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Empirical Relationship between the Conformation and the Direction of Carbonyl Group Pyramidalization of Cyclohexanones

Thomas Laube*

Loker Hydrocarbon Research Institute, University of Southern California, University Park,
Los Angeles, California 90089-1661

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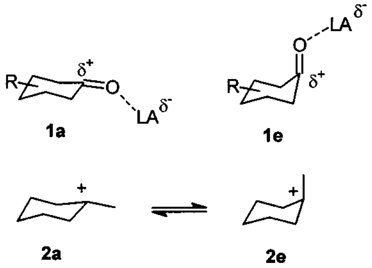
A statistical investigation of precise crystal structures from the Cambridge Structural Database shows that cyclohexanones have a predictable pyramidalization of the carbonyl group in the chair conformation that depends on the puckering of the ring. Flattened cyclohexanones are usually "axially pyramidalized" (see Figure 1), whereas more strongly puckered cyclohexanones are usually "equatorially pyramidalized". It is conceivable that a cooperation between electronic effects (hyperconjugation) and steric effects (relief from torsional strain) leads to this unique correlation. No such conformation/pyramidalization correlations are observed for other ketones.

Introduction

Nucleophilic addition to carbonyl groups is one of the most important reactions for the formation of C−C bonds in organic molecules. The conversion of the sp^2 carbonyl C atom into an sp^3 atom leads in many cases to a stereogenic center and thus to the formation of diastereomers if at least one other stereogenic center is present in the product molecule. Therefore the carbonyl face selection, i.e., the stereochemical control of such reactions, is of fundamental importance to organic chemistry. For more than 30 years, Felkin,[1] Anh,[2] Klein,[3] Houk,[4] Cieplak,[5] le Noble,[6] Ashby,[7a,b] and many others[7c−k] have made important contributions to the current understanding of this problem. The most intensively investigated carbonyl compounds are probably cyclohexanones because of the complicated interaction of steric and electronic effects controlling the outcome of the reactions.[1b,3,4c,d,5,6,7e,f]

Scheme 1



It is known that nominally sp^2 centers are not always planar,[8] and the slight deviations of ligands of carbonyl C atoms from planarity in the presence of suitably arranged nucleophiles in crystals have been interpreted in terms of a beginning nucleophilic attack.[9] It has been suggested that a deviation of a sp^2 center from planarity may generally indicate the preferred direction of the approach of a reaction partner,[4a,10] but there are also reports about cases where this generalization is not valid.[11]

We observed several years ago that three activated cyclohexanones have slightly pyramidal carbonyl C atoms (Scheme 1, conformations **1a** or **1e**, LA = Lewis acid).[12] While we do not have an indication that there may be an equilibrium between **1a** and **1e** in solution, there is a remarkable electronic similarity between the carbocation-like activated cyclohexanones and the 1-methyl-1-cyclohexyl cation,[13] which does exist according to NMR

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* Visiting scientist at USC. Current address: Cilag AG, Hochstrasse 201, CH-8205 Schaffhausen, Switzerland.

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measurements in solution as a pair of rapidly equilibrating chair conformers **2a** and **2e**.[13b] The crystal structure of the 2-phenyl-2-adamantyl cation simultaneously contains fragments with the structures of **2a** and **2e** and shows that hyperconjugation can explain the occurrence of such conformers (see discussion).[14]

It would be of broad interest for synthetic organic chemists to know in which cases ketones have a carbonyl pyramidalization predictable from the conformation[15] and independent from the proximity of a nucleophile,[9] because such information can be useful for the prediction of the preferred direction of nucleophilic attack. It would be of broad interest for physical organic chemists to know when fundamental rules such as the planarity of sp^2 C atoms in ground states[16] are systematically violated. The present paper reports our results of statistical analyses of precise crystal structures from the Cambridge Structural Database (CSD),[17] which is currently the only method yielding generally valid answers to such questions based on experimental data.

Results

For a better comparison of the fragment containing the sp^2 C atom, a unique numbering scheme for **A** to **E** has been selected, see Figure 1. We use the terms axial and equatorial pyramidalization as previously described,[12] i.e., the pyramidalization Δ_{C3} is the (signed) distance of C3 from the plane $P_{(C2,C4,X)}$ defined by C2, C4, and X, and the distances d_{C1} and d_{C5} refer to the same plane.

