acetonitrile (3 mL) as cosolvent. Irradiation of the solution proceeded at 4 °C (refrigerated room) at 300 nm for 30 min. The photolysate was worked up by two extractions with 100 mL of dichloromethane, followed by drying with anhydrous $MgSO_4$. The drying agent was filtered off and the solvent removed by rotary evaporation. The remaining residue was dissolved in 1–2 mL of acetonitrile and injected into the GC (column temperature = 90 °C). 2-Methylbenzoxazole was detected, but in very low yield (<1%). The major of product (>95%) was the hydrolysis product, *o*-hydroxyacetophenone. This was the only substrate exhibiting a low cyclization yield in water.

**(c) Salicylaldoxime, Benzyl Ether.** The oxime ether (80 mg) was irradiated in 450 mL of $H_2O$ and 150 mL $CH_3CN$ (cosolvent). The solution was deoxygenated by bubbling in Ar gas for 20 min. The quartz tube was then equipped with a cold finger and magnetic stirring bar. Photolysis was carried out at 300 nm,[25] with four products being produced. The reaction was worked up in the usual manner. All four products were analyzed and confirmed by gas chromatography at different temperatures, by comparison with authentic samples, and also by proton NMR. Benzaldehyde and salicylaldehyde were each produced in 30% yield, while benzoxazole and benzyl alcohol were the only other products, each being produced in 20% yield.

**(d) 1,2-Benzisoxazole.** 1,2-Benzisoxazole (400 mL), dissolved in of acetonitrile (100 mL), was added to 500 mL of water. This solution was outgassed with argon gas for 20 min in a quartz vessel, which was equipped with a magnetic stirring bar and cold finger, and irradiation proceeded at 254 nm for 1 h. Workup of the reaction consisted of two extractions with dichloromethane (2 × 100 mL each), drying with anhydrous $MgSO_4$, and finally rotary evaporation. As verified by TLC (silica gel with dichloromethane as eluent) by proton NMR, and by comparison with authentic material, benzoxazole was produced cleanly in approximately 50% yield.

**Absolute Quantum Yields.** Quantum yields were determined using potassium ferrioxalate as the actinometer. The preparation and usage of the actinometer has been described elsewhere.[26] The method used for analyzing the product yields was gas chromatography. A sample run is described below. Approximately 20 mg of oxime was dissolved in 18 mL of water and 2 mL of acetonitrile. Ar gas was then bubbled through the solution for a minimum of 20 min. The quartz tube was then placed in a merry-go-round apparatus in a Rayonet photochemical reactor. Either four or eight lamps were used, all at 254 nm, and irradiations usually proceeded for about 45 min. Potassium ferrioxalate was used to calibrate the lamps. This method assumes a certain degree of lamp stability, which our experiments have borne out. The lamps were turned on and allowed to equilibrate for at least 30 min before any measurements were started. The method of calibration is outlined here. A stock solution of potassium ferrioxalate was prepared as described.[26] A 20-mL aliquot of this stock solution was pipetted into a quartz tube which was placed in the merry-go-round apparatus. Because the 254-nm lamps also emit radiation >300 nm, none of which any substrate absorbs, a simultaneous experiment was run to determine how much of this light is produced.[27] Potassium ferrioxalate does absorb above 300 nm, and so this light would certainly affect any measurements of light intensity. To test for this unwanted radiation, 3 mL of actinometer solution was placed in a cuvette which passed only wavelengths greater than 300 nm. Photolysis of both solutions occurred for 20 min, followed by workup of the actinometer solution. The intensity of light from the lamps is simply the number of photons emitted per unit of time. Mathematically, this expression is $I(\text{einsteins/min}) = (\text{number of protons emitted})/\text{time} = (\text{moles of product})/(\phi \times \text{time}) = (A \times \text{volume})/(\epsilon \times \phi \times \text{time})$, where $A$ = optical density of product, $\epsilon$ = molar extinction coefficient, $\phi$ = quantum yield of actinometer reaction, volume = total volume of solution irradiated, and $I$ = intensity of light. The equation then simplifes to $I = [(A \times \text{volume})/\text{time}](7.2072 \times 10^{-7}\ \text{einsteins/mL})$ by using $\epsilon = 1.11 \times 10^4\ \text{L mol}^{-1}\ \text{cm}^{-1}$, length of cell = 1.00 cm, and $\phi = 1.25$ and also incorporating a factor of 10 due to dilution of the photolyte.

