# On Pure Axial Monosubstituted Cyclohexanes

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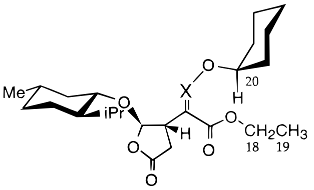
Conformational analysis of six-membered rings occupies one of the cornerstones of organic stereochemistry.[1] The two textbook features that characterize the structural class are the existence of axial (ax) and equatorial (eq) conformations and the predominance of equatorial conformers in the accompanying dynamic equilibrium. To be sure, novel and sterically biased exceptions to the "equatorial rule" have been reported for cyclohexanes bearing more than a single substitutent.[2] In the heterocyclic realm, certain 3-fluoro piperidines, including the monofluoro derivative, are known to be axial.[3] However, *mono*substituted cyclohexanes have persistently demonstrated equatorial preference.[1] Kang and Yin's recent and intriguing proposal of "completely stable axial conformers of monosubstituted cyclohexanes at room temperature" for nitronic ester **1a** and *O*-cyclohexyloxime **1b** derived by $^{1}H$ NMR spectroscopy appears to offer the first anomalies.[4] The finding contrasts with a host of oxygen-monosubstituted cyclohexanes with conformational energies favoring the equatorial isomers by 0.27−0.87 kcal/mol,[1a] corresponding to eq/ax populations of 60/40 to 90/10, respectively.

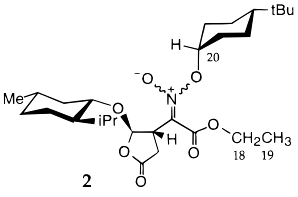
| | X |
|---|---|
| **1 a** | N→O |
| b | N: |



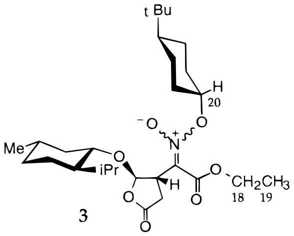
Kang and Yin have argued that oxygen is strictly axial at C-20 in **1** as a consequence of steric effects arising from the presence of a rigid and planar $\pi$-system for the *Z*-configured moiety $C_{20}-O-X{=}C-C(O)-O-C_{18}$.[4,5] In the present work we examine this proposition and conclude that compound **1** is at best a rapidly equilibrating mixture of equatorial and axial conformers.

Attribution of a completely axial cyclohexane conformer in **1a**,**b** was based on both proton chemical shifts and coupling constants for H-20 (200 MHz, $CDCl_3$). Values of 4.8 and 2.8 Hz reported for the latter were assigned as $J_{ea}$ and $J_{ee}$, respectively.[4] There are several reasons for believing that 4.8 Hz is too large to represent $J_{ea}$ for this proton. First, it is well-known that when oxygen is attached to a carbon common to a pair of vicinally coupled protons and held rigidly anti-periplanar with respect to one of them, then $J_{ea}$ is reduced to a value of 2.5 ± 1 Hz.[6] Second, Anet's measurements for C*H*(O) in the chair conformers of deuterated oxy-cyclohexanes yield $J_{ea}$ of 2.7−3.0 and 4.2−4.3 Hz for the equatorial and axial protons, respectively.[7] It is conceivable that the assignments for **1** have been reversed such that the measured couplings of 4.8 and 2.8 Hz correspond to $J_{ee}$ and $J_{ea}$, respectively, instead. To test this idea, we employed gNMR[8] to fit both assignments at 200 MHz. Figure 1a compares the alternatives and illustrates clearly that either pattern is consistent with the published spectrum.[4] If the suggested reversal obtains, it opens the possibility that the larger coupling constant arises from dynamic averaging of $J_{ee}$ and $J_{aa}$.

To examine the extremes of H-20 coupling in a comparable nitronate ester system, we have prepared the *cis*- and *trans*-*tert*-butyl derivatives **2** and **3**, respectively, with unknown C═N configuration from the nitronate anion precursor of **1**[5] and *cis*- and *trans*-*tert*-butylcyclohexanols under Mitsunobu conditions.[9,10] *cis* -**2** with axial oxygen displays H-20 as a narrow symmetrical five-line band centered at 5.06 ppm (400 MHz). The latter can be matched (Figure 1b) with $J_{ea} = 2.91$ and $J_{ee} = 2.70$ Hz, values virtually identical with those for *cis*-4-*tert*-butyl-cyclohexanol.[7] *trans*-**3**, on the other hand, displays H-20 as a well-defined nine-line spectrum centered at 4.65 ppm (400 MHz). Simulation of the splitting pattern likewise suggests coupling constants (4.40 and 11.35 Hz) nearly identical with those for *cis*-4-*tert*-butyl-cyclohexanol (Figure 1c). In addition, the 0.41 ppm downfield shift of eq H-20 in **3** relative to its axial counterpart in **2** is in complete accord with literature precedent for cyclohexanes.[11]