If one assumes that Δ_{C3} is primarily influenced by its direct intramolecular environment, it is reasonable to plot Δ_{C3} depending on the torsion angles around the bonds C3−C2 (τ_{4321}) and C3−C4 (τ_{2345}). The results for **B** and **E** are shown in Figure 2. For **B** one observes a clustering of points in the left part of the diagrams around the function $\tau_{2345} = -\tau_{4321}$ (chair and some boat conformations). Very remarkable is the fact that the cluster can be separated into two subclusters with axial and equatorial pyramidalizations (red and green markers, respectively). This classification is supported by the thick solid contour lines in Figure 2c1. The axially pyramidalized cyclohexanones have absolute τ values of around 47°, and the equatorially pyramidalized ones are around 55°. Cyclohexanones with twist or twist-boat conformations are scattered over the right parts of the diagrams (blue octagons). Methylenecyclohexanes (**E**) preferentially show equatorial pyramidalizations in the chair conformations, but there are not so many data as for cyclohexanones (**B**). From the currently available data, it cannot be judged whether there are significant differences in the point distributions in the τ_{4321} /τ_{2345} diagrams between **B** and **E**.

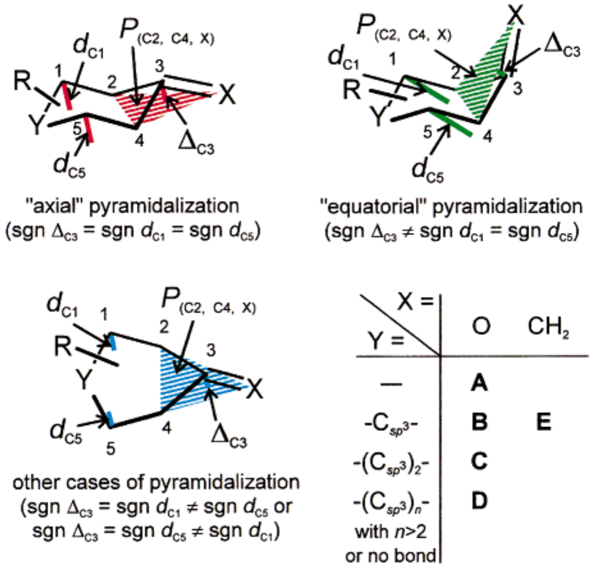

Figure 1. Definition of the geometrical parameters (R = any substituent).

We have also investigated cyclopentanones (**A**), cycloheptanones (**C**), and cycloalkanones with more than seven ring atoms and acyclic ketones (**D**). In none of these cases could comparably resolved clusters for the axially and equatorially pyramidalized systems be detected in the corresponding τ_{4321} /τ_{2345} diagrams, i.e., a correlation between the conformation around a carbonyl group and the direction of its pyramidalization is observed only for cyclohexanones and, to a lesser amount, for methylenecyclohexanes.

A disadvantage of the τ_{4321}/τ_{2345} diagrams is that they have only two independent variables, whereas six-membered rings have three conformational degrees of freedom. We have therefore also plotted all cyclohexanone data in a three-dimensional Cremer−Pople[18] puckering parameter space, see Figure 3. A densely populated cluster[19] lies on the positive z axis, which is magnified in the lower diagram in Figure 3. This cluster corresponds to chair conformers and shows an even better separation into axially and equatorially pyramidalized cyclohexanones than in Figure 2. A comparison with the Cremer−Pople parameters of model compounds shows that the elongated cluster describes conformations with various degrees of flattening of the C1−C2−C3−C4−C5 part of the ring. As in Figure 2, the axially pyramidalized cyclohexanones have smaller absolute values of τ_{4321} and τ_{2345}, and the equatorially pyramidalized cyclohexanones have larger ones.

Discussion

It is not straightforward to explain the origin of the conformation/pyramidalization correlation in cyclohex-

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[14] Laube, T.; Hollenstein, S. *Helv. Chim. Acta* **1994**, *77*, 1773−1780.

[15] The ground state conformation(s) can usually be predicted by computational methods with little effort (molecular mechanics, molecular dynamics). The term "conformation" refers in the present paper to the ring atoms only.