The amount of light centered at 254 nm is equal to the total Rayonet light intensity (i.e., quartz tube) minus the intensity of light greater than 300 nm (i.e., the plastic cuvette). It was found that 6% of the light emitted by the 254-nm lamps comes from wavelengths greater than 300 nm. The numerical value for the intensity of light centered at 254 nm is $3.41 \times 10^{-7}$ einsteins/min/lamp. All experiments carried out show that this number can be experimentally reproduced to within ±10%.

**Acknowledgment.** Grateful acknowledgement is made to the Natural Sciences and Engineering Research Council of Canada (NSERC) for continued financial support.

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[25] When the photolysis was carried out at 254 nm, no isolable products were produced. Since all four products are relatively photostable, no explanation can be found as to why this occurs.

[26] Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1973; p 119.

[27] It is fortunate that the potassium ferrioxalate quantum yield does not change in going from 254 to 300 nm. Thus the light used does not have to be a monochromatic 254-nm line.

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# Molecular Mechanics Treatment of β-Heteroatom-Substituted Cyclohexanones

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Recent NMR studies[1] indicate an axial preference for β-heteroatom-substituted cyclohexanones. The degree of axial preference essentially follows electronegativity: $F > OH \sim OCH_3 > OAc > Cl > Br \sim SEt > CH_3$. In fact, third row substituents actually are more stable in the equatorial position. We carried out ab initio calculations which support NMR data in the literature, and the MM2 program has been parameterized to model these systems correctly.

Recent equilibration studies have been carried out on the axial preferences of electron-withdrawing substituents β-substituted on cyclohexanones.[1,2] The axial–equatorial equilibrium for electronegative functional groups has also

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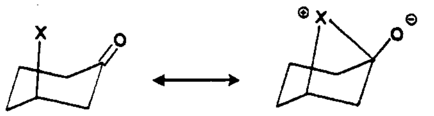

1 2

**Figure 1.** Electron donation from the axial substituent X to the carbonyl moiety may be depicted in valence bond fashion by resonance contributor **2**.

been the focus of some of our own recent research.[3] We have been particularly interested in through-space and through-bond stabilization of axial groups. Considerable attention was earlier directed toward α-halocyclohexane derivatives.[4] On the other hand, fewer studies have dealt with β-substituted cyclohexanones.[1,5] Owing to the importance of these compounds as synthetic intermediates, viz., aldol condensations, we decided to investigate some of these systems with molecular mechanics.[6,7]

Djerassi et al.[1,2] have recently reported, on the basis of NMR studies, that the axial preference for electronegative substituents β to a carbonyl have the following order: $F > OH \sim OCH_3 > OAc > Cl > Br \sim SEt > CH_3$. They concluded that no single mechanism could account for these results. One contribution to these results might be the resonance interaction, depicted below in valence bond fashion by structure **2**, with the X group (a halogen, originally) donating electron density to the carbonyl moiety (Figure 1). The purpose of this paper is twofold: (1) to present some ab initio results which show the unimportance of structure **2** and (2) to report MM2 parameters for treating these systems.

## Results and Discussion

In general, there is a preference for β-alkyl-substituted cyclohexanones to have the alkyl group in the equatorial position, but the population of the axial epimer is larger than in the corresponding cyclohexane. This has been attributed to 1,3-diaxial interactions being reduced by the carbonyl group, and is known as the "3-alkyl ketone effect".[8] Replacement of the alkyl group with a heteroatom, which is expected to have a longer C–X bond length and/or a smaller effective van der Waals radius, tends to reduce the 1,3-diaxial interactions. The order of axial heteroatom stability parallels electronegativity and, quite naturally, suggests some correlation. Electrostatic or dipole–dipole interactions have been discussed as a basis for this effect,[9] as have orbital considerations.[4,5,10]

**Table I. Ab Initio Energies of 3-Chlorocyclohexanone**

| basis set | conformatn | energies, hartrees | rel energy, kcal/mol | % (25 °C) |
|---|---|---|---|---|
| STO-3G* | axial | −758.143250231 | 0.37 | 34.9 |
| | equatorial | −758.143837517 | 0.00 | 65.1 |
| 3-31G | axial | −765.851836220 | 0.57 | 27.7 |
| | equatorial | −765.852738549 | 0.00 | 72.3 |
| 6-21G | axial | −766.388071591 | 0.89 | 18.2 |
| | equatorial | −766.389489013 | 0.00 | 81.8 |