**2**



**3**

In sharp contrast to the clean $^{1}H$ NMR patterns for H-20 in the conformationally immobile *tert*-butylated rings of **2** and **3**, compound **1** is reported to exhibit a broad ill-defined band at 5.19 ppm (200 MHz, Figure 1a). Simulation of the spectrum at 400 MHz furnishes an improvement in resolution but illustrates a different band shape by comparison with the rigidified cyclohexanes (Figure 1b). The H-20 envelope strongly suggests rapid exchange between conformations. Remarkably, the chemical shift of H-20 in **1a** is reported to lie 0.13 ppm *downfield* from that of the corresponding pure equatorial proton of **2**. An alternative indicator of the purity of axial orientation is the $^{13}C$ chemical shift in cyclohexanes. Carbon substituted equatorially by oxygen is found 3.3−5.2 ppm downfield from the corresponding axial

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[10] NMR (400 MHz, $CDCl_3$); Compound **2**, calcd for $C_{28}H_{47}O_7N$: C, 66.01; H, 9.23; N, 2.75; found C, 65.75; H, 9.29; N, 2.66; calcd for $C_{28}H_{48}O_7N$ ($M + H^+$) 510.3446, found 510.3431, $^{1}H$ 5.41 (s, 1H), 5.06 (m, 1H), 4.33 (m, 2H), 3.76 (dd, 1H), 3.41 (dt, 1H), 2.81 (dd, 1H), 2.6 (dd, 1H) 2.15 (m, 2H), 1.9 (m, 2H), 1.7−0.7 (m, 35H), $^{13}C$ 169.9, 158.3, 110.2, 103.48, 82.24, 70.85, 62.19, 48.41, 47.71, 47.55, 43.23, 34.32, 34.05, 32.75, 31.91, 30.78, 27.66, 25.71, 23.26, 22.34, 21.89, 21.25, 16.29, 14.44; **3**, calcd for $C_{28}H_{47}O_7N$: C, 66.01; H, 9.23; N, 2.75; found C, 65.81; H, 9.19; N, 2.7; calcd for $C_{28}H_{48}O_7N$ ($M + H^+$) 510.3446, found 510.3431, $^{1}H$ 5.39 (s, 1H), 4.65 (n, 1H) 4.35 (m, 2H), 3.75 (dd, 1H), 3.4 (dt, 1H), 2.75 (dd, 1H), 2.57 (dd, 1H), 2.15 (m, 2H), 2.0 (m, 2H), 1.89 (m, 2H), 1.65−1.5 (m, 3H), 1.4−0.75 (m, 31H), $^{13}C$ 169.8, 158.8, 110.24, 103.36, 82.06, 74.98, 62.13, 48.38, 47.76, 47.18, 43.23, 34.29, 33.98, 32.51, 32.19, 31.87, 31.17, 27.79, 25.69, 25.61, 23.26, 22.32, 21.25, 16.35, 14.44.

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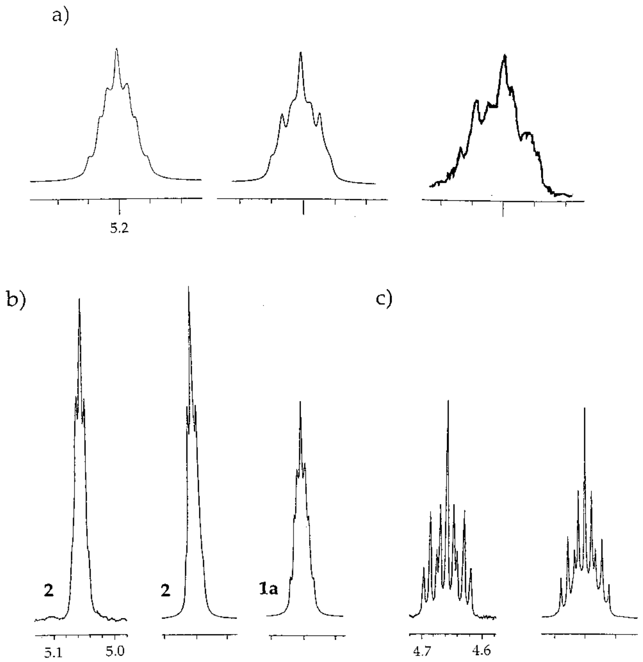
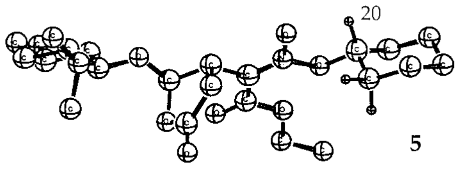


**Figure 1.** Measured and simulated (sim) $^1$H NMR spectra for H-20. (a) Nitronate **1a**; $J_{ea} = 4.8$ Hz (sim, 200 MHz), $J_{ee} = 4.8$ Hz (sim, 200 MHz), expt (200 MHz);[4] (b) **2**, expt/sim, 400 MHz; **1a**; $J_{ea} = 4.8$ Hz (sim, 400 MHz); (c) **3**, expt/sim, 400 MHz. Spectra in (a) are on a common scale as are all spectra in (b) and (c).

system.[12] For example, ax- and eq-OH in the 4-*tert*-butylcyclohexanols shows $^{13}$C(OH) shifts at 66.2 and 71.4 ppm, respectively ($\Delta\delta = 5.2$ ppm, 400 MHz). The corresponding values for **2** and **3** are 69.9 and 75.0 ppm, respectively ($\Delta\delta = 5.1$ ppm). Inexplicably, the reported shift for C-20 in **1** is 78.0 ppm, a quantity considerably downfield from that for equatorially substituted **3**.

