On "Pure Axial" Monosubstituted Cyclohexanes: Cyclohexyl Nitronate Esters Adopt O-Equatorial Conformations

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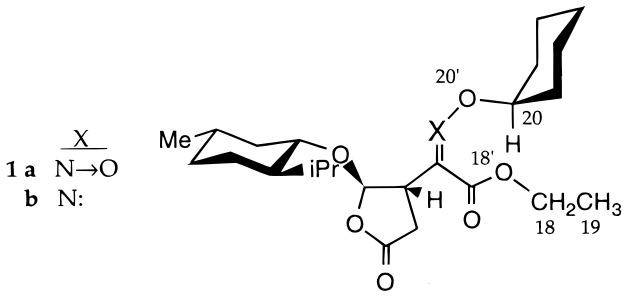
Abstract: It has been reported recently by Kang and Yin that a complex *O*-cyclohexyl nitronate and the corresponding *O*-cyclohexyloxime constitute the "first completely stable axial conformers of monosubstituted cyclohexanes at room temperature." If true, this claim violates a central principle of alicyclic conformational analysis. We have evaluated it by performing ab initio and molecular mechanics calculations to show that energy barriers in the C−O−X═C−C(O)−O−C system (X = N and N^+-O^-) are low and that the equatorial−axial ratio is 2−3:1. To experimentally verify the predictions, we have synthesized seven analogues of the previously reported *O*-cyclohexyl nitronate using Mitsunobu chemistry, including genuine O-axial and O-equatorial conformers anchored by a 4-*tert*-butyl group. Both the ^{1}H and ^{13}C NMR spectra of the compounds have been carefully analyzed to be in complete accord with literature precedent. Finally, we have also prepared the compound claimed to be monosubstituted and O-axial. NMR analysis shows the O-cyclohexyl nitronate to be predominately O-equatorial with an estimated eq/ax = 3:1, again in full agreement with previous measurements of *O*-cyclohexyl *A* values. Configuration about the C═N bond is tentatively assigned to be *E*. Both the O-axial conformational proposition and the empirical shift rule of Kang and Yin's study are found to be compromised by the finding that a cyclopentyl derivative was, in fact, confused for the cyclohexyl analogue in the synthetic work and subsequent NMR analysis.

Introduction

Cyclohexane conformational analysis is one of the bedrock principles that provides an understanding of structure and equilibrium in organic chemistry.[1] Data accumulated over many years have taught that cyclohexane derivatives exist primarily in the chair conformation and that bulkier substituents prefer the equatorial position. Monosubstituted cyclohexanes are the prototypes. The equatorial and axial conformers exist in equilibrium, but the equatorial isomer persistently dominates since its substituent avoids unfavorable 1,3-diaxial interactions. For a wide range of analogues the equatorial form is favored by $\Delta G = -0.5$ to -5.0 kcal/mol.[2]



The only known exception to the equatorial rule in monosubstituted cyclohexanes is found in mercuric derivatives such as cyclohexylmercuric acetate with an *A* value of −0.17 to −0.30, depending on solvent. Other mercury analogues exhibit similar free energy differences reflecting an effective steric volume smaller than a proton.[3]

In light of this history, the recent report by Kang and Yin describing the preparation of two pure axial monosubstituted cyclohexanes **1a** and **1b** came as an unprecedented surprise.[4] Utilizing ^{1}H NMR chemical shifts, these authors argued that the oxygen at C-20 in the compounds is strictly axial. During the course of a preliminary investigation of this claim, we concluded that the compounds are at best a rapidly averaged mixture of equatorial and axial conformers with a significant population of the equatorial isomer.[5] The present work combines computations, synthesis, and NMR spectroscopy to substantiate this conclusion. In addition, we present the unambiguous synthesis of **1a** and show that this compound is a conformationally heterogeneous population that contains mostly the O-equatorial monosubstituted cyclohexane.

Computational Analysis

Two interesting questions raised by the Kang and Yin paper can be addressed computationally. In a preliminary evaluation of the problem, we took this approach to learn whether a complementary synthetic effort was justified. The first concerns the degree of flexibility of the atoms flanking the nitronic ester and oxime functionalities in **1a** and **1b**, respectively, and the attendant potential for steric forcing of the axial conformation at C-20. The second pertains to the possible blend of axial and

(1) Hassel, O. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1971; Vol 6, pp 11−17. Barton, D. H. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1971; Vol 6, pp 1−10.

(2) (a) *Stereochemistry of Organic Compounds*, Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1994; pp 1142−1163. (b) *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995.

(3) Bushweller, C. H. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995; pp 25−58.

(4) Kang, F.; Lin, C. *J. Am. Chem. Soc.* **1997**, *119*, 8562−8563.

(5) Cornett, B.; Davis, M.; Wu, S.; Nevins, N.; Snyder, J. *J. Am. Chem. Soc.* **1998**, *120*, 12146−12147.