**Table II. Gross Orbital Charges for Axial and Equatorial Conformations of 3-Chlorocyclohexanone**

| entry | basis sets | conformatn[a] | oxygen | chlorine |
|---|---|---|---|---|
| 1 | 4-31G | axial | 8.55807 | 17.06884 |
| 2 | 4-31G | equatorial | 8.55630 | 17.06466 |
| 3 | 6-21G | axial | 8.53118 | 16.99429 |
| 4 | 6-21G | equatorial | 8.53049 | 16.98841 |
| 5 | 6-21G | axial[b] | 8.53104 | 16.99422 |
| 6 | 6-21G | axial[c] | 8.53104 | 16.99422 |

[a] The geometries were taken from MM2 minimized structures, unless otherwise noted. [b] The $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–Cl dihedral angle was fixed at 65.0° in order to bring the chlorine substituent closer to the carbonyl group. The ab initio energy is −766.38806705 hartrees. [c] Dihedral angle fixed slightly smaller than 65.0°.

**Table III. Molecular Mechanics Parameters for Electronegative Substituents of β-Carbonyl Compounds**

| | | $V_1$ | $V_2$ | $V_3$ |
|---|---|---|---|---|
| $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–F | 3-1-1-11 | −1.000 | 0.000 | 0.200 |
| $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–Cl | 3-1-1-12 | −0.585 | 0.000 | 0.200 |
| $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–Br | 3-1-1-13 | −0.465 | 0.000 | 0.200 |
| $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–O | 3-1-1-6 | −0.140 (−0.586)[b] | 0.000 | 0.200 |
| $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–S[a] | 3-1-1-15 | 0.000 | 0.000 | 0.483 |

[a] Current values already present in the MM2 force field. [b] MM2 force field without hydrogen-bonding potential. See ref 15.

We were intrigued by the possibility of electron donation from the electronegative axial substituent into the π* CO orbital as depicted by structure **2**. The stabilization of four-membered chloronium systems has been reported.[11] The π* CO orbital, however, is relatively high lying in energy, and the overlap with the halogen would be small.[12] Furthermore, one would expect to observe more effective electron donation and, consequently, greater percentages of the axial isomer with second and third row elements than with first row atoms. This enhanced interaction for the halogens, as an example, might be predicted on the basis of greater overlap, polarizability, and longer bond lengths (F < Cl < Br). The opposite trend, however, is observed experimentally (See Table IX). Moreover, through-space interactions were shown by Hoffman[13] to be negligible at distances greater than about 2.5 Å. This is consistent with our findings for negligible nonbonded overlap in 3-cyclohexene-1-carboxaldehyde systems.[3] For axial β-halocyclohexanones, MM2 calculations give the distances between fluorine, chlorine, and bromine and the carbonyl carbon moiety to be 2.92, 3.28, and 3.40 Å, respectively.

Ab initio calculations[14] do not show any preference for

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(6) The program MM2(82), which is an extended but otherwise unchanged version of MM2 (Allinger, N. L.; Yuh, Y. *QCPE* **1980**, *12*, 395) is available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, IN 47401, and from Molecular Design, Ltd., 47405 Faralon Drive, San Leandro, CA 94577.

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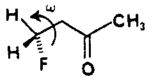

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**Figure 2.** STO-3G and 6-31G* calculations on 4-fluoro-2-butanone indicated that the trans conformation about the C(3)–C(4) bond was the most stable.

the axial chloro group, as indicated in Table I. Presumably the overlap would be present for this halogen for the previously stated reasons. If the mechanism of stabilization is a consequence of electron donation from the axial chlorine substituent to the carbonyl group, then we should be able to detect this phenomenon by observing the buildup of negative charge on the carbonyl oxygen in the axial epimer. A similar positive charge should be present on the chlorine atom, as reflected in 2. However, we did not find any "excess" charges on the critical atoms of the axial conformation as compared to the equatorial one (see Table II), and consequently there is no basis to consider structure 2 as a significant resonance contribution.[1,2]

In the absence of additional or conflicting evidence, we decided to treat the preferred axiality in MM2 as a result of ordinary dipole–dipole and through-bond electrostatic interactions. This requires only the addition of new torsional parameters as are listed in Table III. We were able to duplicate the axial–equatorial ratios by adjusting the $V_1$ terms, setting $V_2$ equal to zero in each case. (One could have adjusted $V_2$ instead or a combination of $V_1$ and $V_2$. The data available did not permit a choice between these alternatives and adjustment of $V_1$ was arbitrary.) A negative $V_1$ stabilizes the axial (or gauche) conformer relative to the equatorial (or trans) one. Fluorine is the most electronegative element and consequently has the largest negative $V_1$ term. Our order of decreasing negative $V_1$ values (F > Cl > Br > O > S) corresponds closely with the list reported by Djerassi (F > O > Cl > Br > S).[1,2] The only difference is the transposition of oxygen. This transposition is mainly due to the hydrogen-bonding potential which has recently been incorporated into the MM2 force field.[15] Older MM2 versions, however, essentially match the order of electronegativity. The $V_1$ term in parentheses in Table III should be used for the programs without the hydrogen-bonding function.