[16] Precise gas-phase structures of simple ketones have been determined by various methods. Cyclopentanone: Kim, H.; Gwinn, W. D. *J. Chem. Phys.* **1969**, *51*, 1815−1819. Cyclohexanone: Alonso, J. L. *J. Mol. Struct.* **1981**, *73*, 63−69. Dillen, J.; Geise, H. J. *J. Mol. Struct.* **1980**, *69*, 137−144. Cycloheptanone: Dillen, J.; Geise, H. J. *J. Mol. Struct.* **1981**, *72*, 247−255. 3-Pentanone: Crowder, G. A., Lin, Q. *Vib. Spectrosc.* **1997**, *14*, 287−297. Kuze, N.; Kojima, E.; Fujiwara, H.; Takeuchi, H.; Egawa, T.; Konaka, S. *J. Mol. Struct.* **1996**, *375*, 231−241. In all of these cases, carbonyl planarity is assumed. For carbonyl pyramidalization in electronically excited states see, e.g.: van der Burgt, M. J.; Huizer, A. H.; Varma, C. A. G. O.; Wagner, B. D.; Lusztyk, J. *Chem. Phys.* **1995**, *196*, 193−210. Laane, J.; Zhang, J.; Chiang, W.-Y.; Sagear, P.; Cheatham, C. M. In *Structure and Dynamics of Non-Rigid Molecular Systems*; Smeyers, Y. G., Ed.; Kluwer: Dordrecht, 1995; pp 181−201.

[17] Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187−204.

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[19] The small cluster of strongly pyramidalized molecules on the negative x axis close to the direction (90°, 180°) on the equator (upper diagram in Figure 3) corresponds to boat conformations (C=O in bow position) with short Nu⋯C=O contacts[9] (Nu = nucleophile).