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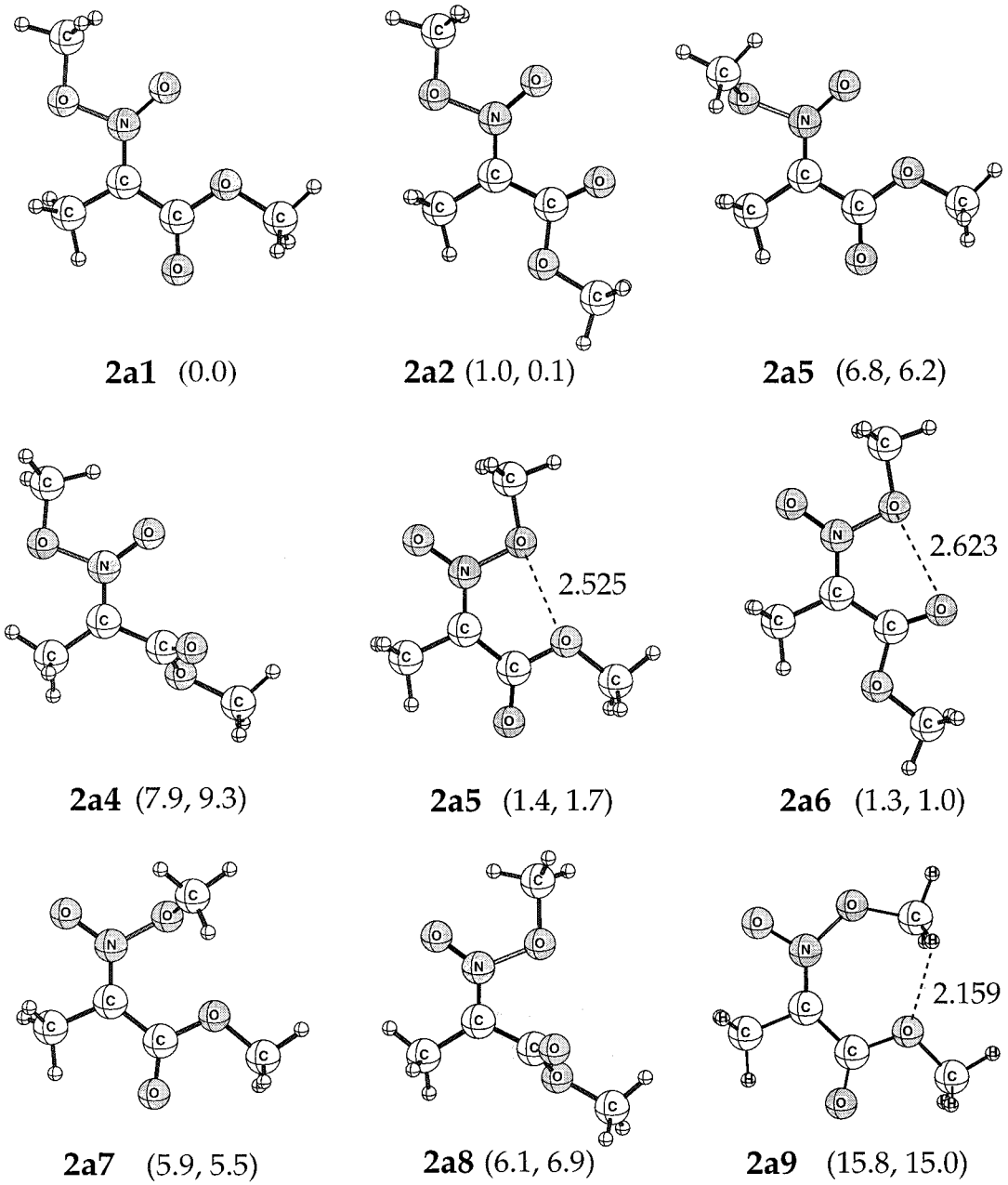


Figure 1. Becke3LYP/3-21G MeON(O)═C(Me)CO_2Me optimized structures. Energies relative to **2a1** for fixed point Becke3LYP/6-31G* and MP2/6-31G* basis sets, respectively, are given in parentheses (kcal/mol). Certain atomic distances are illustrated with a dashed line; Å.

equatorial conformers in a chloroform solution of **1**. We apply ab initio methods to the first issue, and subsequently use the results to parameterize the MM3* force field[6] so as to address the second.

In an attempt to justify the interpretation of the presumed ^{1}H NMR spectrum of **1**, Kang and Yin postulated that favorable π-type interactions from O-20′ to O-18′ create a "rigid polyatomic coplanar structure consisting of nine atoms (**1a**) or eight atoms (**1b**) ... between C-20 and C-18."[7] Assuming the *Z*-configuration, such a structural constraint was viewed as bringing C-20 and O-18′ together in space so as to "severely hinder" rotation of the C-20−O-20′ bond. The O-axial conformer was thereby presumed to be stabilized as depicted by **1**. If the train of 8−9 atoms in the latter (C−O−X═C−C(O)−O−C, X = N and N^+-O^-) is not rigid at room temperature, then the postulated steric congestion is inoperable. We tested the inflexibility hypothesis as follows.

Ab Initio Evaluation. The geometries of conformers and intervening rotational transition states for MeOX═C(Me)CO_2-Me (N^+-O^-, *O*-methyl nitronic ester **2a**, and X = N, *O*-methyl oxime **2b**) were optimized with the Becke3LYP/3-21G basis set.[8] For **2a**, both *Z* and *E* configurations were considered (Figure 1); for **2b**, only the *Z* form (see Supporting Information). To obtain reliable energy differences, single-point calculations on optimized geometries were obtained with Becke3LYP/6-31G*, MP2/6-311G* (X = N), and MP2/6-31G* (X = N^+-O^-). The relative energy results are recorded in Figure 1, while absolute energies are deposited in the Supporting Information. For **2a**, energy barriers for rotation around the CO−N(═C) and (N═C)−C(O)O bonds are evaluated at 4−7 and 5−9 kcal/mol. For **2b**, the values are in the 8−10 and 6−9 kcal/mol ranges, respectively, and well below that necessary for inflexibility of

(6) (a) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129; (b) http://www.schrodinger.com/macromodel2.html

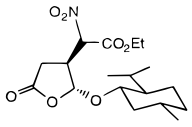
(7) Ref 4, footnote 13.

the C−O−X═C−C(O)−O−C unit at room temperature (18−20 kcal/mol). Constrained optimization of the *Z*-constituted fragment as shown in **1a** and **2a9** (Figure 1) delivered a nonstationary state 15−16 kcal/mol higher in energy than the planar ground state **2a1**. The corresponding value for the oxime fragment corresponding to **1b** is 17 kcal/mol (see Supplementary Information). All attempts to locate an unconstrained planar local minimum of this type for **2a** and **2b** led to twisted or alternative planar forms relatively free of steric strain (Figure 1). These results are in complete accord with structural data retrieved from the Cambridge Crystallographic database.[9] Numerous compounds contain a planar X═C−C(O)−O−C moiety, though a similar number show the CO_2Me fragment twisted out-of-plane by 40−80°.