For fluorine, we had to match the experimentally observed axial/equatorial ratio (see Tables VI and IX) of 3-fluoro-2,2-dimethylcyclohexanone. We used a dielectric constant of 4.81 in order to simulate the $CDCl_3$ solution conditions. Since we were adjusting the 3-1-1-11 ($C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–F) torsion potential to match NMR data, we also wanted some independent calculation or experiment to confirm our V1 selection. An ab initio calculation at the STO-3G level had indicated that axial 3-fluorocyclohexanone would be present to the extent of 41%. We also did full geometry optimized STO-3G and 6-31G* (for selected conformers) calculations on 4-fluoro-2-butanone (3) and found the energy difference between the gauche and trans (see Figure 2) conformations to be 0.35 and 0.90 kcal/mol, respectively (Table IV). Using the new $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–F torsional parameter, we calculated this difference of 0.47 kcal/mol. When the dielectric constant was increased from 1.500 to 4.81, reflecting the change from gas phase to solution conditions, we observed a reversal of the relative energies. Solution conditions shifted the equilibrium so as to stabilize the gauche conformation relative to the trans by 0.27 kcal/mol. This is certainly reasonable for the C–F and C–O dipole reinforce each other more intensely in the gauche arrangement and are solvated more effectively, resulting in the energy change. (The calculations on 3 were an independent check for the generality of our selection of the $V_1$ term.)

**Table IV. Ab Initio and Molecular Mechanics Energies for 4-Fluoro-2-butanone**

| conformatn[a] | STO-3G energies, hartrees | rel energies, kcal/mol | % (25 °C) |
|---|---|---|---|
| 0 | -325.554495751 | 5.30 | |
| 60[b] | -325.562451447 | 0.35 | 52 |
| 120 | -325.560385425 | 1.65 | |
| 180 | -325.563010107 | 0.00 | 48 |

Molecular Mechanics Results

| conformatn | final steric energies, kcal/mol | rel energy, kcal/mol | % (25 °C) |
|---|---|---|---|
| 0 | 7.5417[c] | 6.53 | |
| 60[b] | 1.4725[c] | 0.47 | 48 |
| 120 | 4.7445[c] | 3.74 | |
| 180 | 1.0071[c] | 0.00 | 52 |
| 0 | 5.3647[d] | 4.98 | |
| 60[b] | 0.3833[d] | 0.00 | 56 |
| 120 | 4.2577[d] | 3.97 | |
| 180 | 0.6484[d] | 0.27 | 44 |

[a] Molecular geometries were fully optimized with GAUSSIAN 80. [b] Dihedral angle was optimized to 68.5° with ab initio results and 65.5° with MM2. This conformation is double degenerate. [c] Gas-phase dielectric constant of 1.500 (MM2 default value). [d] Dielectric constant of 4.81 was used for $CDCl_3$ solution.

**Table V. Ab Initio Energies for 3-Hydroxycyclohexanol**

| basis set | conformatn | | energies, hartrees | rel energy, kcal/mol | % (25 °C) |
|---|---|---|---|---|---|
| STO-3G | AX | CON I | -377.948642562 | 0.19 | 16.3 |
| | | CON II | -377.948948091 | 0.00 | 22.4 |
| | | CON III | -377.946229733 | 1.71 | 1.3 |
| STO-3G | EQ | CON I | -377.948947843 | 0.00 | 22.4 |
| | | CON II | -377.948755453 | 0.12 | 18.3 |
| | | CON III | -377.949095824 | 0.09 | 19.3 |
| STO-4G | AX | CON I | -380.662255625 | 0.30 | 14.4 |
| | | CON II | -380.662607661 | 0.08 | 20.8 |
| | | CON III | -380.660066635 | 1.67 | 1.4 |
| STO 4G | EQ | CON I | -380.662561497 | 0.10 | 20.1 |
| | | CON II | -380.662531680 | 0.12 | 19.5 |
| | | CON III | -380.662727313 | 0.00 | 23.8 |
| 4-31G | AX | CON I | -382.187378936 | 0.78 | 13.6 |
| | | CON II | -382.188635025 | 0.00 | 50.7 |
| | | CON III | -382.185093596 | 2.22 | 1.2 |
| 4-31G | EQ | CON I | -382.187390591 | 0.78 | 13.6 |
| | | CON II | -382.186135075 | 1.57 | 3.6 |
| | | CON III | -382.187599591 | 0.64 | 17.2 |
| 6-31G | AX | CON I | -382.582274363 | 0.79 | 12.9 |
| | | CON II | -382.583538539 | 0.00 | 49.1 |
| | | CON III | -382.579712337 | 2.40 | 0.9 |
| 6-31G | EQ | CON I | -382.582416814 | 0.70 | 15.1 |
| | | CON II | -382.580986902 | 1.60 | 3.3 |
| | | CON III | -382.582624161 | 0.57 | 18.8 |