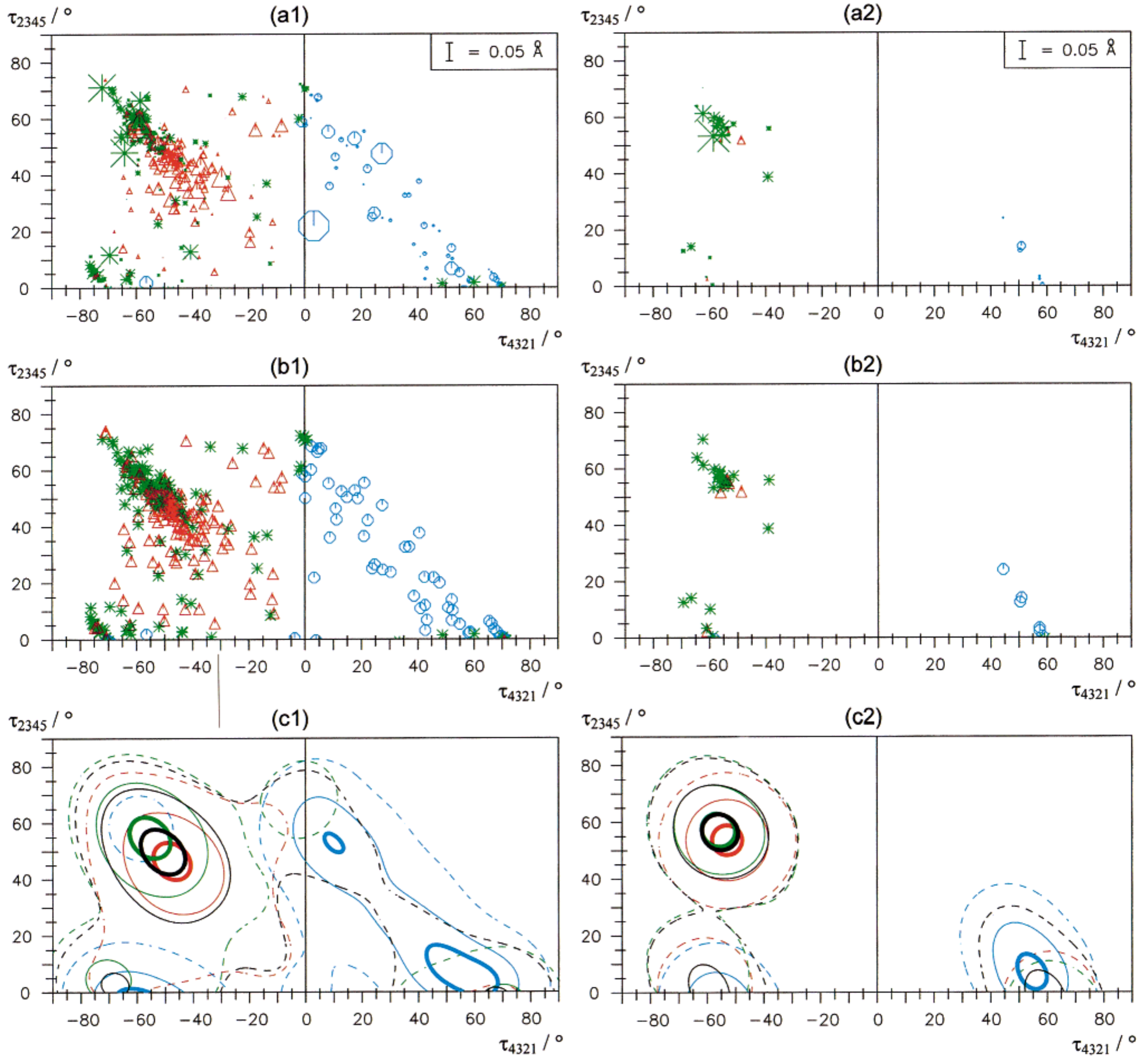

Figure 2. Scatterplots of the pyramidalization Δ_{C3} of cyclohexanones (**B**, left) and of methylenecyclohexanes (**E**, right) depending on the torsion angles τ_{4321} and τ_{2345}. The absolute configuration is ignored, i.e., all data points are also plotted at $(-\tau_{4321}, -\tau_{2345})$. Orientation of the pyramidalization: axial = red triangle; equatorial = green star; other = light blue octagon. Top: marker heights proportional to $|\Delta_{C3}|$; a scale is given in the inset. Middle: marker heights constant. Bottom: contour lines of empirical continuous probability density functions derived from the point distributions; the colors correspond to the types of pyramidalization. The black contour lines refer to all points without classification according to the pyramidalization. The contour lines enclose the following probabilities: thick solid = 0.10, thin solid = 0.50, dashed = 0.90.

anones. There are at least two possibilities: an electronic explanation involving, for example, hyperconjugation and a steric explanation involving the equatorial substituents at C2 and C4. Hyperconjugation, i.e., the interaction between an empty p orbital (e.g., on carbon) with suitably aligned σ orbitals (e.g., C−C, C−H etc.) occurs primarily in carbocations.[20] A good reference molecule is the 2-phenyl-2-adamantyl cation (**3**, see Figure 4). It contains the cyclohexyl cation fragment twice, but with different conformation. One is axially pyramidalized (**3a**), and the other equatorially (**3e**). Carbon−carbon hyperconjugation occurs only on one side of the slightly pyramidal cationic C atom. The strongest case of C−C hyperconjugation has so far been observed in the 1-adamantyl cation **5**, which contains a constrained equatorially pyramidalized cyclohexyl cation three times. Examples for weaker C−C or C−H hyperconjugation are found in the iminium ion **4** or the activated ketones **6** and **7**. In all of structures **3**−**7**,

