

# A Semiempirical Study of the Effect of Geometry and Methyl Substituents on the Stabilities of Protonated Cyclopropylcarbinyl Ketones: Resolution of the 7-Nortricyclanone Anomaly

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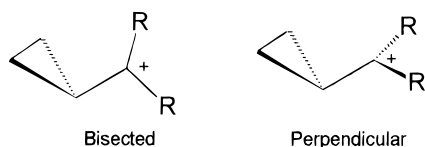
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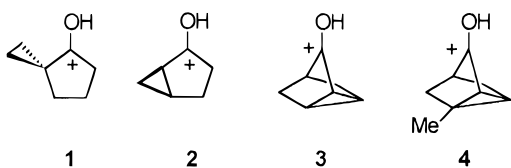
A long-standing anomaly regarding the difference in stabilities of a series of protonated cyclopropylcarbinyl ketones has been resolved. The enthalpies of protonation of the ketones to the oxocarbenium ions ( $\Delta H_f^\ddagger$ ) were calculated from the PM3 heats of formation of the ketones and ions using isodesmic cycles. The values of  $\Delta H_f^\ddagger$  correlate well with the experimentally determined values of  $pK_{R^+}$  for the ketones in concentrated sulfuric acid. Methyl substitution on the cyclopropyl ring uniformly stabilizes the resulting ions. Orientation of the  $-\text{OH}^+$  to the cyclopropyl affects stability as well: a *syn* (periplanar) orientation lowers stability, while an *anti* (antiperiplanar) orientation increases it, apparently because of charge repulsion between the protonated carbonyl and the partial positive charges on the ring carbons caused by carbinyl "resonance" stabilization. Decreasing the angle about the carbonyl carbon leads to a decrease in stability for all systems tested and appears to be a major source of destabilization of the nortricyclic system relative to skeletal analogs with more open carbonyl bond angles. The more stable ions have  $\pi$  HOMOs, while the nortricyclic and related ions have  $\sigma$  HOMOs, which is another source of destabilization of the nortricyclic system. For comparison, the corresponding hydrocarbon carbenium ions were examined; similar orders of stability were identified.

## Introduction

In 1963, Richey et al.<sup>1–4</sup> provided the first incontrovertible evidence that the bisected form of cyclopropylcarbinyl carbenium ions was the most stable conformation. This conclusion was based on the UV and <sup>1</sup>H NMR

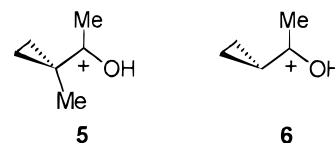


spectra<sup>1,2</sup> and  $pK_{R^+}$  values in sulfuric acid of the protonated rigid cyclopropylcarbinyl ketones **1–4**. While these



results were widely disseminated in reviews,<sup>3,4</sup> they were never published because of a glaring anomaly among the data. The spiro compound **1** was the most stable in the series by all criteria, but the nortricyclic compounds **3** and **4**, which have a bisected geometry, are less stable than the bicyclic compound **2** in which the cyclopropyl is

twisted out of the plane required to achieve a bisected geometry. It was assumed that this disparity was related to different alkyl substitutions on the cyclopropyl.<sup>4</sup> Nonetheless, the  $\alpha$  methyl compound **5** is more stable than **6**. **5** is a flexible analog of **1** and is more stable, suggesting that the rigidity of a ring system is in some way destabilizing.



The geometric requirements for stabilization of cyclopropylcarbinyl systems were resolved by Olah and Pittman<sup>5</sup> who found that the 2-cyclopropyl-2-propyl carbenium ion in magic acid had two methyl signals, consistent with the bisected but not the perpendicular geometry. Subsequent experimental work, discussed in detail by Richey,<sup>4</sup> confirmed this geometric requirement. Early semiempirical and low-level *ab initio* calculations reported by Schmitz and Sorensen<sup>6</sup> were consistent with the experimental results for the hydrocarbon carbenium ions. A recent high-level *ab initio* study by Saunders et al.<sup>7</sup> showed that the bisected form of the simple unsubstituted cyclopropylcarbinyl methyl carbenium ion was slightly more stable than the edge form and was isoenergetic with the bicyclobutonium ion. Finally, Childs and co-workers<sup>8</sup> recently reported crystal structures of  $\text{SbF}_6^-$  and  $\text{SbCl}_6^-$  salts of several protonated flexible cyclopropyl ketones, all of which had bisected geometries.