The cases of 3-hydroxycyclohexanone and 3-hydroxy-2,2-dimethylcyclohexanone are interesting. We had to consider six possible rotamers. The axial and equatorial conformations each have three possible O–H orientations (see Figure 3). In order to fit the observed NMR equi-

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(14) All ab initio calculations were performed with Pople's GAUSSIAN 80 and GAUSSIAN 82 programs. GAUSSIAN 80 is available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, Indiana 47405. GAUSSIAN 82 can be obtained directly from Professor J. A. Pople, Department of Chemistry, 4400 Fifth Avenue, Carnegie-Mellon University, Pittsburgh, PA 15213.

(15) The development of the hydrogen-bonding potential will be the subject of future papers. This potential is not included in the 1982 and earlier versions of the program. Table III lists the H-bonding parameters which may be read into the older MM2 programs.

**Table VI. Molecular Mechanics Energies for 3-X-2,2-Dimethylcyclohexanone**

| X | conformatn | | final steric energy[a] | rel energy[a] | % (25 °C) |
|---|---|---|---|---|---|
| fluoro | AX | | 10.2007$^{b}$ | 0.00 | 70.6 |
| | EQ | | 10.7204$^{b}$ | 0.52$^{b}$ | 29.4 |
| chloro | AX | | 11.7956$^{b}$ | 0.54$^{b}$ | 28.7 |
| | EQ | | 11.2589$^{b}$ | 0.00$^{b}$ | 71.3 |
| bromo | AX | | 12.6103$^{b}$ | 0.93$^{b}$ | 17.2 |
| | EQ | | 11.6794$^{b}$ | 0.00$^{b}$ | 82.8 |
| ethylthio | AX | CON I | 14.5377$^{b}$ | 0.84$^{b}$ | 12.7 |
| | | CON II | 15.0420$^{b}$ | 1.35$^{b}$ | 5.4 |
| | | CON III | 17.7384$^{b}$ | 4.04$^{b}$ | <0.1 |
| | EQ | CON I | 13.6946$^{b}$ | 0.00$^{b}$ | 52.6 |
| | | CON II | 15.0549$^{b}$ | 1.36$^{b}$ | 5.3 |
| | | CON III | 14.1600$^{b}$ | 0.47$^{b}$ | 24.0 |
| hydroxy | AX | CON I | 11.3515 (11.3517)$^{b,c}$ | 0.27 (0.02)$^{b,c}$ | 15.1 (25.1)$^{c}$ |
| | | CON II | 11.0838 (11.3269)$^{b,c}$ | 0.00 (0.00)$^{b,c}$ | 23.7 (26.1)$^{c}$ |
| | | CON III | 11.2780 (12.2977)$^{b,c}$ | 0.19 (0.97)$^{b,c}$ | 17.1 (5.1)$^{c}$ |
| | EQ | CON I | 11.1606 (11.3951)$^{b,c}$ | 0.08 (0.07)$^{b,c}$ | 20.8 (23.3)$^{c}$ |
| | | CON II | 11.9641 (12.3155)$^{b,c}$ | 0.88 (0.99)$^{b,c}$ | 5.4 (4.9)$^{c}$ |
| | | CON III | 11.2487 (11.6383)$^{b,c}$ | 0.16 (0.31)$^{b,c}$ | 17.9 (15.5)$^{c}$ |
| methyl | AX | | 12.8299$^{b}$ | 0.85$^{b}$ | 19.2 |
| | EQ | | 11.9791$^{b}$ | 0.00$^{b}$ | 80.8 |
| | | | In the Gas Phase | | |
| fluoro | AX | | 11.4794$^{d}$ | 0.00$^{d}$ | 69.6 |
| | EQ | | 11.9645$^{d}$ | 0.49$^{d}$ | 30.4 |
| chloro | AX | | 13.1910$^{d}$ | 0.77$^{d}$ | 21.4 |
| | EQ | | 12.4162$^{d}$ | 0.00$^{d}$ | 78.6 |
| bromo | AX | | 13.8864$^{d}$ | 1.19$^{d}$ | 11.9 |
| | EQ | | 12.6948$^{d}$ | 0.00$^{d}$ | 88.1 |
| ethylthio | AX | CON I | 15.2065$^{d}$ | 1.02$^{d}$ | 9.9 |
| | | CON II | 15.6751$^{d}$ | 1.49$^{d}$ | 4.5 |
| | | CON III | 18.3049$^{d}$ | 4.12$^{d}$ | <0.1 |
| | EQ | CON I | 14.1898$^{d}$ | 0.00$^{d}$ | 54.7 |
| | | CON II | 15.6723$^{d}$ | 1.48$^{d}$ | 4.5 |
| | | CON III | 14.6225$^{d}$ | 0.43$^{d}$ | 26.4 |
| hydroxy | AX | CON I | 11.6297 (11.6157)$^{c,d}$ | 0.39 (0.15)$^{c,d}$ | 14.8 (23.8)$^{c}$ |
| | | CON II | 11.2432 (11.4666)$^{c,d}$ | 0.00 (0.00)$^{c,d}$ | 28.5 (30.6)$^{c}$ |
| | | CON III | 11.7571 (12.9899)$^{c,d}$ | 0.51 (1.52)$^{c,d}$ | 12.0 (2.3)$^{c}$ |
| | EQ | CON I | 11.3699 (11.5951)$^{c,d}$ | 0.13 (0.13)$^{c,d}$ | 23.0 (24.6)$^{c}$ |
| | | CON II | 12.5507 (12.8782)$^{c,d}$ | 1.31 (1.41)$^{c,d}$ | 3.1 (2.8)$^{c}$ |
| | | CON III | 11.4947 (11.8554)$^{c,d}$ | 0.25 (0.39)$^{c,d}$ | 18.6 (15.9)$^{c}$ |
| methyl | AX | | 12.8299$^{d}$ | 0.85$^{d}$ | 19.2 |
| | EQ | | 11.9791$^{d}$ | 0.00$^{d}$ | 80.8 |