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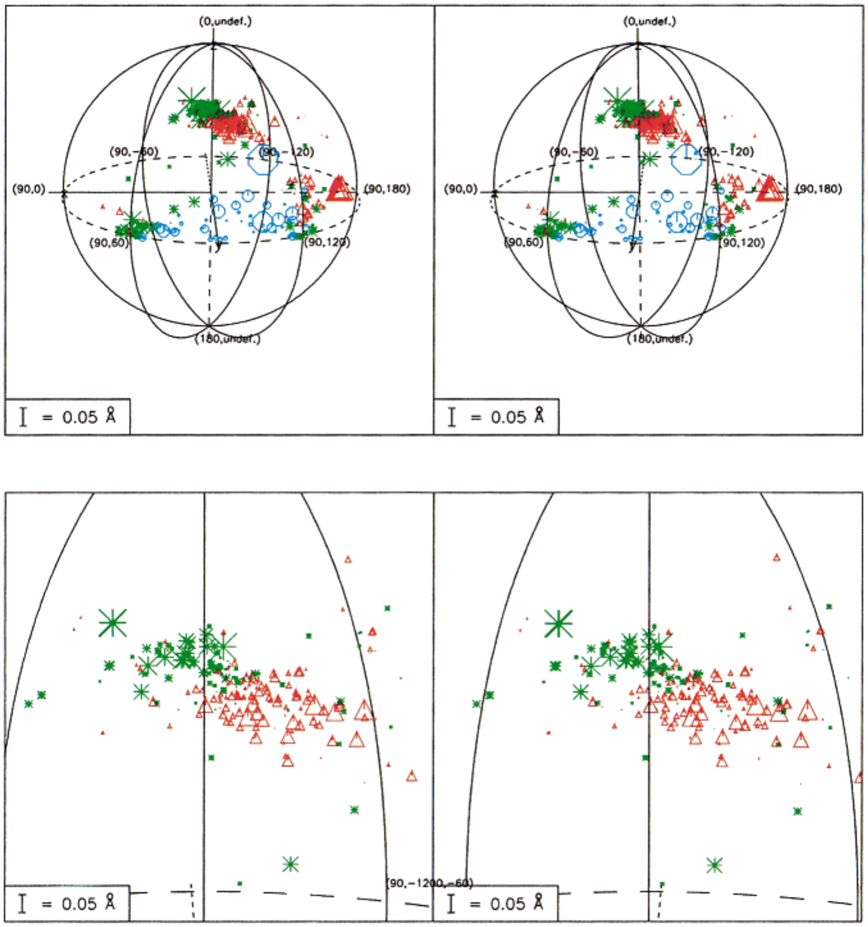

Figure 3. Stereo scatterplot of the Cremer−Pople puckering parameters Q, θ, and φ of cyclohexanones (**B**). The radius of all arcs is $Q = 1$ Å, and some points on the surface are marked by (θ, φ) in degrees (undef. = undefined; equator dashed). The axes of the corresponding Cartesian coordinate system are marked by x, y, and z (negative axes dashed). Orientation of the pyramidalization: axial = red triangle; equatorial = green star; other = light blue octagon. The marker heights are proportional to $|\Delta_{C3}|$; a scale is given in the inset. All data have been transformed into the quadrant with $y \geq 0$, $z \geq 0$. Top: whole unit sphere; bottom: magnification of the cluster on the z axis, seen in the direction of the negative y axis.

the smaller empty orbital lobe of C3 shows an overlap with the filled σ orbitals, whereas the larger lobe is often oriented toward a potential nucleophile in the crystal (counterions in **3** and **5**, intramolecular double bond in **4** and **6**). We thus assume that the electronic effects derived from the structures of **3**−**7** are also to some degree operative in cyclohexanones, i.e., hyperconjugation between the unoccupied $\pi_{C=O}$* orbital and the filled σ_{C2-C1} and σ_{C4-C5} orbitals favors the more puckered conformer with equatorially pyramidalized C3 (Figure 5, **8e**), and the interaction between the $\pi_{C=O}$* orbital and the filled $\sigma_{C2-Z(ax)}$ and $\sigma_{C4-Z'(ax)}$ orbitals favors the more flattened conformer with axially pyramidalized C3 (**8a**). This interpretation agrees with the interpretation of **3**−**7** and the 1-methyl-1-cyclohexyl cation,[13b,c] but unactivated ketones are not as electron-deficient as carbocations. A steric explanation could involve a simple steric repulsion[4b] between the carbonyl oxygen and large equatorial substituents at C2 and C4 (**9a** or **9e**), leading to partial staggering around the C3−C2 and C3−C4 bonds. Both effects can be simultaneously operative, and together with the nearly ideal alignment of filled σ orbitals in six-membered rings, this could explain why the conformation/pyramidalization relationship is observed with the currently available data in cyclohexanones only.[23] Other effects on the conformation of a molecule (electrostatic, dipole interactions, nonbonding contacts) are of course also operative in ketones, but no selection with regard to these effects or the substituents has been carried out in this work. This means that from the conformation of a cyclohexanone (determined by crystal structure analysis or computation[15]) one can derive the direction of the pyramidalization with some confidence (see Figures 2 and 3), independent from the substituents that have caused a particular conformation.