Molecular Mechanics Conformational Analysis. Geometries and energies derived from the ab initio calculations were translated into parameters suited to enhancement of the MM3* force field in Macromodel[6] for nitronates (Supporting Information). *Z* and *E* configurations of nitronate **1a** were subjected to 59,000 step Monte Carlo MM3*/GBSA/$CHCl_3$ conformational searches leading to 4185 and 5789 fully optimized chair conformations, respectively, within 12 kcal/mol of the global minimum. The corresponding global minima were found 24 and 10 times. A Boltzmann energy distribution for the sets of conformers from the two chair isomers led to an estimated ratio of axial and equatorial cyclohexane chair forms. For the *Z* and *E* configurations, the eq/ax population ratios are 2.8:1 and 2.2:1 corresponding to energy differences of 0.62 and 0.47 kcal/mol (273.2 K), respectively. These quantities are well within the range of experimental *A* values tabulated for monosubstituted *O*-cyclohexane derivatives (0.27−1.04 kcal/mol).[10] Given the prediction that both the *E* and *Z* isomers of **1a** are predominately O-equatorial, we undertook synthesis of the compound and several analogues for NMR analysis.

Synthesis of Nitronate Analogues

Numerous attempts to prepare **1a** by the reaction of nitro compound **3** with cyclohexyl bromide in the presence of K_2CO_3[11] failed in our hands, though we were able to repeat the synthesis of other reported nitronates by this method. Fortunately, nitronate esters can also be prepared by the Mitsunobu reaction.[12,13,14] Thus, a compound with the elemental composition for **1a** was obtained from **3** and cyclohexanol in 62% yield after recrystallization. No trace of **1b** was observed. The ^1H NMR spectrum displays a septet for H-20 at 4.76 ppm (Figure 2), while the ^{13}C trace shows C-20 at 73.76 ppm. These results are at odds with the published values for **1a** (5.19 and 78.0 ppm, respectively[4,11]). Equally striking, our chemical shift values are characteristic of equatorial O-substitution rather than axial.[15,16] One possible interpretation of these results is that we had inadvertently synthesized the *E*-isomer of **1a**. In apparent agreement with this supposition, a number of 1D-nOe and NOESY measurements (400 MHz) yielded no diagnostic cross-peaks between H-20 and the OCH_2CH_3. Confirmation via X-ray crystallography was unsuccessful, as we were unable to obtain suitable crystals under a variety of conditions.



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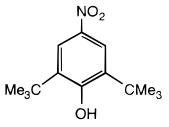

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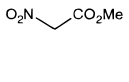

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In an attempt to resolve both the vexing conformational and configurational issues, we prepared a number of additional analogues (**6**−**12**) from the corresponding nitro precursors under Mitsunobu conditions. Cyclohexyl nitronates **8**, **11**, and **12** were prepared by reaction of 2,6-di-*tert*-butyl-nitrophenol (**4**) or ethyl nitroacetate (**5**) with cyclohexanol. Compounds **11** and **12** were obtained as a mixture of isomers (1:2) and separated by chromatography. The trans 4-*tert*-butylcyclohexyl nitronates, **6** and **9**, were prepared by reaction of **3** or **4** and cis 4-*tert*-butylcyclohexanol. By contrast, the cis 4-*tert*-butylcyclohexyl nitronates, **7** and **10**, were prepared from **3** or **4** and a mixture of 4-*tert*-butylcyclohexanol isomers in low yields followed by chromatography of the resulting diastereomers. Interestingly, no products could be isolated by combining **3** or **4** and trans 4-*tert*-butylcyclohexanol under the same conditions. In general, inversion reactions of *trans*-4-*tert*-butylcyclohexyl compounds tend to give poor yields presumably as a result of attack from the hindered axial location. NMR chemical shifts for selected protons and carbons are reported in Table 1.

Table 1. ^1H and ^{13}C Chemical Shifts, Multiplicities, and Half-Widths for the NMR Spectra of Nitronate Esters **1a** and **6**−**13**; $CDCl_3$

	OC*H* ^1H NMR, ppm[a]			OC*H* ^{13}C NMR, ppm		
	t-Bu *trans*	t-Bu *cis*	C_6H_{11}	t-Bu *trans*	t-Bu *cis*	C_6H_{11}
1a			5.19[b]			78.0[b]
			4.78 (s, 19)[c,d]			73.76[c]
6		4.65 (n, 23)[e]			74.98	
7	5.06 (p, 6)[f]			70.87		
8			4.95 (s*, 16)[g]			
9		4.80 (n, 22)				
10	5.20 (p, 6)					
11			4.92 (s*, 16)[g]			76.80
12			4.77 (s, 18)			74.68
13[h]			5.19 (s, 13)			78.06

[a] The multiplicity and peak half-width ($W_{1/2}$, Hz) are in parentheses. [b] Reference 4. [c] This work. [d] s = apparent septet, broadened. [e] n = nonet, i.e., triplet of triplets. [f] p = pentet. [g] s* = apparent septet, sharp. [h] Cyclopentyl nitronate.

Cyclohexane Conformation: NMR Chemical Shifts and Line Shape

Assessment of cyclohexyl conformation in the nitronate system is facilitated by having genuine samples of the two

(8) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Gaussian, Inc.: Pittsburgh, PA, 1994. Becke, A. D. J. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Stevens, P. J.; Devlin, F. F.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. Rauhut, G.; Pulay, P. *J. Phys. Chem.* **1995**, *99*, 3093−3100. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

(9) Cambridge Crystallographic Data Centre: http://csdvx2.ccdc.cam.ac.uk/

(10) *Stereochemistry of Organic Compounds*, Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1994; p 696.

(11) Kang, F.; Yin, C.; She, S. *J. Org. Chem.* **1996**, *61*, 5523−5527.

(12) Kimura, J.; Kawashima, A.; Sugizaki, M.; Nemoto, N.; Mitsunobu, O. *J. Chem. Soc., Chem. Commun.* **1979**, 303−304.

(13) Mitsunobu, O.; Yoshida, N. *Tetrahedron Lett.* **1981**, *22*, 2295−2296.