[a] Energies are in kcal/mol. [b] With a dielectric constant of 4.81. [c] MM2 force field without hydrogen-bonding potential. [d] With a dielectric constant of 1.500 (MM2 default value).

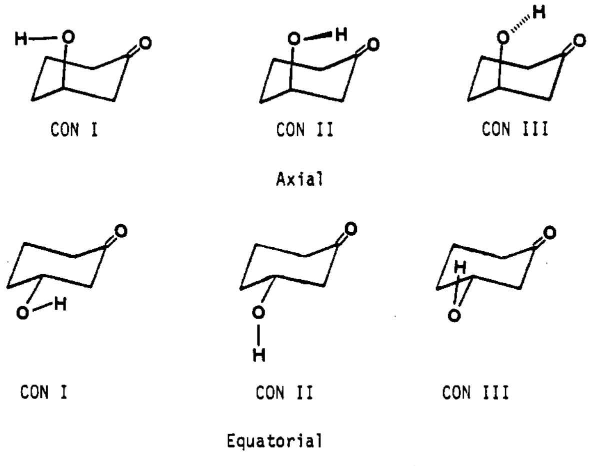

**Figure 3.** Six conformations had to be considered for 3-hydroxycyclohexanone.

librium data, we adjusted the $V_1$ torsional term for atom types 3–1–1–6 ($C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–O). With $V_1$ set equal to −0.140, we calculated the axial conformer to be the most abundant (56%).[16] See Tables VI and VII.[17]

Ab initio calculations on the parent compound 3-hydroxycyclohexanone indicate that the axial conformation varies from approximately 40% to 60% at the STO-3G to 6-31G levels, respectively (see Table V). STO-4G calculations have been reported to be more reliable than STO-3G for treating hydrogen bonding.[18] We found only slight differences using this basis set. Nevertheless, the energy difference between 40% and 60% corresponds to a free-energy differences of ca. 0.2 kcal/mol. We calculate with MM2, using a gas-phase dielectric constant of 1.500, 56% of the axial conformation. Changing the dielectric constant to 4.81 reduces the axial conformation negligibly, to 51%. Our ab initio and molecular mechanics calculations agree well with the NMR data.

