

## Communications to the Editor

### First Completely Stable Axial Conformers of Monosubstituted Cyclohexanes at Room Temperature

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Since the postulation of the existence of the chair conformation of cyclohexane,<sup>1</sup> the possibility of separating axial and equatorial conformers of comparable stabilities of monosubstituted cyclohexanes has intrigued chemists. Claims of the isolation of conformational isomers of monosubstituted cyclohexanes have been made,<sup>2</sup> but the validity of these reports can be effectively challenged on thermodynamic and kinetic grounds.<sup>3</sup> Conformationally pure equatorial conformers of certain monosubstituted cyclohexanes such as chlorocyclohexane<sup>4,5</sup> and trideuteriomethoxycyclohexane<sup>5</sup> have been declared to be obtained by ordinary recrystallization techniques at low temperatures. However, no success has been gained so far in obtaining conformationally pure axial conformers of monosubstituted cyclohexanes. In this communication, we report our discovery of the first completely stable axial conformers at room temperature of monosubstituted cyclohexanes which result from steric hindrance.

Recently,<sup>6</sup> we achieved the first synthesis of stable and enantiomerically pure chiral alkyl nitronic esters via asymmetric *O*-alkylation of the alkali metal salt of compound **1** (Scheme 1) with various alkyl halides and found that optically pure chiral *O*-alkyloximes were produced as minor byproducts when secondary alkyl halides or an allyl halide were used. In the analysis of the <sup>1</sup>H NMR spectra of cyclohexyl nitronic ester **2** and *O*-cyclohexyloxime **3** (Scheme 1), we noticed that their H<sub>20</sub> signals appear at about δ 5.2 ppm (Figure 1). Judging from intuition, we felt that these chemical shifts seemed to be in a lower magnetic field than expected. To verify this judgment, we studied the chemical shifts<sup>7</sup> of the α-protons of alkyl acetates (CH<sub>3</sub>CO<sub>2</sub>C<sub>α</sub>C<sub>β</sub>C<sub>γ</sub>) to see if there is something regular among them. Very unexpectedly, when placing the chemical shifts of the α-protons in order from high magnetic field to low magnetic field, we found an empirical shift rule of oxygen-containing homologues, that is, the chemical shift of the α-protons depends on the number of the β-protons, or in other words, the more β-protons, the larger the chemical shift of the α-protons (Table 1). Besides, when the numbers of the β-protons are equal, the chemical shift of the α-protons seems to further depend on the

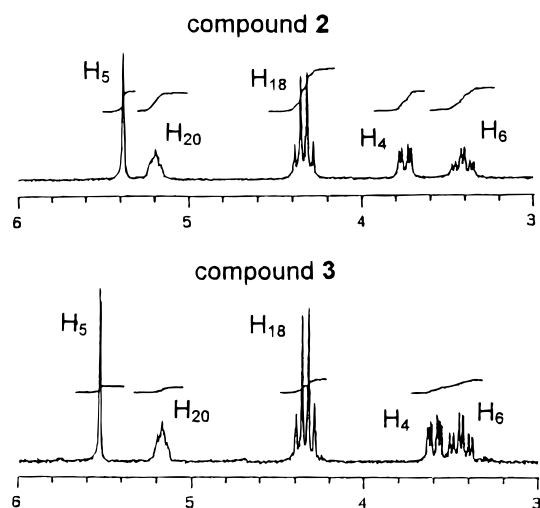



Figure 1. <sup>1</sup>H NMR spectra (200MHz, in CDCl<sub>3</sub>) of compounds **2** and **3** at room temperature.

