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Axial Monoalkyl Cyclohexanes

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Summary: On the basis of steric considerations, it is concluded that monoalkyl cyclohexanes, in which the alkyl is a bulky V-shaped group, may prefer an axial disposition of the alkyl substituent.

One of the unchallenged rules of the conformational analysis of cyclohexane rings is that their monoalkyl derivatives prefer the equatorial over the axial disposition of the alkyl group.[1-3] In general, the bulkier the alkyl substituent, the larger its preference for the equatorial position (*A* value).[4] We have shown recently that for polysubstituted cyclohexanes the usual equatorial preference of the alkyl substituents may be reversed. X-ray diffraction of *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane (1) showed that the compound exists in a conformation in which all the groups are located at axial positions.[5] This axial preference was rationalized based on repulsive steric interactions and torsional effects in the equatorial conformation.[5] The conformational preferences of the polyalkylcyclohexane 1 raised the question whether a similar behavior could be displayed by a monoalkylcyclohexane system; i.e., could a *mono*substituted cyclohexane, in which the substituent is a hydrocarbon moiety, prefer an axial disposition of the group over the equatorial one?

Finding the substituent with the desired conformational properties among all possible substituents could be like looking for a needle in a haystack, unless some kind of structural guidance is used. Tertiary alkyl groups were ruled out as potential substituents, since the steric interactions in the axial conformation should be too large. Secondary substituents seemed to be good candidates since the conformational bias for the equatorial conformation is not too large.[4a] On the basis of these considerations, an adamantane structure attached to the cyclohexane by one of the nonbridgehead positions was chosen as the basic skeleton of the substituent.[6] From steric considerations it could be expected that from the three possible staggered conformations around the C(cyclohexane)–C(alkyl) bond, the one with an antiperiplanar H–C(adamantane)–C(cyclohexyl)–H arrangement should be preferred in both the axial and equatorial conformations. To a first approximation, the equatorial and axial conformations can be seen as differing in the location of three methylenic groups of the cyclohexane ring, while the methine carbon to which the substituent is attached and the two remaining methylenes can be seen as common for both conformations (Figure 1). Based on these considerations, and after inspection of Dreiding models, we were able to choose a system with (potentially) the desired conformational properties. *If a concave V-shaped structure is attached to the adamantane, it could be expected that the steric interactions between the substituent and the ring will be larger in the equatorial form* (Figure 1), and therefore that the axial form should be of lower energy than the equa-

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(1) For reviews on conformational analysis see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965. Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Lund, 1978. For a review on the conformational analysis of hydrocarbons see: Anderson, J. E. In *The Chemistry of the Alkanes and Cycloalkanes*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1992.

(2) For a review on the stereochemistry of cyclohexanes see: Mann, G. *Z. Chem.* **1990**, *30*, 1.

(3) A crowded cyclohexane which exists in a planar (i.e., nonchair) conformation has been recently reported: Mohler, D. L.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 436.

(4) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (b) Monoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267.

(5) Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 893. Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300.

(6) The molecule is reminiscent of 2-phenyladamantane which has been used as a model for axial phenylcyclohexane. See: Schaefer, T.; Beaulieu, C.; Sebastian, R. *Can. J. Chem.* **1991**, *69*, 503.

0022-3263/92/1957-2979$03.00/0

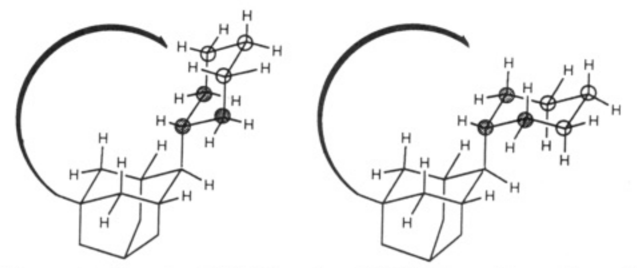
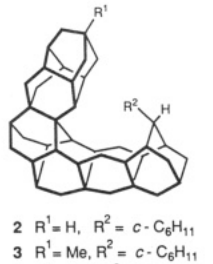


Figure 1. Equatorial (left) and axial (right) conformations of a monoalkylcyclohexane. The three shaded circles denote to the carbon atoms which, in a first approximation, are situated at similar environments. The three open circles correspond to the carbon atoms which are situated at different positions in the two conformations. The arc represents a concave V-shaped substituent which causes larger repulsive interactions in the equatorial conformation.

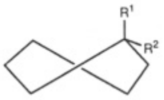
torial.

Since we wanted to approach this question computationally using molecular mechanics,[7] two additional considerations were taken into account in order to choose the V-shaped substituent. Firstly, the substituent should be locked in a single conformation or be limited to a small number of conformations in order to restrict the conformational freedom of the molecule and to reduce the number of calculations. This should not only save time, but it should increase the reliability of the calculations. Secondly, all carbon atoms should be saturated and should have sp^3 hybridization, since this type of atom is best treated by the calculations. On the basis of these considerations, the V-shaped substituent was constructed by fusing to the adamantane skeleton one tricyclo[3.3.1]nonane and four additional adamantyl systems (cf. **2**).