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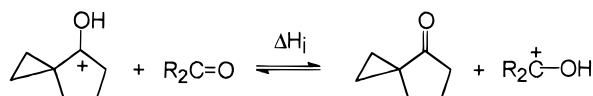
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Despite these experimental and computational successes, the question of stability in the original series of Richey et al.<sup>1–4</sup> has never been answered adequately. Recent work in other oxocarbenium ion systems<sup>9</sup> showed that semiempirical methods, in particular the PM3 Hamiltonian,<sup>9a</sup> faithfully reproduced experimental gas-phase<sup>9b</sup> and high-level *ab initio* relative energies.<sup>9c,d</sup> This success prompted the work reported here, the results of which provide a definitive answer regarding the relative stabilities of the cations in the Richey series.

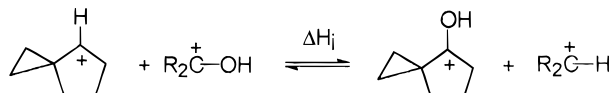
## Methods

**Computational Methods.** All structures were fully minimized in PM3<sup>10</sup> using the semiempirical package in the Hyperchem 4.0 software. Minimizations were restricted Hartree–Fock with the wavefunction calculated to a convergence limit of <0.001. The Polak–Ribiere block diagonal algorithm was used for all minimizations to a root mean square gradient of <0.1 kcal/(Å mol). Torsional and other angles, where appropriate, were constrained to a force constant of 10<sup>3</sup>–10<sup>5</sup>. Frontier orbitals were displayed using the ChemPlus option to Hyperchem.

**Isodesmic Cycles.** Enthalpies of ionization  $\Delta H_i$  (in kcal/mol) were calculated using PM3 enthalpies of formation ( $\Delta H_f$ ) in the isodesmic cycle keyed to the reaction of **1**  $\equiv$  0 kcal/mol.



In cases where constrained geometries were used, the cation and ketone used in the calculation have the same geometric constraints.<sup>11</sup>  $\Delta H_i$  for the hydrocarbon carbenium ions were calculated using the isodesmic cycle that anchors the energies to the rigid spiro system and provides a common reference point for comparison of the two series.



**Vibrational Analysis.** The force constant matrices for all compounds were calculated from second derivatives of the energy with respect to the Cartesian coordinates using finite differencing of the analytical gradients. No ion had an imaginary first normal mode, which establishes each structure as a minimum on the potential energy surface. All had a first normal mode in the range of 50–100 cm<sup>-1</sup>, which shows that the potential energy surface is relatively flat in the region of the minimum.

## Results and Discussion

The PM3  $\Delta H_i$  and the  $pK_{R+}$  values for **1–7** are summarized in Figure 1. All geometric and other factors

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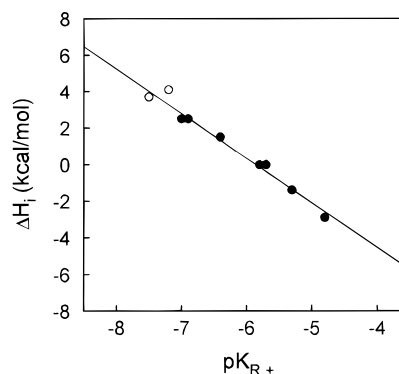
(11) Using the same geometry for the ketone and protonated ketone can have small effects on  $\Delta H_i$ . For instance, for **5–7**, use of the most stable ground state structure for the ketones gives  $\Delta H_i$  of -1.4, 0, and -3.0 kcal/mol, respectively, which differ by -1.8, -1.0, and -0.1 kcal/mol from the values obtained using a ground state structure with the same geometry. While the correlation with  $pK_{R+}$  is better with the former values (Figure 2,  $r = 0.992$ ), the latter values have only a small effect on the correlation with  $pK_{R+}$  ( $r = 0.970$ ).