(14) Falck, J.; Yu, J. *Tetrahedron Lett.* **1992**, *33*, 6723−6726.

(15) (a) Lemeiux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098−6105. (b) Jensen, F. R.; Beck, B. H. *J. Am. Chem. Soc.* **1968**, *90*, 3251−3253. (c) Anet, F. A. L.; Henrichs, P. M. *Tetrahedron Lett.* **1969**, 741−744. (d) ref 1a, pp 712−713.

(16) (a) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866−3873; (b) ref 2a, Table 11.15, p 717, 1994.

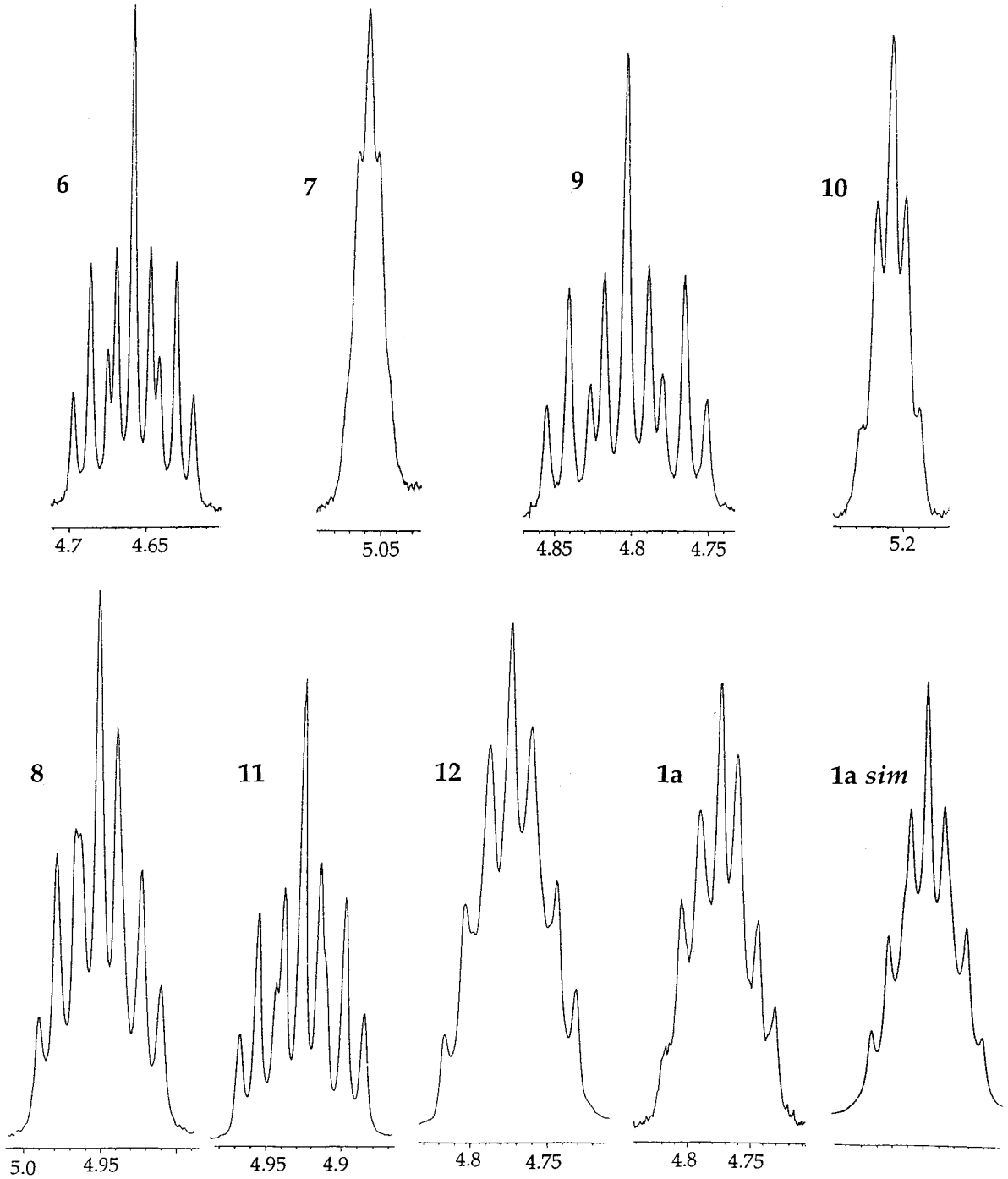


Figure 2. Proton chemical shifts and splitting pattern for nitronates **1a** and **6**−**12**. The **1a *sim*** multiplet was obtained by simulating the 5-spin system for **1a** with $J_{ee} = 9.3$ and $J_{ea} = 3.9$ Hz.

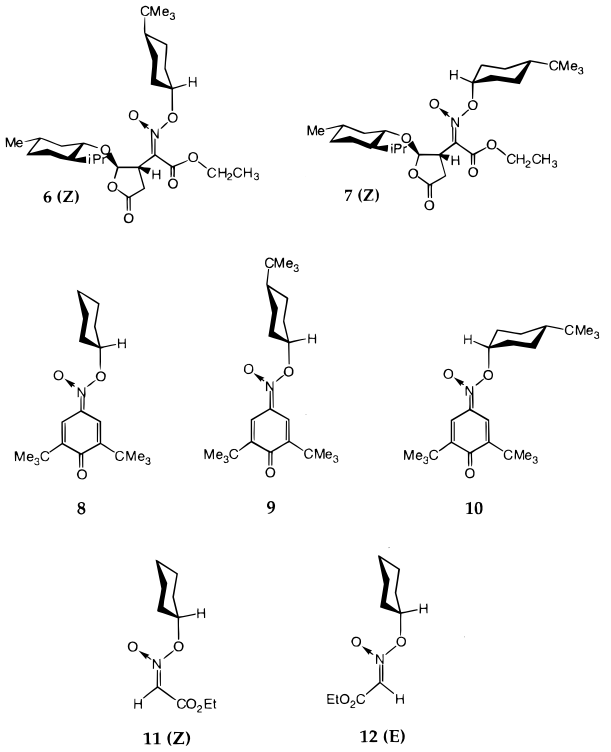
isomers. The equatorial−axial pairs **6**, **7** and **9**, **10** utilizing a 4-*tert*-butyl anchor achieve this purpose. For determination and designation of stereochemistry, the ^{1}H and ^{13}C chemical shifts of the proton geminal to oxygen on the cyclohexyl ring (H_{gem}) and the carbon bearing both of these atoms (C_{gem}), respectively, are diagnostic (Table 1).