Finally, one can predict the preferred direction of a nucleophilic attack with some confidence from the direction of the pyramidalization of C3. This has been mentioned by Houk[4c] and many others.[10,24] The approach of a nucleophile toward a slightly pyramidal C atom from the side of the larger empty C orbital lobe agrees also with the principle of least motion,[25] i.e., the system chooses the shortest path on the reaction coordinate from a pyramidalized trigonal C atom in the educt to a

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[23] Additional Nu···C=O contacts may lead to particularly strong pyramidalizations.[9]

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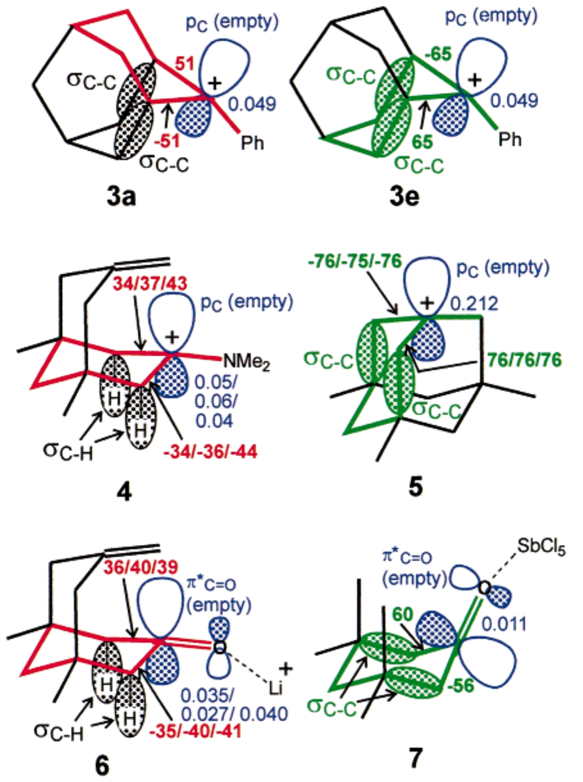

Figure 4. Ions and molecules whose experimentally determined structures contain cyclohexyl cation-like fragments (**3**,[14] **4**,[21] **5**,[22] **6**,[12] and **7**[12]). Six-membered rings with an axially pyramidalized center: red; six-membered rings with an equatorially pyramidalized center: green. Red or green integers: torsion angles τ_{4321} and τ_{2345} (deg) in the corresponding fragments (atom numbering according to Figure 1). Dark blue decimal numbers: absolute values of the pyramidalization $|\Delta_{C3}|$ (Å); independently determined values are separated by a slash. The empty orbital involved in the assumed hyperconjugation is shown in dark blue, and suitably aligned filled orbitals are shown in the color of the corresponding bond. Significant shortenings of the C2−C3 and C3−C4 bonds and elongations of the C1−C2 and C4−C5 bonds in **3** and **5** can be interpreted as the result of strong C−C hyperconjugation as indicated by the depicted orbitals. Corresponding bond length changes in **4**, **6**, and **7** are generally weaker as a result of the smaller electron deficiency, and C−H bond elongations can only be assumed because of the known problems of hydrogen position determination in X-ray crystal structure analysis.

tetrahedral C atom in the product. Experimental examples for a preferred nucleophilic attack on the side with the larger empty orbital lobe are **6**, which cannot be attacked from the equatorial side,[12] and **7**, which is preferentially attacked from the equatorial side.[26] The crystal structure of **3** shows that the two sides of the cationic center are very different,[27] and a nucleophilic attack seems to be possible only from the top side, i.e., on the larger empty orbital lobe. More examples are discussed in reference 10. Nevertheless there are also counterexamples for the correlation between pyramidalization and direction of nucleophilic attack.[11]