	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
$pK_{R+}$	-5.8	-6.4	-6.9	-7.0
$\Delta H_i$	0	1.5	2.5	2.5

	<b>5</b>	<b>6</b>	<b>7</b>
$pK_{R+}$	-5.3	-5.7	-4.8
$\Delta H_i$	-1.4	0	-2.9

**Figure 1.** Values of  $pK_{R+}$  (ref 4) and the PM3  $\Delta H_i$  (kcal/mol, this study) for protonation of cyclopropylcarbonyl ketones.

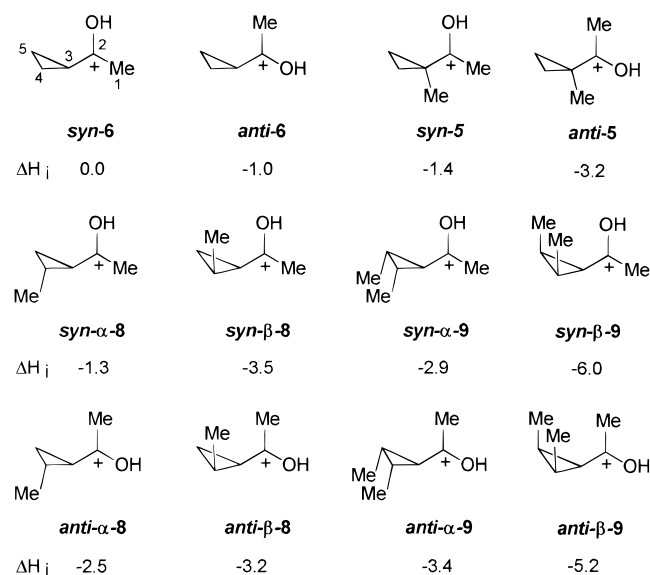


**Figure 2.** Plot of  $pK_{R+}$  vs the PM3  $\Delta H_i$  (kcal/mol) for the compounds in Figure 1 ( $r = 0.992$ ).  $\Delta H_i$  was calculated relative to the most stable ketone (see ref 11). The open symbols are for protonated cyclopentanone and acetone.

that affect stabilization of the protonated ketones are included in the values of  $\Delta H_i$  computed for each ground state ketone and oxocarbenium ion used in the isodesmic cycle. There is an excellent correlation of  $\Delta H_i$  with the measured<sup>4,12</sup>  $pK_{R+}$  (Figure 2) that shows the relative stabilities, whatever the source of their variation, are not anomalous in terms of the total energies of formation of the oxocarbenium ions. In the absence of other results, however, it is not readily apparent why the bisected nortricyclic oxocarbenium ions **3** and **4** are not as stable as or more stable than **2**. To examine this question, the effects of geometry and substitution of methyl groups on the cyclopropyl ring were examined in a series of flexible cyclopropyl methyl ketones (Figure 3).

**Geometry.** There are several geometric factors to consider in the protonated ketones. One is the stability of bisected and perpendicular forms, and the other is the orientations of the protonated carbonyl group. In the spiro compound **1**, the bisected and *syn* orientation of the protonated carbonyl group to the cyclopropyl are fixed, and this compound was used to anchor the energies in

(12) The values of  $pK_{R+}$  anchored to the  $H_R$  scale were determined by Dr. Jane Liu in aqueous sulfuric acid and are tabulated by Richey (ref. 4).



**Figure 3.** PM3  $\Delta H^\ddagger$  (kcal/mol) for protonated cyclopropylcarbinyl ketones with different geometries and levels of methyl substitution.

the isodesmic cycle calculations. The *anti* orientation of the protonated carbonyl group corresponds to the geometry of the nortricyclanone compounds **3** and **4**.