Table 1. Empirical Shift Rule of the Chemical Shifts of the α-Protons of Oxygen-Containing Homologues

no. of H <sub>β</sub>	alkyl	nitronic ester	δH <sub>α</sub> <i>O</i> -alkyloxime	acetate	serial number <sup>a</sup>
0	CH <sub>3</sub>	3.79	3.72 <sup>b</sup>	3.65	10261
1	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>			3.80	8590
1	CH <sub>2</sub> CH(CH <sub>3</sub> )-CH <sub>2</sub> CH <sub>3</sub>			3.83	21892
2	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4.08		3.95	115
2	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4.12		3.99	10348
2	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -CH <sub>2</sub> CH <sub>3</sub>			4.00	6710
3	CH <sub>2</sub> CH <sub>3</sub>	4.18		4.02	10291
4		5.19	5.18	4.76 (4.73) <sup>c</sup>	12447
5	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	4.88 <sup>b</sup>	4.86 <sup>b</sup>	4.76	6787
6	CH(CH <sub>3</sub> ) <sub>2</sub>	5.03 <sup>b</sup>	4.97 <sup>b</sup>	4.98	99

<sup>a</sup> Excerpted from ref 7. <sup>b</sup> Unpublished data. <sup>c</sup> Determined at 200 MHz.

total number of protons on the alkyl groups bonded to the C<sub>β</sub> atom. This empirical shift rule can be elucidated by the comprehensive deshielding effect of C–C and C–H single bonds. It is noteworthy that discovery of this empirical shift rule provides evidence for the questioned anisotropy of a C–H single bond.<sup>8</sup>

As for the two homologues of the chiral alkyl nitronic esters and *O*-alkyloximes, it was observed that, except for compounds **2** and **3**, all other known compounds also comply with this empirical shift rule (Table 1). Therefore, the H<sub>20</sub> signals of compounds **2** and **3**, as predicted, are indeed in an anomalously lower magnetic field.

There seems to be only one interpretation for the anomalous downfield shifts of the H<sub>20</sub> signals, which is that the monosubstituted cyclohexanes in compounds **2** and **3** are not the usually expected equatorial chair conformers, but are the axial chair conformers, or the H<sub>20</sub> protons are equatorial protons. It is well-known that, influenced by the anisotropy of C–C bonds, the equatorial proton in a cyclohexane is generally deshielded 0.1–0.7 ppm with respect to the corresponding axial proton.<sup>9</sup> If the

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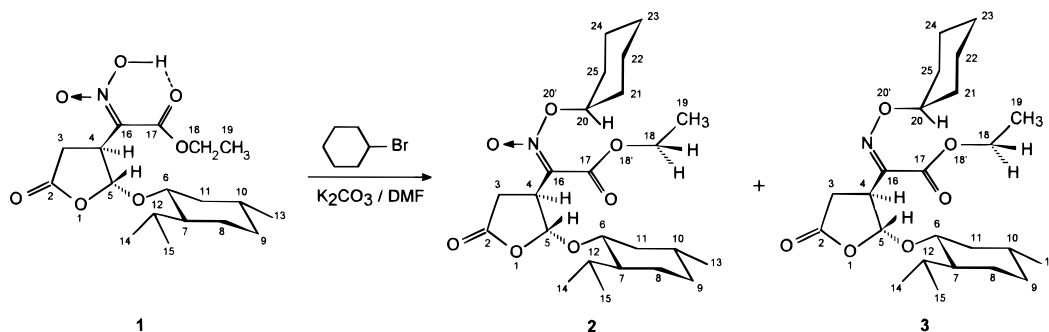
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**Scheme 1.** Synthesis of the Completely Stable Axial Conformers of Monosubstituted Cyclohexanes

chemical shifts of the “axial H<sub>20</sub> protons” of compounds **2** and **3** are regarded to be close to those of the H<sub>20</sub> protons of the *sec*-butyl-containing compounds (see the case of alkyl acetates), then the equatorial H<sub>20</sub> signal is about 0.3 ppm lower than the “axial H<sub>20</sub> signal”, which just falls in the range of 0.1–0.7 ppm.