We have evaluated the extent of rigidity for the C$-$O$-$X$=$C$-$C(O)$-$O$-$C functionality by optimizing the geometry of conformers of MeOX$=$C(Me)CO$_2$Me (X = N, *O*-methyl-oxime; X = N$^+-$O$^-$, *O*-methyl nitronic ester), **4**, with the Becke3LYP/3-21G basis set.[13] The global minima correspond to MeO and CO$_2$Et situated *trans* about the N$=$C bond. The corresponding *Z*-isomers fall 1.3$-$6 kcal/mol higher. Single point calculations with the Becke3LYP/6-31G*, MP2/6-311G* (X = N) and MP2/6-31G (X = N$^+-$O$^-$) protocols yield the same result. For X = N$^+-$O$^-$, energy barriers for rotation around the CO$-$NC and NC$-$C(O)O bonds were evaluated at 5$-$6 and 11$-$14 kcal/mol, respectively, relative to **4**. The quantities are well below that necessary for rigidity at room temperature (18$-$20 kcal/mol) and in complete accord with known structural data. A search of the Cambridge Crystallographic database reveals numerous compounds containing the C$-$O$-$X$=$C$-$CO$_2$Me fragment.[14] Many are planar.[15] However, an equal number of structures show the CO$_2$Me unit twisted out-of-plane by 40$-$80°.[16] Constrained optimization of the fragment as depicted in **1** led to a nonstationary state 16$-$21 kcal/mol higher than **4**. All attempts to model the planar, all-*cis* C$-$O$-$X$=$C$-$CO$-$O fragment postulated by Kang and Yin in **1** as an energy minimum led to alternative conformational minima relatively free of steric strain.

To examine the conformational surface of **1**, we have enhanced the MM3* force field in Macromodel[17] with C$-$O$-$N$^+$($-$O$^-$)$=$C$-$CO$_2$C parameters derived from the DFT/ab initio calculations.[18] Separate 5000 step Monte Carlo conformational searches[19] including the GBSA$-$CHCl$_3$ solvent continuum model[20] were carried out for the C-20 equatorial and axial conformations of the *Z*-isomer **1a**. A Boltzmann energy distribution of the 68 conformers within 3.0 kcal/mol of the equatorial global minimum **5** suggests an 80/20 eq/ax ratio translating to an overall energy difference of 0.8 kcal/mol (298 K). Single point Becke3LYP/6-31G* energies of the most stable ax and eq conformers are confirmatory ($\Delta E = 1.0$ kcal/mol). Structure **5** and other low energy conformers illustrate that not only are the bonds flanking C$=$N free to rotate at ambient temperatures, but they also do so as pictured in **2** and **3** by removing the *O*-cyclohexyl moieties from close contact with groups situated *Z* or *E* across the C$=$N double bond. NOESY and NOE difference spectra at 400 MHz (23°, degassed, sealed tube) are confirmatory. No cross-peaks between H-20 and the OCH$_2$CH$_3$ protons are observed for either isomer. The steric hindrance postulated by Kang and Yin[4] to induce the axial-only conformer shown in **1** does not appear to operate. Unfortunately, the lack of any readily interpretable cross-molecule proton contacts makes it impossible to comment on the *E* or *Z* configuration around the C$=$N bond for **2**, **3**, and presumably **1** as well.[21]



**5**

We conclude that while the C$=$N configuration is uncertain for nitronate esters **1**$-$**3**, the *O*-cyclohexyl conformation for **2** and **3** is assured by *tert*-butyl anchoring. Distinctive conformational signatures are portrayed by the $^1$H-20 and $^{13}$C-20 chemical shifts, $\Delta\delta$(ax $-$ eq), and the sharp spin$-$spin couplings at H-20. By contrast, the reported H-20 and C-20 shieldings for **1a** are atypical. Furthermore, the broad and ill-defined band shape of H-20 in the proton NMR, a $^{1,2}J = 4.8$ Hz (Figure 1) and the MM3* analysis are all strongly suggestive of cyclohexane equilibration. We surmise that if structure **1** is accurate as reported, its NMR spectra reflect a rapidly averaged axial and equatorial conformational blend with a considerable population of the equatorial *O*-cyclohexyl conformer.

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