Nitronates **6** and **9** with equatorial oxygen display H_{gem} from 4.6 to 4.8 ppm as the X part of an AA′BB′X spin system. These axial protons are characterized by sharp, well-defined, first-order nonets (triplets of triplets) with half-widths ($W_{1/2}$) of 23 and 22 Hz, respectively (Figure 2, Table 1). The multiplicity and band shape is identical to that recorded for C*H*O in 3,3,4,4,5,5,-hexadeuteriocyclohexane.[17] The ^{1}H NMR of O-axial isomers **7** and **10** display the equatorial H_{gem} at 0.4 ppm downfield from 5.1 to 5.2 ppm.

In addition to the typical axial−equatorial chemical shift difference, the band shapes are narrow, sharp pentets that almost appear as triplets (Figure 2). The splitting pattern is that expected for an AA′BB′X system in which $J_{AX} \approx J_{BX}$. Peak shapes are further distinguished by the diminutive half-widths of 6 Hz. The $W_{1/2}$ observations are in accord with many previous observations for cyclohexanes showing that $^1H_{ax}$ J splittings are uniformly larger than $^1H_{eq}$ couplings.[15] In the ^{13}C spectra the same pairs of configurational isomers show a typical[16] 4 ppm downfield

(17) Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 1053−1054.

shift for C_{gem} as oxygen occupies the axial and equatorial positions, respectively (**Table 1**).



The monosubstituted cyclohexanol derivatives are represented by **8**, **11**, and **12**. Quinone **8** displays H_{gem} as a sharp apparent septet at 4.95 ppm. Expansion of the multiplet illustrates that the third and fifth peak components are narrowly separated doublets (Figure 2). When compared with the nonets of **6** and **9** arising from purely axial H_{gem}, the "septet" or coalesced nonet of **8** signifies that the conformational equilibrium has shifted from pure O-equatorial cyclohexane chair to a weighted mixture of O-axial and O-equatorial chairs. The downfield shift of H_{gem} (from 4.65/4.80 (**6**/**9**) to 4.95 ppm (**8**)), the narrowing of $W_{1/2}$ (from 22 to 16 Hz), and the C_{gem} at 77.0 ppm corroborates the interpretation.

The stereochemistry of cyclohexanol isomers **11** and **12** is assigned by comparing the relative chemical shifts of the vinyl protons. The upfield value for **11** (6.41 ppm) vs that for **12** (6.75 ppm) indicates the *Z* and *E* configurations about the C═N bond, respectively.[14,18] Both exhibit H_{gem} as multiplets in the range for predominately O-equatorial structures with complementary $W_{1/2}$ from 16 to 18 Hz (Table 1). As for cyclohexyl **8**, the collapse of nonets to septets with different band shapes reflects an equilibrium drift with small but dissimilar amounts of O-axial isomers. The corresponding C_{gem} shifts are confirmatory. In agreement with the above-mentioned molecular mechanics conformational analysis, the *Z*-oriented carboethoxy and O-cyclohexyl functionalities clearly do not occasion steric crowding sufficiently potent to cause the cyclohexyl group to adopt a predominant O-axial orientation.

We now turn to the controversial **1a**. The Mitsunobu route yielded a compound with the elemental analysis of the target but an H_{gem} = H-20 as an apparent septet at 4.76 ppm ($W_{1/2}$ = 19 Hz), a value identical with that for cyclohexyl acetate. The proton data coupled to the corresponding C_{gem} = 73.76 ppm and compared to the other values of Table 1 lead to the inescapable conclusion that **1a** incorporates predominately equatorial oxygen. The result can be quantitated with an experimental estimate of the equatorial and axial populations.

In a previous communication we performed gNMR simulations of the proton NMR spectra for **6** and **7**.[5,19] Figure 2 illustrates the analogous result for the broadened septet of **1a**, the simulated spectrum depicted as **1a-sim**. In this way we estimate that J_{ee} and J_{ea} correspond to 9.3 and 3.9 Hz, respectively. The former is the value that exchanges with J_{aa} during the course of an equatorial−axial interconversion. We can now use eq 1 to estimate conformer populations.[20]

$$\eta_{eq} = [\, J_{obs} - J_{ee} \,]/[\, J_{aa} - J_{ee} \,] \qquad (1)$$

Symbol η_{eq} corresponds to the chair conformation with O-20 in an equatorial location; J_{obs}, the experimental J_{ee}. For the extreme constants J_{ee} and J_{aa}, we take the 163 K values measured for 3,3,4,4,5,5,-hexadeuteriocyclohexyl acetate, 2.7 and 11.4 ppm, respectively.[17] With J_{obs} = 9.3, η_{eq} = 0.76, eq/ax = 3.2/1, and the estimated *A* value is 0.68 kcal/mol at 298 K. The result corresponds closely to our MM3* conformational estimate (0.5−0.6 kcal/mol) as well as to the ΔG(ax−eq) = 0.66 recorded for cyclohexyl acetate.[17]

C═N Configuration, *E* or *Z*?

The work of Kang and Yin pictures the *O*-cyclohexyl nitronates and *O*-cyclohexyloximes as the *Z* isomers, i.e., **1a** and **1b**, although no supporting evidence was reported.[4,11] Unable to obtain suitable crystals of **1a** for an X-ray structure analysis or to observe distinguishing nOe cross-peaks in the NMR,[5] we have failed to unambiguously specify the C═N bond stereochemistry. However, the data in Figure 2 and Table 1 tentatively suggest an assignment. The ^{1}H NMR spectra of *Z* and *E* isomers **11** and **12** differ both in peak position and shape. The H_{gem} for *E* **12** appears as a broadened septet at 4.77 ppm. The same proton for *Z* **11** presents at 4.92 ppm as a sharp apparent septet shifted downfield by 0.15 ppm. In the previous section, we noted that H_{gem} for **8** is likewise an apparent septet with δ = 4.95 ppm. Presumably, the π-system of the planar cis CO_2Et moiety in **11** and the π-system of the quinonoid **8** exert both a similar shielding effect at H_{gem} and a nearly identical eq/ax population ratio.