The axial conformers of monosubstituted cyclohexanes are confirmed by the coupling constants of the H<sub>20</sub> signals. The two coupling constants of the H<sub>20</sub> signals (at 200 MHz) of compounds **2** and **3** are  $J_{ea} = 4.8$  and  $J_{ee} = 2.8$  Hz, while the two coupling constants of the H<sub>α</sub> signal (at 200 MHz) of cyclohexyl acetate<sup>10</sup> are  $J_{aa} = 9.0$  and  $J_{ae} = 4.0$  Hz. With the vicinal coupling constants of *cis*- and *trans*-3,3,4,5,5-pentadeu-

terio-4-*tert*-butylcyclohexanols<sup>11</sup> as parameters,  $J_{ea} = 3.00$ ,  $J_{ee} = 2.72$ ,  $J_{aa} = 11.07$ , and  $J_{ae} = 4.31$  Hz, it is safe to say that H<sub>20</sub> is an equatorial proton and H<sub>α</sub> is an axial proton.<sup>12</sup>

We think that the axial conformers of monosubstituted cyclohexanes in compounds **2** and **3** are caused by steric hindrance. If the monosubstituted cyclohexanes in compounds **2** and **3** are equatorial conformers, the C<sub>22</sub> and C<sub>24</sub> atoms as well as their bonded axial protons would suffer from steric hindrance by the C<sub>18</sub> ethoxy group.<sup>13</sup> When they are axial conformers, this steric hindrance can be relieved. In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position because in the axial position there are 1,3-diaxial interactions.<sup>14</sup> However, in fact, there is still a proportion (5%) of axial conformers in certain monosubstituted cyclohexanes (e.g., methylcyclohexane) at room temperature.<sup>14a</sup> Compared to that of the methyl group, the van der Waals radius of the O<sub>20'</sub> atom is much smaller, so there should be much smaller repulsions between the O<sub>20'</sub> atom and the axial protons on the C<sub>22</sub> and C<sub>24</sub> atoms.

In summary, an empirical shift rule of the chemical shifts of the α-protons of oxygen-containing homologues was found, which provides evidence for the anisotropy of the C–H single bond. According to the anomalous downfield shift of the H<sub>20</sub> signals and their coupling constants, stable and conformationally pure axial monosubstituted cyclohexanes are obtained for the first time in the chiral alkyl nitronic ester and *O*-alkyloxime, which is rationally explained by steric effects.

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(12) Coupling is believed to be mediated by the interaction of orbitals within the bonding framework. It is therefore dependent upon overlap and hence upon the dihedral angle. The relationship between the dihedral angle and the vicinal coupling constant <sup>3</sup>*J* is given theoretically by the well-known Karplus equations, which demonstrate that the coupling constant is largest when the dihedral angle is 180°, in other words, when the hydrogens are antiperiplanar and the orbitals overlap most efficiently. In rigid cyclohexanes, the axial–axial coupling constant,  $J_{aa}$ , is usually large, in the range 9–13 Hz, because the dihedral angle is close to 180°. The axial–equatorial and equatorial–equatorial coupling constants,  $J_{ae}$  and  $J_{ee}$ , are much smaller, usually in the range 2–5 Hz, because the dihedral angles are close to 60°. See: Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; McGraw-Hill: London, 1995; pp 92–94.

(13) The lone pair electrons of the oxygen atoms O<sub>18'</sub> and O<sub>20'</sub> might participate in the delocalized π–π conjugation formed by the C=N and C=O bonds (p → π conjugation), which therefore makes the two oxygen atoms possess some character of sp<sup>2</sup> hybridization. Thus, a rigid polyatomic coplanar structure consisting of nine atoms (compound **2**) or eight atoms (compound **3**) is assembled between the C<sub>20</sub> and C<sub>18</sub> atoms, in which the O<sub>18'</sub> atom is close to the C<sub>20</sub> atom in space and severely hinders the free rotation of the C<sub>20</sub> methylene about the C<sub>20</sub>–O<sub>20'</sub> bond. For oxygen atoms possessing some character of sp<sup>2</sup> hybridization, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, U.K., 1983; pp 54–56.

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