**(a) Bisected vs Perpendicular.** In all forms of the flexible protonated cyclopropyl methyl ketones, the bisected form is the most stable, including compounds such as *syn-β-9* and *anti-β-9* in which there is significant steric hindrance from Me–Me interactions. For instance, the unconstrained perpendicular form of **6** minimizes to the bisected form; from the energy of the constrained perpendicular form, the bisected form is 1.3 kcal/mol more stable. Depending on the method, the difference in energy for the cyclopropylcarbinyl carbenium ion is 25–30 kcal/mol. Schmitz and Sorensen<sup>7</sup> found, however, that successive replacement of the carbinyl protons with methyls lowered the energy difference between the two forms, such that  $\Delta\Delta H$  for the dimethyl carbenium ion was ca. 13 kcal/mol. For the protonated ketones, there is substantial stabilization by the hydroxyl, and the lower energy difference for **6** is not surprising.

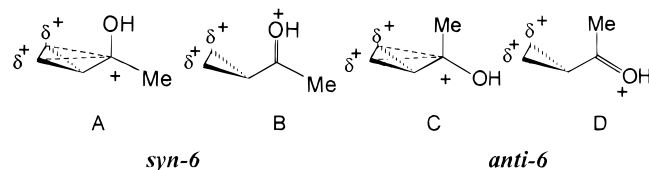
**(b) Syn vs Anti.** For **6**, the *anti* form is slightly more stable (1.0 kcal/mol) than the *syn*, in contrast to the finding of Childs et al.<sup>8</sup> that the *syn* form is preferred in the crystal. For **5**, however, the *anti* form is much more stable (2.2 kcal/mol) than the *syn* form, in agreement with the crystal structure. The fact that **3** and **4** have the *anti* form but are less stable than **1** suggests that other factors influence stability in the nortricyclanone system.

**Substitution on the Cyclopropyl Ring.** C3–C5 protons in **6** were successively replaced with Me groups and the stabilities computed using the isodesmic cycle anchored to **1**. The  $\alpha$  (“down”) and  $\beta$  (“up”) designations refer to the orientation of the C4 and C5 Me’s to the hydroxyl on C2, not to the position of methyl substitution on the cyclopropyl ring (Figure 3). In all compounds studied, addition of a methyl group to the C3 or C4 position of the ring increases the stability of the protonated ketone. For the C3 methyl compounds (*syn*- and *anti*-**5**), the *anti* form is more stable than the *syn*, but in the C4 Me compounds (*syn*- and *anti*- $\alpha$ - and  $\beta$ -**8**), the *syn* forms are slightly more stable than the *anti*, which may reflect a destabilizing Me–Me steric repulsion in the

$\beta$  compounds. The diMe compounds **9** are more stable than the monoMe compounds. The order of stabilities is roughly that found by Schmitz and Sorensen<sup>6</sup> for methyl stabilization of the cyclopropylcarbinyl carbenium ion; as discussed below, the differences between the series are related to hydroxyl stabilization in the protonated ketones.

The flexible compounds have much different stabilities than their rigid equivalents. For instance, *syn-5* has a skeletal geometry equivalent to **1** but is 1.4 kcal/mol more stable, and *anti-β-9* has a skeletal geometry equivalent to **3** but is 5.2 kcal/mol more stable than **1** and 7.7 kcal/mol more stable than **3**. [The flexible trimethyl compound equivalent to **4** (*anti*-4,4-diMe- $\beta$ -5-Me, not shown) is 6.1 kcal/mol more stable than **1** and 8.6 kcal/mol more stable than **4**.] Thus Me substitution on the cyclopropyl ring uniformly increases the stabilities of the flexible protonated ketones and cannot be the source of the apparently anomalous  $pK_{R^+}$  values for **3** and **4**.