In clear contrast, compound **1a** exhibits its H_{gem} = H-20 with precisely the same chemical shift and band shape as *E* **12**. The implication is that **1a** exists in the *E* configuration. Single-point Becke3LYP/6-31G* calculations for the O-equatorial *E* and *Z* global minima from the MM3* conformational searches for **1a** are supportive. The *E* isomer is predicted to be 4.2 kcal/mol more stable than the *Z* form. H_{gem} chemical shifts in **6** and **9** (4.65 and 4.80 ppm, respectively) suggest that they likewise adopt *E* forms.

Conclusions

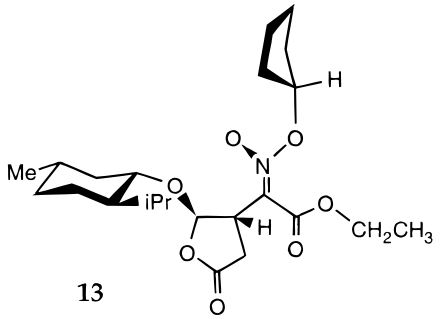
All available evidence points to **1a** as a compound with the O-cyclohexyl moiety engaged in an equilibrium in which eq/ax ≈ 3:1 and the two conformations are rapidly interconverted. With respect to other monooxy-substituted cyclohexanes, the compound exhibits no unusual properties. In fact, its confor-

(18) Gree, R.; Carrie, R. *Bull. Soc. Chim. Fr.* **1975**, 1314−1318.

(19) gNMR: Cherwell Scientific Publishing Limited; http://www.cherwell.com/ ProdHome.gnmrhome.html.

(20) Equation 1 is derived by simple manipulation of previous expressions used to determine conformer populations by the *J*-value method: (a) Eliel, E. L. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1971; pp 5−7. (b) Terui, Y.; Tori, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 127−133. (c) Abraham, R. J.; Medforth, C. J.; Smith, P. E. *J. Comput.-Aided Mol. Design* **1991**, *5*, 205−212.

mational profile is virtually identical to that of cyclohexyl acetate. How then can the discrepancy between our findings and those reported by Kang and Yin be explained? At the conclusion of the work reported here, we received word from Dr. Kang that structure **1a** pictured in the original publications[4,11] was in error.[21] Apparently cyclopentyl bromide had been inadvertently substituted for cyclohexyl bromide in the original preparation. To confirm this observation, we prepared the corresponding cyclopentyl analogue **13** by the Mitsunobu procedure without complication (68% yield). The nitronic ester exhibits all chemical shift and band shape characteristics previously ascribed to **1a** and to a genuine sample reported in the same publication.[11]



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The H_{gem} chemical shift of 5.19 ppm is peculiar. Not only does the latter fall precisely where a cyclohexyl equatorial proton is expected, but it is a compound that violates the Kang-Yin proposal for an empirical chemical shift rule for oxygen-containing homologues.[4] In fact it was the anomalous value of 5.19 ppm in the context of the shift rule that inspired the suggestion that **1a** is "completely stable axial conformer of (a) monosubstituted cyclohexane". It would appear that not only structure **1a** but also the shift rule is subject to revision.

Experimental Section

General. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are reported without correction. Mass spectrometric analysis was provided by the Emory University Mass Spectrometry Center. Proton and carbon NMR spectra were obtained on Varian Inova-400 (400 MHz) or Varian Mercury-300 (300 MHz) spectrometers. Solvent for NMR was deuteriochloroform with residual chloroform (δ 7.26 ppm for proton and δ 77.0 ppm for carbon) taken as internal reference and reported in parts per million (ppm). TLC and preparative thin-layer chromatography (PTLC) were performed on precoated, glass-backed plates (silica gel 60 F_{254}; 0.25 mm thickness) from EM Science and were visualized by UV lamp. Chromatography was performed with silica gel 60 (230−400 mesh ASTM) or neutral alumina (80−200 mesh) from EM Science using the "flash" method.[22] Elemental analyses were performed by Atlantic Microlab Inc. Norcross, Georgia. The nitro compounds (4*S**,5*R*)-(+)-4-(1′-nitro-1′-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone, **3**, and 2,6-di-*tert*-butyl-4-nitrophenol, **4**, were prepared[11,23] and fully characterized. All solvents and other reagents were purchased from Aldrich Chemical Co., Milwaukee. The 4-*tert*-butylcyclohexanol was a mixture of cis/trans isomers, 1:2.5 according to the proton NMR integration, and was separated by column chromatography (Al_2O_3).[24] The solvents were dehydrated and distilled before use.[25] The reagents were used as received. All reactions were performed under anhydrous nitrogen atmosphere in oven-dried glassware.