For the calculations we used the MM2(87) force field as implemented in MACROMODEL V3.0.[8] In addition to the axial and equatorial chair conformations, the energies of the twist boat forms **5–7** were also calculated.



2 R^1 = H, R^2 = c-C$_6$H$_{11}$
3 R^1 = Me, R^2 = c-C$_6$H$_{11}$
4 R^1 = t-Bu, R^2 = c-C$_6$H$_{11}$



5 R^1 = Alkyl, R^2 = H
6 R^1 = H, R^2 = Alkyl

7

The molecular mechanics calculations indicate that for **2–4** the HCCH antiperiplanar arrangement is the lowest in energy. Conformation **5** is the favored twist form for **2** and **3**, while for **4** the preferred form is **7**. The twist-boat form in which the substituent is attached to a quasiequatorial position (**6**) is of much higher energy in all cases. For **2** the ground state corresponds to the equatorial form, with the axial form and twist-boat **5** lying 0.3 and 3.5 kcal mol^{-1} above the equatorial form. The small equatorial/axial energy gap suggests that the steric crowding affects more the equatorial conformation than the axial one. The steric crowding was increased by replacing the terminal bridgehead hydrogen in **2** by a methyl group. For system **3**, *the relative stabilities of the axial and equatorial conformation are reversed.* The ground-state structure corresponds to the axial conformation, with the equatorial and twist-boat forms lying 0.4 and 4.3 kcal mol^{-1} above it. The axial/equatorial energy gap can be increased by increasing the steric hindrance. In **4**, the equatorial form is less stable than the axial by 5.0 kcal mol^{-1} while the twist-boat form lays 2.2 kcal mol^{-1} above the equatorial form. The calculated geometries for these conformations are shown in Figure 2.[9] On the basis of the molecular mechanics data, one can conclude that the equatorial preference of monoalkyl cyclohexanes is not universal and that for some monoalkyl cyclohexanes existing in crowded environments the axial conformation may be the preferred one. We arrived to system **4** from stereochemical as well as computational considerations (i.e., rigidity of the substituent) but other simpler and more synthetically amenable systems could display the phenomena. Work is in progress to test experimentally this prediction.

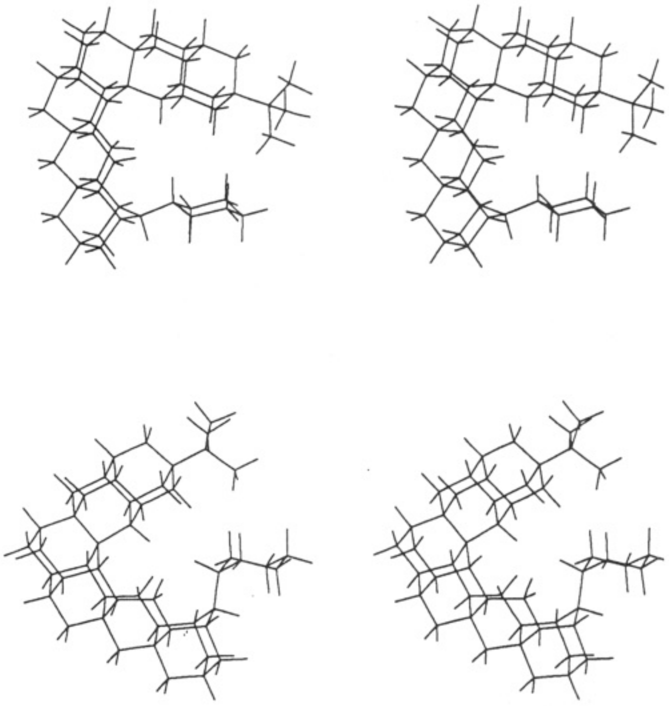


Figure 2. Stereoscopic views of the calculated geometries for the equatorial and axial conformations of **4**.

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Registry No. **2**, 140462-77-7; **3**, 140462-78-8; **4**, 140462-79-9; **5**, 92-51-3; **6**, 1130-24-1; **7**, 3178-22-1.

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[7] For reviews on molecular mechanics see: Ermer, O. *Aspekte von Kraftfeldrechnungen*; Baur: Munchen, 1981. Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982. Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1. Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985, Chapter 2.

[8] Still, W. C.; Mohamadi, F.; Richards, N. J. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufiled, C.; Chang, G.; Hendrickson, T. MACROMODEL V3.0, Department of Chemistry, Columbia University, New York, NY 10027. For a description of the program see: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

[9] All calculated H/H nonbonded distances between the cyclohexyl ring and the substituent were longer than 2.0 Å.