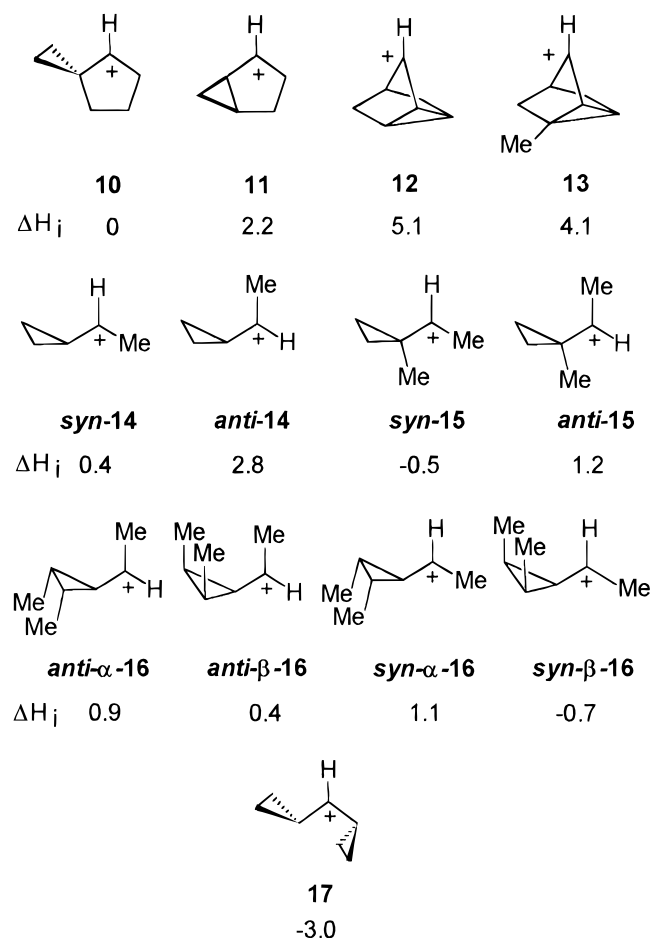
The greater stability of the *anti* conformations may be the result of charge repulsion. Two sources of stabilization are expected: that arising from cyclopropylcarbinyl interactions and that arising from direct oxygen resonance stabilization of the cationic center. With carbinyl interactions, positive charge should build up on C4 and C5 (A and C) consistent with the large <sup>1</sup>H and <sup>13</sup>C NMR shifts exhibited in hydrocarbon cyclopropylcarbinyl systems.<sup>4</sup> In *syn-6*, positive charge on the oxygen would be repulsive with the charge on C4 and C5 (B), while this repulsion would be shielded and reduced in *anti-6* (D).



Thus it would be expected that the *anti* geometry would be more “oxocarbenium ion”-like than the *syn* geometry and would be expected to be more stable because of the direct conjugation between the oxygen and the positively charged C2. This is borne out by the Mulliken charges. The oxygen is more positive in *anti-6* than in *syn-6* (−0.089 vs −0.104, respectively); in addition, the C4 and C5 carbons are slightly more positive in the *syn* than *anti* conformer (−0.035 vs −0.048, respectively). Thus the *syn* forms can be described properly as bisected cyclopropylcarbinyl carbenium ions with significant oxocarbenium ion character, while the *anti* forms are clearly oxocarbenium ions with some cyclopropylcarbinyl character. While these effects are modest, they appear to be sufficient to provide the additional stabilization found.<sup>13</sup> In addition, the reversal in geometric requirements found for the more stable geometric isomer for the hydrocarbon carbenium ions is consistent with this analysis (see below).

**Energy Consequences of Carbonyl Carbon Bond Angle.** A major difference between the flexible and rigid

(13) The charge analysis is consistent with spectra obtained by diagonalization of the force constant matrix. In *syn*- and *anti*-**5**, the *syn* flexible compounds corresponding to **1**, the most prominent stretch is the coupled vibration of the positive C2 with the cyclopropyl C4–C5 followed closely by a C2–O stretch. In the *anti* flexible compounds corresponding to **3** and **4**, however, the C2–O stretch is far more prominent than the coupling of C2 with the cyclopropyl. The intensity of the C1–C2 stretch is ca. 2-fold greater. The same pattern is found for the *syn* and *anti* forms of **6**.