General procedure for Preparation of Alkyl Nitronic Esters: (*Z*)-Cyclohexyl Nitronic Ester of (4*S, 5*R*)-4-(1′-Nitro-1′-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-di-hydro-2(5*H*)-furanone (1a).** Compound **3** (520 mg, 1.4 mmol), cyclohexanol (210 mg, 2.1 mmol, 1.5 equiv), and triphenylphosphine (400 mg, 1.5 mmol, 1.1 equiv) were dissolved in THF (4 mL). To this magnetically stirred solution, cooled to 0 °C, was added dropwise diethyl azodicarboxylate (270 mg, 1.5 mmol, 1.1 equiv) and the mixture stirred for 2 h then allowed to warm to room temperature and stirred another 2 h. The solvent was evaporated under reduced pressure and the residue was column chromatographed (SiO_2) eluting with a mixture of hexanes and ethyl acetate (8:1). The white solid (390 mg, 62%) was recrystallized from petroleum ether: mp 65−70 °C (lit.[11] 73−75 °C). ^{1}HMR (300 MHz) 5.36 (s, 1H), 4.78 (sept, 1H), 4.29 (q, 2H), 3.75 (dd, 1H), 3.4 (dt, 1H), 2.74 (dd, 1H), 2.55 (dd, 1H), 2.11 (m, 2H), 1.82−1.5 (m, 7H), 1.38−1.18 (m, 9H), 1.08−0.74 (m, 13H). ^{13}CMR (300 MHz) 169.457, 158.541, 109.945, 103.103, 81.79, 73.761, 61.866, 48.128, 47.218, 42.962, 34.034, 33.7, 31.61, 31.49, 25.424, 25.188, 23.709, 22.981, 22.063, 20.978, 16.05, 14.166. Elem. Anal. Calcd for $C_{24}H_{39}NO_7$: C, 63.58; H, 8.61; N, 3.09. Found: C, 63.65; H, 8.56; N, 3.09. HRMS (FAB) calcd for $C_{24}H_{39}NO_7Li$ (M+Li^+) 460.2887, found 460.2852 (+1.8 ppm).

(*Z*)-*trans*-4-*tert*-Butylcyclohexyl Nitronic Ester of (4*S, 5*R*)-4-(1′-Nitro-1′-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-di-hydro-2(5*H*)-furanone (6).** Compound **3** (100 mg, 0.27 mmol) and *cis*-4-*tert*-butylcyclohexanol (63 mg, 0.4 mmol, 1.5 equiv) were combined as described above to provide the title compound (38 mg, 28%) as a white solid. ^{1}HMR (400 MHz) 5.4 (s, 1H), 4.65 (non, 1H), 4.34 (dq, 2H), 3.75 (dd, 1H), 3.41 (dt, 1H), 2.77 (dd, 1H), 2.57 (dd, 1H), 2.15 (d, 2H), 2.0 (d, 2H), 1.82 (d, 2H), 1.66−1.5 (m, 4H), 1.38−1.2 (m, 18H), 1.16−0.94 (m, 4H), 0.91 (t, 4H), 0.84 (s, 9H), 0.78 (d, 4H). ^{13}CMR (400 MHz) 169.8, 158.8, 110.24, 103.36, 82.06, 74.98, 62.13, 48.38, 47.46, 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. Elem. Anal. Calcd for $C_{28}H_{47}NO_7$: C, 66.01; H, 9.23; N, 2.75. Found: C, 65.81; H, 9.19; N, 2.7. HRMS (FAB) calcd for $C_{28}H_{47}NO_7$ 510.3431, found 510.3434 (+0.5 ppm).

(*Z*)-*cis*-4-*tert*-Butylcyclohexyl Nitronic Ester of (4*S, 5*R*)-4-(1′-Nitro-1′-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-di-hydro-2(5*H*)-furanone (7).** Compound **3** (200 mg, 0.54 mmol) and 4-*tert*-butylcyclohexanol (diastereomer mixture, 127 mg, 1.5 equiv) similarly yielded a mixture of nitronate product after column chromatography. Further, separation by PTLC furnished **7** (46 mg, 10%) and the title compound (10 mg, 5%) as a white solid. ^{1}HMR (400 MHz) 5.41 (s, 1H), 5.06 (pent, 1H), 4.32 (dq, 2H), 3.75 (dd, 1H), 3.42 (dt, 1H), 2.82 (dd, 1H), 2.61 (dd, 1H), 2.18−2.1 (m, 2H), 1.93 (d, 2H), 1.65−1.42 (m, 6H), 1.35 (t, 3H), 1.3−1.2 (m, 4H), 1.14−0.95 (m, 5H), 0.9 (dd, 4H), 0.85 (s, 9H), 0.78 (d, 4H). ^{13}CMR (400 MHz) 169.9, 158.5, 110.1, 103.49, 82.24, 70.87, 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. Elem. Anal. Calcd for $C_{28}H_{47}NO_7$: C, 66.01; H, 9.23; N, 2.75. Found: C, 65.75; H, 9.29; N, 2.66. HRMS (FAB) calcd for $C_{28}H_{47}NO_7$ 510.3431, found 510.3446 (+3.1 ppm).

(*Z*)-Cyclopentyl Nitronic Ester of (4*S, 5*R*)-4-(1′-Nitro-1′-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-di-hydro-2(5*H*)-furanone (13).** Compound **3** (100 mg, 0.27 mmol) and cyclopentanol (46 mg, 0.54 mmol) resulted in the title compound (81 mg, 68%) as a white solid that was recrystallized from petroleum ether: mp 66−69 °C (lit.[11] 80−81 °C). ^{1}HMR (300 MHz) 5.38 (s, 1H), 5.19 (sept, 1H), 4.32 (q, 2H), 3.85 (dd, 1H), 3.4 (dt, 1H), 2.78 (dd, 1H), 2.55 (dd, 1H), 2.19−2.1 (m, 2H), 1.95−1.6 (m, 10H), 1.35 (t, 3H), 1.25−0.8 (m, 12H). ^{13}CMR (300 MHz) 169.66, 158.6, 109.8, 103.12, 81.89, 78.06, 61.92, 48.25, 47.27, 43.05, 34.15, 33.76, 32.73, 32.64, 31.73, 25.54, 23.75, 23.11, 22.18, 21.10, 16.17, 14.3. Elem. Anal. Calcd for $C_{23}H_{37}NO_7$: C, 62.87; H, 8.43; N, 3.19. Found: C, 62.91; H, 8.34; N, 3.08. HRMS (FAB) calcd for $C_{23}H_{37}NO_7Li$ (M+Li^+) 446.2730, found 446.2797 (+4.0 ppm).

