Highly Fluorinated Cyclopentanones and Their Enols

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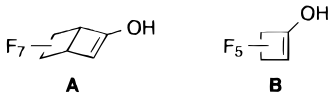
2*H*-Perfluorocyclopentanone **(1k)** and its enol **(1e)** have been independently synthesized and equilibrated. In carbon tetrachloride, the enol is the only detectable form at equilibrium. In addition to its high relative stability, this enol displays interesting reactivity, including reversible bromination and hydrolysis reactions. Replacing the vinyl fluorine of **1e** with hydrogen changes the relative enol stability dramatically as the enol is only present to the extent of 13% in carbon tetrachloride under equilibrating conditions. In Lewis basic solvents, however, the enol is the only detectable form because of its strength as a hydrogen bond donor. Quantum mechanical calculations on both systems suggest that ketone destabilization, but not enol stabilization, by fluorination is responsible for the remarkable relative stability of the enols.

Introduction

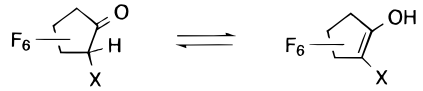
Keto−enol equilibria have been investigated for over a century.[2] In general, unhindered and unconjugated enols are much less stable thermodynamically than their keto tautomers.[3,4] Recent reports from this laboratory, however, have shown that cyclic, highly fluorinated keto−enol systems stand in stark contrast with their hydrocarbon counterparts.[5] For instance, enol **A** comprised 7% of the equilibrium mixture (i.e., $K_{E/K} = 0.07$) in carbon tetrachloride but was the sole detectable tautomer in Lewis basic solvents such as acetonitrile.



A **B**

The relative stability of enol **B** was even more impressive as no keto tautomer was detected at equilibrium in carbon tetrachloride. This was the first example of a simple, unhindered, unconjugated keto−enol system in which the enol has been demonstrated to be stabler than its ketone even in non-hydrogen-bonding media.

It seemed possible at this stage that the strained four-membered rings play an important role in raising the energy of the ketones relative to their enols. We therefore set out to explore the generality of this phenomenon by synthesizing keto−enol systems with far less ring strain, *viz*. cyclopentane-derived systems **1** and **2**. The enol of system **1** is fully fluorinated, while that of system **2** has a hydrogen at the vinyl position. This subtle difference has a marked effect on enol stability. Quantum mechanical calculations at reasonably high levels of theory have proven useful in describing both systems. The equilibration and computational results are reported



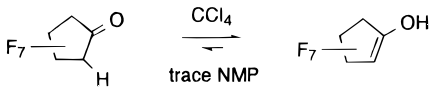
System **1** X = F

System **2** X = H

first, followed by the synthetic pathways used to prepare each of the compounds in this study.

Results and Discussion

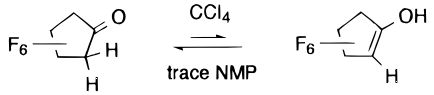
Equilibration Studies. Establishment of equilibrium in the cyclobutane-derived keto−enol systems was facile at 25 °C in carbon tetrachloride containing a trace of *N*-methylpyrrolidone (NMP) as catalyst. Subjecting enol **1e** to these conditions resulted in no detectable keto tautomer, but adding of 0.01 equiv of NMP to ketone **1k** in carbon tetrachloride resulted in complete enolization after only 5 h as determined by ^{19}F NMR spectroscopy. Thus, enol **1e**, like **B**, is much more stable than its ketone in carbon tetrachloride. Since equilibrium constants could



1k **1e**

not be measured by ^{19}F NMR spectroscopy for these systems, a quantitative measure of the keto−enol energy differences is not available at this time.

The relative energy of the tautomers for system 2 was quite different, as enol **2e** was present to the extent of only 13% ($K_{E/K} = 0.15$) in carbon tetrachloride containing a trace of NMP. A modest shift in the equilibrium



2k **2e**

constant was observed in benzene ($K_{E/K} = 0.44$), which can be attributed to the stabilization of the enol form by formation of a hydrogen bond between the benzene and enol hydroxyl group.[6] The hydrogen bond stabilization is great enough in acetonitrile so that no ketone is

⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1996.

(1) Walter H. Stockmayer Fellow, 1995−96.

(2) *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 1990.