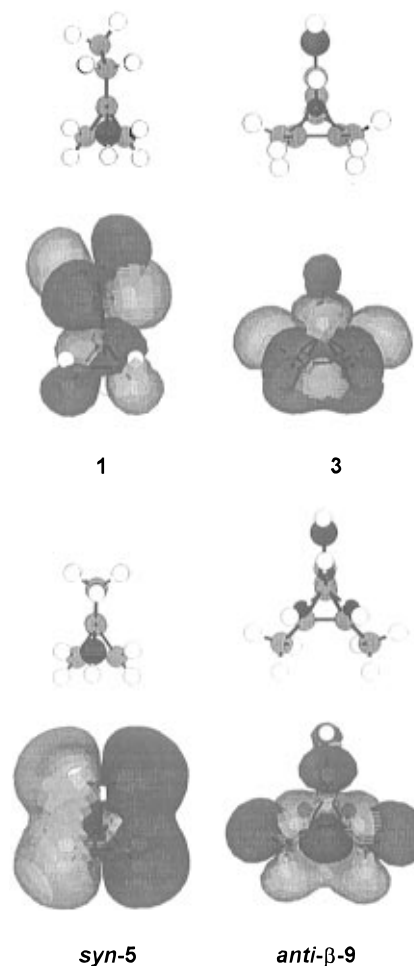


**Figure 4.** PM3  $\Delta H_f$  (kcal/mol) for hydrocarbon carbenium ions corresponding to the protonated cyclopropylcarbinyl ketones shown in Figures 1 and 3.

structures is the angle about the carbonyl carbon. To test the effect on energy of reducing this angle, the C1–C2–C3 angle in *syn*-5 was decreased progressively from its initial value of 123°, close to that found by Childs et al.,<sup>8</sup> in the crystal structure of this compound, to 112.6°, which corresponds to the angle in **1**, and finally to 103.9°, which corresponds to the angle in **3**. The values of  $\Delta H_f$  obtained are -1.4, 0.9, and 3.9 kcal/mol, respectively, a total decrease in stability of 5.3 kcal/mol. The same pattern was found for *anti*- $\beta$ -9, with  $\Delta H_f$  values of -5.2, -1.6, and 1.3 kcal/mol with decreasing carbonyl angle, for a total decrease in stability of 6.5 kcal/mol. Some of this energy increase may no doubt be the result of Me–cyclopropyl steric interaction; nonetheless, similar treatment of the protonated *anti*-cyclopropylaldehyde, in which there is a proton–cyclopropyl interaction only, gives energy increases, relative to the heat of formation of the parent compound, of 2.1 and 6.6 kcal/mol for restriction of the carbonyl angle from the normal angle of 124.3° to 112.6° to 103.9°, respectively. Thus even in the absence of modest (*syn*-5) or severe (*anti*- $\beta$ -9) steric effects, restricting the carbonyl angle leads to destabilization of the oxocarbenium ion. This effect shows why, despite similar skeletal geometries, **5** is more stable than **1**. It also appears to be the major factor that accounts for the relative energies of **3** and **4**.

#### Comparison with Hydrocarbon Carbenium Ions.

The effects on energies and conjugation of replacing the hydroxyl with a proton were evaluated in 13 of the compounds (**10**–**17**, Figure 4). Values of  $\Delta H_f$  were evaluated



**Figure 5.** HOMOs for rigid (**1** and **3**) and flexible (*syn*-5 and *anti*- $\beta$ -9) protonated cyclopropylcarbinyl ketones shown in the same relative orientation. The HOMOs for **1** and *syn*-5 are  $\pi$  but are  $\sigma$  for **3** and *anti*- $\beta$ -9.

using the isodesmic cycle described in the Methods section, which anchors the energies to the rigid spiro compound geometry of the protonated ketone. In most instances, the PM3 relative stability values agree well with those of Schmitz and Sorensen computed at the MNDO/STO-3G level.<sup>6</sup> As found for the series **1**–**4**, **10**–**13** all showed an increase in  $\Delta H_f$ ; **13**, however, is 1.0 kcal/mol more stable than **12**. In the flexible series, *syn*-15 and **17** are both more stable than **10**, as found in the protonated ketone series, but the other Me-substituted compounds are slightly less stable than **10**. In fact, the orders of stability are reversed. For instance, in the protonated ketone series *anti*-6 is 1.0 kcal/mol more stable than *syn*-6, but in the hydrocarbon series the structurally equivalent *anti*-14 is 2.4 kcal/mol less stable than *syn*-14. The same reversal is found for *syn*- and *anti*-15. Thus in **14** and **15**, the two compounds in which the Me is antiperiplanar to the cyclopropyl ring are more stable. While *syn*- $\beta$ -16 has the antiperiplanar Me and is the most stable in the diMe series, *syn*- $\alpha$ -16 is the least stable of the flexible carbenium ions. Me–Me repulsion does not seem to be important because *anti*- $\beta$ -16 is more stable than *anti*- $\alpha$ -16 by 0.5 kcal/mol. While there are a number of factors that could affect the stabilities, including a stabilizing effect by the  $\pi$  MOs on the slightly lower-lying  $\sigma$  MOs,<sup>6</sup> the reversal is most probably merely the result of the greater stability of oxocarbenium

