **5** both diffracted well enough to provide the structural information depicted in Figures 1 and 2. Although somewhat flattened chair conformations are adopted in both cases, it is especially striking that all six heteroatoms in **4** are projected equatorially. Since this major oxymercuration product is likely formed by trans-diaxial opening of the mercurinium ion intermediate, arrival at the final conformation necessitates that chair−chair equilibration be subsequently operative. This is not so for **5** wherein the axial C−Hg and C−O bonds generated along the reaction coordinate involving intramolecular nucleophilic attack are preserved. Noteworthy in this instance is the strong preference for the methylene groups from four tetrahydrofuran rings to remain axially disposed.

The predilection of the C−O bonds in **4** and **5** for equatorial occupancy appears to be indicative of a systematic trend. The

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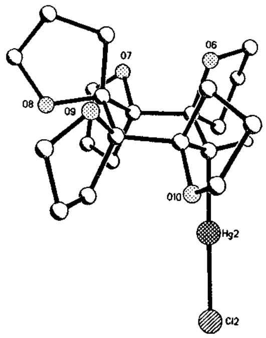


Figure 2. Computer-generated perspective drawing of the final X-ray model of **5**.

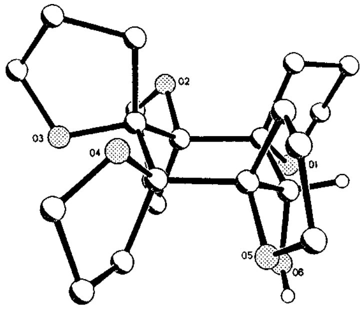


Figure 3. Computer-generated perspective drawing of the final X-ray model of **6a**.

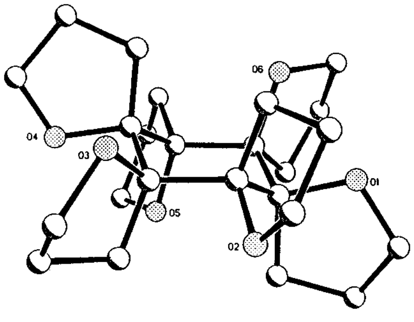
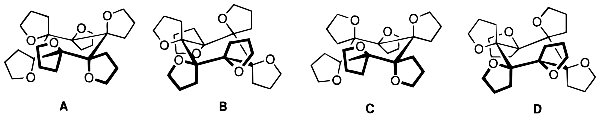


Figure 4. Computer-generated perspective drawing of the final X-ray model of **9**.

α-carbinol **6a**, which was obtained as the principal reductive oxygenation product of **4**, formed clear crystals belonging to the centric $P2_1/c$ space group. The conformation adopted by this alcohol is shown in Figure 3. The five constituent tetrahydrofuran rings are once again arranged such that their methylene groups are all directed axially along with the hydroxyl substituent. An even more spectacular example is given by **9**, which features a spirocyclic tetrahydrofuran unit at all six available cyclohexyl sites. The prevailing stereodisposition of the oxygen centers in **9** is seen to provide for adoption either of conformer **A** (two equatorial + four axial C−O bonds) or **B** (two axial + four equatorial C−O bonds). The informative crystal structure (Figure 4) shows the pattern adopted in the solid state to be that defined by **B**.



Detailed structural calculations were performed on **A**−**D**, the latter two arrangements representing the chair options available to **7**, with the MacroModel (version 5.0) software package.[17] Each MM3-minimized input structure was subjected to a Monte-Carlo multiconformational search[18] which incorporated ≥500 geometries encompassing each of the tetrahydrofuran rings as well. During each search, the 10 lowest energy conformations were generated multiple times in order to ensure that the global energy conformation had been converged upon. The five unique lowest energy conformations (all minimized to less than 1.0 kJ/mol·Å) were then further subjected to a full matrix Newton-Raphson minimization using the modified MM3 force field. The final energies and the energy differences so-obtained clearly show **B** and **D** to be of lower energy.

	A	**B**	**C**	**D**
MM3 energies (in kcal/mol)	154.10	152.01	158.56	154.82
	$\Delta E_{B/A} = 2.09$ kcal/mol		$\Delta E_{D/C} = 3.74$ kcal/mol	

Relevantly, comparisons of X-ray crystal structures (solid-state minima) with those derived from MM3 calculations (gas-phase minima) reflect high reproducibility, especially with respect to eclipsing interactions[19] and torsion angles involving oxygen.[20] The present examples are no exception. The measurement of ΔG values for **A/B** and **C/D** equilibria in solution has not been possible because of the substantive overlap of key signals.

The picture that emerges from the present limited survey is interesting and provocative. The obvious preference accorded to those conformations possessing the larger number of equatorial C−O bonds does not appear to have its basis in electrostatics,[21] since the dipole−dipole interaction of two vicinal equatorial oxygens should be larger than that of corresponding axial ones.[22−26] Nor is solvation a factor in the solid or gaseous state. However, tertiary centers are involved at the majority of if not at every carbon atom of the ring, the cyclohexane chairs are somewhat flattened, and buttressing is certainly operational. In fact, the torsional strain present in **A**−**D** (75.1, 71.0, 78.0, and 68.6 kcal/mol, respectively) constitutes the largest distinctive contribution for each conformer. Gauche $CH_2 \cdots CH_2$ interactions, obviously less favorable than those of the O···O type in the present context, bring about increased steric congestion because the spirocyclic nature of the pendant rings significantly limits rotational degrees of freedom.

Acknowledgment. We are indebted to the National Science Foundation for financial support.

Supporting Information Available: Complete description of the X-ray crystallographic determinations on **4**, **5**, **6a**, and **9**, including tables of atomic coordinates, isotropic and anisotropic displacement parameters, bond lengths, and bond angles (41 pages). Ordering information is given on any current masthead page.

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