One point, however, concerning the current hydrogen-bonding function deserves critical comment (see Table VIII). For the case of axial CONIII, we see a decrease in its relative energy with the incorporation of the hydrogen-bonding potential we are using in MM2.[15] Clearly this represents an overestimation of hydrogen bonding for situations, represented by axial CONIII, where the hy-

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(16) When several conformations of a single compound have similar steric energies, a Boltzmann calculation should be carried out to determine the mole fractions of each conformer present in an equilibrium mixture.

(17) We have been unable to ascertain the origin of the 56% Djerassi reported in footnote 50 of ref 1. MM2 without the appropriate $V_1$ adjustment gives an axial population of approximately 40% at room temperature.

(18) Del Bene, J.; Pople, J. A. *J. Chem. Phys.* 1970, *52*, 4858.

**Table VII. Molecular Mechanics Energies for 3-X-Cyclohexanone**

| X | conformatn | | final steric energy$^{a}$ | rel energy$^{a}$ | % (25 °C) |
|---|---|---|---|---|---|
| fluoro | AX | | 5.9733$^{b}$ | 0.00$^{b}$ | 72.3 |
| | EQ | | 6.5417$^{b}$ | 0.57$^{b}$ | 27.3 |
| chloro | AX | | 6.7541$^{b}$ | 0.00$^{b}$ | 47.2 |
| | EQ | | 6.6875$^{b}$ | 0.07$^{b}$ | 52.8 |
| bromo | AX | | 7.1176$^{b}$ | 0.21$^{b}$ | 41.1 |
| | EQ | | 6.9045$^{b}$ | 0.00$^{b}$ | 58.9 |
| hydroxy | AX | CON I | 6.9896 (6.9414)$^{b,c}$ | 0.24 (0.12)$^{b,c}$ | 14.5 (22.0)$^{c}$ |
| | | CON II | 6.7519 (6.8176)$^{b,c}$ | 0.01 (0.00)$^{b,c}$ | 21.6 (27.1)$^{c}$ |
| | | CON III | 6.9952 (7.9063)$^{b,c}$ | 0.25 (1.09)$^{b,c}$ | 14.4 (4.3)$^{c}$ |
| | EQ | CON I | 6.7450 (6.9720)$^{b,c}$ | 0.00 (0.15)$^{b,c}$ | 21.9 (20.9)$^{c}$ |
| | | CON II | 7.5171 (7.7717)$^{b,c}$ | 0.77 (0.95)$^{b,c}$ | 6.0 (5.4)$^{c}$ |
| | | CON III | 6.7501 (6.9951)$^{b,c}$ | 0.01 (0.18)$^{b,c}$ | 21.7 (20.1)$^{c}$ |
| methyl | AX | | 7.4261$^{b}$ | 1.36$^{b}$ | 9.1 |
| | EQ | | 6.0634$^{b}$ | 0.00$^{b}$ | 90.9 |
| | | | In the Gas Phase | | |
| fluoro | AX | | 7.2147$^{d}$ | 0.00$^{d}$ | 72.0 |
| | EQ | | 7.7735$^{d}$ | 0.57$^{d}$ | 28.0 |
| chloro | AX | | 8.1240$^{d}$ | 0.28$^{d}$ | 38.4 |
| | EQ | | 7.8440$^{d}$ | 0.00$^{d}$ | 61.6 |
| bromo | AX | | 8.3734$^{d}$ | 0.45$^{d}$ | 31.9 |
| | EQ | | 7.9232$^{d}$ | 0.00$^{d}$ | 68.1 |
| hydroxy | AX | CON I | 7.2271 (7.1673)$^{c,d}$ | 0.34 (0.24)$^{c,d}$ | 14.9 (21.7)$^{c}$ |
| | | CON II | 6.8830 (6.9271)$^{c,d}$ | 0.00 (0.00)$^{c,d}$ | 26.5 (32.6)$^{c}$ |
| | | CON III | 7.4728 (8.6431)$^{c,d}$ | 0.59 (1.72)$^{c,d}$ | 9.8 (1.8)$^{c}$ |
| | EQ | CON I | 6.9528 (7.1720)$^{c,d}$ | 0.07 (0.24)$^{c,d}$ | 23.6 (21.6)$^{c}$ |
| | | CON II | 8.1216 (8.3631)$^{c,d}$ | 1.24 (1.44)$^{c,d}$ | 3.3 (2.9)$^{c}$ |
| | | CON III | 6.9975 (7.2330)$^{c,d}$ | 0.11 (0.31)$^{c,d}$ | 21.9 (19.94)$^{c}$ |
| methyl | AX | | 7.4261$^{d}$ | 1.36$^{d}$ | 9.1 |
| | EQ | | 6.0634$^{d}$ | 0.00$^{d}$ | 90.9 |