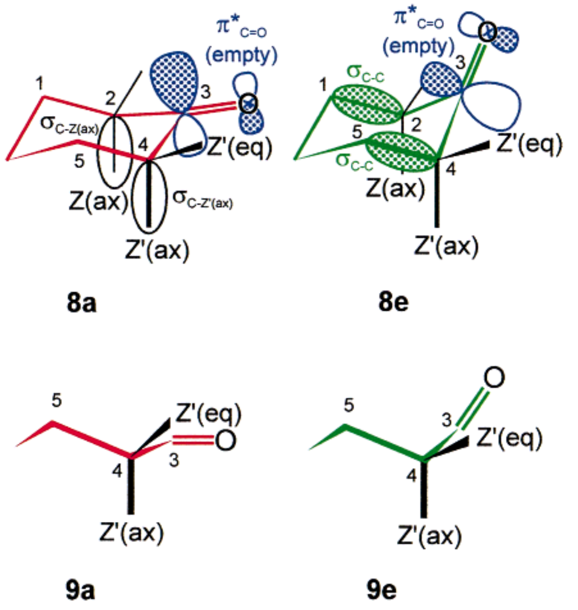

Figure 5. Interpretation via hyperconjugation (**8a**, **8e**) or steric repulsion (**9a**, **9e**). Z and Z′ are any substituents. For the color coding and the orbitals see the caption of Figure 4.

Conclusion

A unique relationship between chair conformations and the direction of carbonyl pyramidalizations of cyclohexanones was found, which is not observed for other types of ketones. If the absolute values of the torsion angles τ_{4321} and τ_{2345} are around 55° or greater, the carbonyl group is preferentially equatorially pyramidalized; if they are around 47° or less, the carbonyl group is preferentially axially pyramidalized. This information may help to predict the stereochemical course of nucleophilic additions to cyclohexanones, and it shows that the potential energy surfaces for cyclohexanones around the chair conformation are possibly more complicated than usually assumed due to carbonyl nonplanarity.

Computations

The crystal structures containing the fragments **A**−**E** were retrieved from the CSD[17] version 5.15 and analyzed with the programs PARST 88[28] (locally modified version), SYBYL 6.0,[29] and several FORTRAN programs developed by us. Figures 2 and 3 and our conclusions are based only on the most precise structures ($R \leq 0.05$, average $\sigma_{C-C} \leq 0.005$ Å). According to our experience, the esd's of carbon pyramidalizations ($\sigma_{\Delta C}$) are usually in the same range as those of C−C bond lengths (σ_{C-C}), i.e., $\sigma_{\Delta C3}$ is about $^{1}/_{10}$ or less of the bars in the insets in Figures 2 and 3. This means that a bar indicating the significance level ($3\sigma_{\Delta C3}$) would be less than one-third of the drawn bars. Out of the 353 points in Figures 2 (left) and 3, 151 have significant pyramidalizations, i.e., $|\Delta_{C3}| \geq 0.015$ Å $\approx 3\sigma_{\Delta C3}$. We have repeated all searches with not so good structures ($R \leq 0.07$, average $\sigma_{C-C} \leq 0.01$ Å, excluding the structures with $R \leq 0.05$,

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(28) Nardelli, M. *PARST 88*, Release April 1988. Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.

(29) SYBYL Version 6.0 for Sun Computers, November 1992, Tripos Associates, Inc., St. Louis, MO 63144-2913.

average $\sigma_{C-C} \leq 0.005$ Å), and practically the same results were found in all cases (see Supporting Information).

The empirical probability density functions contoured in Figure 2c1 and 2c2 were derived from the point distributions by summing up simple Gaussian functions of the type $\exp(-f_1((x - x_i)^2 + (y - y_i)^2))$ over all structures, where x and y correspond to the torsion angles, and each structure is represented by a point (x_i, y_i). The optimal factor $f_1 = 0.005$ deg^{-2} has been arbitrarily chosen after a visual comparison of series of plots with various values of f_1; see Supporting Information.

Molecular dynamics calculations[29] have been carried out for cyclopentanone, cyclohexanone, cycloheptanone, and 3-pentanone to ensure that the conformation distributions observed in the crystal structures with the fragments **A**−**D** are comparable to those computed for the parent compounds at higher temperatures.

Acknowledgment. The author thanks Prof. George A. Olah for support and the ETH (Zurich, Switzerland) for access to the CSD.

Supporting Information Available: General remarks about the computations; listings of the input files for the CSD programs; tables of the torsion angles (**A**−**E**) and of the Cremer−Pople parameters (**B**,**E**); source code of the FORTRAN programs used in this paper; discussion of location of conformations and symmetry elements in the puckering parameter space; additional diagrams of CSD data and of molecular dynamics calculations (PDF). Lists of the references and fragments (ASCII). This information is available free of charge via the Internet at http://pubs.acs.org.

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