ions in which the protonated carbonyl is antiperiplanar to the ring.

**Molecular Orbitals.** Schmitz and Sorensen<sup>6</sup> have reported the HOMOs for an extensive series of Me-substituted cyclopropylcarbinyl carbenium ions. As a control for the protonated ketone series, some compounds from the Schmitz–Sorensen series, calculated at the MNDO/STO-3G level, were recalculated in PM3; in the seven compounds compared the same MOs were obtained by both methods. As expected, the  $\pi$  MO is more important for stabilization than the  $\sigma$  MO for bisected forms. It is worth noting that in ions such as the 3,4-dimethyl cyclopropylcarbinyl carbenium ion, in which the  $\pi$  and  $\sigma$  MOs are very close in energy, a slight change—in the torsional angle between the plane of the positive carbon and the ring can switch the HOMO from  $\pi$  to  $\sigma$ . In most ions, however, the  $\pi$ – $\sigma$  gap was sufficiently large that assignment of the HOMO was unambiguous and not affected by very small changes in geometry.

As shown in Figure 5, the HOMOs for **1** and its flexible analog *syn*-**5** are the same  $\pi$  MOs, with a change in sign and overlap in the latter as expected for differences between cyclic and open-chain structures, while those for **3** and its flexible analog *anti*- $\beta$ -**9** are  $\sigma$  MOs, with a change in sign but the same essential shape. The same patterns are found in the hydrocarbon analog pairs **10** and *syn*-**15** and **12** and *anti*- $\beta$ -**16**, respectively, which conform to the MOs reported by Schmitz and Sorensen.<sup>6</sup>

(14) Schmitz and Sorensen (ref. 6) found that addition of a Me to the carbon bearing the positive charge had the greatest stabilizing effect. The equivalent maneuver in this system is the difference in energy between protonated cyclopropyl aldehyde and **6**. Anchored to **1**, protonated cyclopropyl aldehyde is 6.4 kcal/mol less stable than *syn*-**6** and 7.4 kcal/mol more stable than *anti*-**6**, which is the largest effect found for addition of a single methyl.

## Summary and Conclusions

These results show that a variety of factors acting together and in opposition lead to the relative energies among the protonated ketones. The *anti* bisected form of **3** and the greater alkyl substitution of **3** confer greater stability relative to **1**; crudely, by comparing *anti*- $\beta$ -**9** with *syn*-**5**, this is worth ca. 3.8 kcal/mol in favor of the tricyclic structure. In the flexible compounds, *syn* forms are cyclopropylcarbinyl carbenium ions with some oxocarbenium character, while *anti* forms are oxocarbenium ions with some cyclopropylcarbinyl carbenium ion character. In the ring structures, however, closing down the ketone carbonyl angle destabilizes the ion. Of the effects reported here, this appears to be the one most responsible for the stability of the tricyclic structures. That the oxocarbenium ion influences stability synergistically is shown by comparison of equivalent hydrocarbon structures (Figure 4), in which the *anti* forms are more stable than the *syn* and the tricyclic structure **12** (equivalent to **3**) is 2-fold less stable than **10** (equivalent to **1**). Finally, the more stable structure **1** (and the hydrocarbon **10**) has a  $\pi$  HOMO, while **3** (and the hydrocarbon **12**) has a  $\sigma$  HOMO. The former are more important for charge delocalization than the latter,<sup>6</sup> which is another source of the difference in stabilities in the series.

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**Supporting Information Available:** MOPAC Z-matrix files for **1–7** are provided (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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