$^{a}$ Energies are in kcal/mol. $^{b}$ With a dielectric constant of 4.81. $^{c}$ MM2 force field without hydrogen-bonding potential. $^{d}$ With a dielectric constant of 1.500.

**Table VIII. Relative Energies for 3-Hydroxycyclohexanone**

| conformatn | | STO-3G | STO-4G | 4-31G | 6-31G | MM2$^{a}$ | MM2$^{b}$ |
|---|---|---|---|---|---|---|---|
| AX | CON 1 | 0.19 | 0.30 | 0.78 | 0.79 | 0.24 | 0.34 |
| | CON 2 | 0.00 | 0.08 | 0.00 | 0.00 | 0.00 | 0.00 |
| | CON 3 | 1.71 | 1.67 | 2.22 | 2.40 | 1.72 | 0.59 |
| EQ | CON 1 | 0.00 | 0.10 | 0.78 | 0.70 | 0.24 | 0.07 |
| | CON 2 | 0.12 | 0.12 | 1.57 | 1.60 | 1.44 | 1.24 |
| | CON 3 | 0.09 | 0.00 | 0.64 | 0.57 | 0.31 | 0.11 |

$^{a}$ No hydrogen bonding: atom pair, 7–21; EPS, 0.049; sum of *R*, 2.940. $^{b}$ H bonding: atom pair, 7–21; EPS, 2.95; sum of *R*, 2.10. Hydrogen, 21; EPS, 0.032; sum of *R*, 0.95.

**Table IX. Percentage of Axial Substituents for 2,2-Dimethyl-3-X-cyclohexanone at 25 °C**

| X | exptl (NMR)$^{a}$ | MM2$^{b}$ | MM2$^{c}$ |
|---|---|---|---|
| OH | 55 | 56 | 55 |
| $OCH_3$ | 51 | | |
| F | 73 | 71 | 70 |
| Cl | 29 | 29 | 21 |
| Br | 17 | 17 | 12 |
| SEt | 17 | 18 | 14 |
| $CH_3$ | 18 | 19 | 19 |

$^{a}$ Measurements were taken in $CDCl_3$ (see ref 1). $^{b}$ Dielectric constant was taken to be 4.81 ($CDCl_3$). $^{c}$ Gas-phase effective dielectric constant (1.5) was used.

droxyl hydrogen is interior to a ring system.

## Conclusion

MM2 parameters for $\beta$-heteroatom-substituted cyclohexanones have been developed based on recent NMR studies.[1,2] Our ab initio calculations indicate that no significant contribution by structure **2** can explain the preferred axiality for these $\beta$-substituents. We, therefore, attributed this axial effect to through-bond orbital interactions and/or electrostatic interactions and adjusted the torsion $V_1$ term for $C_{sp^2}$–$C_{sp^3}$–$C_{sp^3}$–X to fit 3-heteroatom-substituted 2,2-dimethylcyclohexanone and our ab initio data.

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**Registry No.** $F(CH_2)_2C(O)CH_3$, 461-48-3; 3-hydroxycyclohexanol, 504-01-8; 3-chlorocyclohexanone, 21299-27-4; 3-fluoro-2,2-dimethylcyclohexanone, 107408-96-8; 3-chloro-2,2-dimethylcyclohexanone, 107408-97-9; 3-bromo-2,2-dimethylcyclohexanone, 107408-98-0; 3-(ethylthio)-2,2-dimethylcyclohexanone, 107408-99-1; 3-hydroxy-2,2-dimethylcyclohexanone, 61447-86-7; 2,2,3-trimethylcyclohexanone, 39257-08-4; 3-fluorocyclohexanone, 107409-00-7; 3-bromocyclohexanone, 62784-60-5; 3-hydroxycyclohexanone, 823-19-8; 3-methylcyclohexanone, 591-24-2; 3-methoxy-2,2-dimethylcyclohexanone, 17429-00-4; 3-acetoxycyclohexanone, 53164-77-5.