Cyclohexyl Nitronic Ester of 2,6-Di-*tert*-butyl-4-nitrophenol (8). Compound **4** (100 mg, 0.4 mmol) and cyclohexanol (60 mg, 1.5 equiv) furnished the title compound (39 mg, 30%) after PTLC (Al_2O_3; hexanes/EtOAc). ^{1}HMR (300 MHz) 7.61 (d, 1H), 7.41 (d, 1H), 4.95 (sept, 1H), 1.95−1.85 (m, 2H), 1.8−1.7 (m, 2H), 1.6−1.35 (m, 6H), 1.3 (s, 18H).

(21) Private communication from Dr. F. -A. Kang, Beijing Normal University.

(22) Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(23) Barnes, T.; Hickinbottom, W. *J. Chem. Soc.* **1961**, 953−956.
(24) Winstein, S.; Holness, N. *J. Am. Chem. Soc.* **1955**, *77*, 5562−5578.
(25) Perrin, D.; Armarego, W. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Elmsford, 1988.

^{13}CMR (300 MHz) 185.86, 151.33, 148.14, 126.78, 122.81, 121.49, 77.0, 36.08, 35.87, 30.34, 29.65, 25.53, 23.83. HRMS (FAB) calcd for $C_{20}H_{32}NO_3$ ($M+H^+$) 334.2382, found 334.2374 (−2.5 ppm).

***trans*-4-*tert*-Butylcyclohexyl Nitronic Ester of 2,6-Di-*tert*-butyl-4-nitrophenol (9).** Compound **4** (100 mg, 0.4 mmol) and *cis*-4-*tert*-butylcyclohexanol (93 mg, 1.5 equiv) furnished the title compound (31 mg, 20%) after PTLC (Al_2O_3; hexanes/EtOAc). ^{1}HMR (300 MHz) 7.55 (d, 1H), 7.41 (d, 1H), 4.8 (non, 1H), 2.1−1.5 (m, 6H), 1.3 (s, 18H), 1.2−1.0 (m, 3H), 0.9 (d, 9H). ^{13}CMR (300 MHz) 185.88, 151.32, 148.15, 126.79, 122.83, 121.48, 78.77, 47.33, 36.09, 32.55, 31.08, 29.66, 29.36, 27.82, 25.65, 22.58. HRMS (FAB) calcd for $C_{24}H_{40}O_3N$ 390.3008, found 390.3027 (+4.8 ppm).

***cis*-4-*tert*-Butylcyclohexyl Nitronic Ester of 2,6-Di-*tert*-butyl-4-nitrophenol (10).** Compound **4** (100 mg, 0.4 mmol) and 4-*tert*-butylcyclohexanol (diastereomer mixture, 93 mg, 1.5 equiv) furnished **9** (20%) and the title compound (15.6 mg, 10%) after PTLC (Al_2O_3; hexanes/EtOAc). ^{1}HMR (300 MHz) 7.5 (d, 1H), 7.4 (d, 1H), 5.2 (pent, 1H), 2.25 (d, 2H), 1.7−1.5 (m, 4H), 1.3 (s, 18H), 1.15−1.0 (m, 3H), 0.9 (s, 9H). ^{13}CMR (300 MHz) 185.86, 151.25, 148.23, 126.61, 122.85, 121.26, 73.70, 47.75, 36.08, 35.86, 32.75, 29.66, 29.64, 29.36, 27.64, 22.57. HRMS (FAB) calcd $C_{24}H_{40}O_3N$ 390.3008, found 390.3011 (+0.6 ppm).

***cis*-(11) and *trans*-(12) Cyclohexyl Nitronate Esters of Ethyl Nitroacetate.** Obtained from 500 mg **5** (3.76 mmol) as described for **8**. After stirring for 3 h, the solvent was evaporated at room temperature under reduced pressure. The mixture was chromatographed (Al_2O_3) eluting with hexanes/ethyl acetate. Eluting first was **11** (15%), a colorless liquid. ^{1}HMR (300 MHz) 6.41 (s, 1H), 4.92 (sept, 1H), 4.2 (q, 2H), 1.9−1.62 (m, 5H), 1.6−1.45 (m, 1H), 1.38 (t, 4H), 1.3 (t, 3H). ^{13}CMR (300 MHz) 159.2, 107.11, 76.807, 60.94, 29.90, 25.37, 23.47, 14.24. HRMS (FAB) calcd for $C_{10}H_{17}NO_4Li$ ($M + Li^+$) 222.1318, found 222.1315 (−1.4 ppm). Later, **12** (30%) eluted, also a colorless liquid. ^{1}HMR (300 MHz) 6.75 (s, 1H), 4.77 (sept, 1H), 4.25 (q, 2H), 1.9−1.65 (m, 5H), 1.55 (m, 1H), 1.45−1.35 (t, 4H), 1.3 (t, 3H). ^{13}CMR (300 MHz) 160.20, 106.16, 74.68, 61.11, 30.17, 25.352, 23.78, 14.27. HRMS (FAB) calcd for $C_{10}H_{17}NO_4Li$ ($M + Li^+$) 222.1318, found 222.1283 (−1.0 ppm).

Computational Aspects. Ab initio and DFT calculations were performed with the *Gaussian 94* series of programs.[8a] All ground states and transition states were optimized to convergence with the Becke3LYP/3-21G protocol. Torsional transition states were obtained by constraining the N−OMe or C−CO_2Me bonds to 90° during the course of the geometry optimization. High energy structures **2a9** and **2b6** were refined similarly by constraining the corresponding five central heavy atoms in (H_3)C−O−N═C−C(O_2Me) to a plane. The MM3* force field for nitronates was developed by successively and iteratively adjusting bond lengths, angles, and torsions to fit the Becke3LYP/3-21G geometries and the MP2/6-31G* energies. Following the conformational searches for *Z* and *E* configurations of **1a** in Macromodel as described in the text, a Boltzmann distribution of energies for the separate sets of conformations was computed with a program written for this purpose. Simulating the spectrum of **1a** was accomplished by altering the values of J_{ee} and J_{ea} in gNMR[19] on a Power Macintosh until the best visual match was obtained (**1a *sim***, Figure 1).

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Supporting Information Available: A summary of geometries for **2b** conformers, absolute energies for **2a** and **2b** (Figure 3; Table 2), and force field parameters for nitronate esters (Table 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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