(3) Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862.

(4) Toullec, J. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: London, 1982; Vol. 18, pp 1−77. Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000.

(5) (a) Correa, R. A.; Lindner, P. E.; Lemal, D. M. *J. Am. Chem. Soc.* **1994**, *116*, 10795. (b) Lindner, P. E.; Correa, R. A.; Gino, J.; Lemal, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 2556. (c) Portions of this work were reported by P.E.L. at the 12th Winter Fluorine Conference, St. Petersburg Beach, FL, Jan 22−27, 1995, Poster 78.

(6) For an example of benzene as a hydrogen-bonding base see: Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W. A.; Blake, G. A. *Science* **1992**, *257*, 942.

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Table 1. Keto−Enol Energy Gaps for Systems 1 and 2

level of theory[a]	**1k**	**1e (syn)**	ΔE^b	**2k**	**2e(syn)**	ΔE^b
HF/6-311G**//3-21G	−961.054760	−961.052984	1.1	−862.197557	−862.189629	5.0
HF/6-31G**//6-31G**	−960.814603	−960.810180	2.8 (2.9)[c]	−861.974225	−862.974225	6.3 (6.5)[c]
HF/6-311G**//6-31G**	−961.065984	−961.062312	2.3	−862.206837	−862.197747	5.7
MP2/6-311G**//6-31G**	−963.335041	−963.331450	2.3	−864.281868	−864.271419	6.6

[a] The geometries were optimized with Gaussian 92.[21] Initial optimizations were at the 3-21G level of theory, and the coordinates were used as starting points for the higher level geometry optimizations. [b] ΔE = *E*(syn enol) minus *E*(ketone) in kcal/mol. [c] The values in parentheses are corrected for zero point vibrational energies, 298 K, and estimated entropy differences. The corrections are based on the HF/6-31G** calculation with frequencies larger than 500 cm^{-1} scaled by 0.893.[22]

detectable by ^{19}F NMR; the same is true in THF and diethyl ether.

Computational Results. The quantum mechanical calculations we have carried out on a series of highly fluorinated keto−enol systems have underestimated the relative stability of the enols, but the underestimation is consistent enough that useful comparisons can be made between systems.[5] The calculated keto−enol energy gaps for systems **1** and **2** at various levels of theory are shown in Table 1. The weakly interacting carbon tetrachloride solvent should provide for meaningful comparisons between experiment and the gas phase calculations.

While we have shown enol **1e** to be much stabler than **1k** experimentally, ab initio theory even at high levels predicts the ketone to be the stabler form. The same is true for system **2** where the experimental difference in free energy for **2e** and **2k** is 1.1 kcal/mol ($K_{E/K} = 0.15$); at the HF/6-31G**//6-31G** level the difference is calculated to be 6.5 kcal/mol after corrections for zero point vibrational energy, 298 K and the estimated entropy difference. It is noteworthy that the underestimation is worse for the HF/6-311G**//6-31G** calculations than for the HF/6-311G**//3-21G results. Including electron correlation up to second-order Möller-Plesset perturbation theory for the former level of theory offers no improvement to the calculated keto−enol energy gaps.

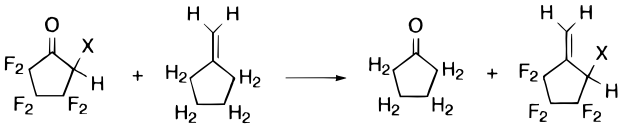
The failure of high-quality ab initio calculations to correctly order the relative stability of the keto−enol systems is somewhat disconcerting. A possible explanation would be that the experimental data in solution are biased toward the enol because hydrogen-bonded dimers or higher aggregates are formed. This does not appear to be the case, however, as the chemical shift for the vinyl fluorine of **1e** does not change significantly through a concentration range of 1−150 mM. We have previously shown that the vinyl fluorine chemical shifts in the cyclic enols are very sensitive to hydrogen-bonding interactions.

Alternatively, the enols could form weak hydrogen bonds to the solvent. Carbon tetrachloride is generally considered to be non-Lewis-basic, but recent high-level quantum mechanical calculations show that a complex is formed between hydrogen chloride and CCl_4 in the gas phase. The strength of the hydrogen bond at the MP2/cc-PVTZ+//MP2/6-31+G** level of theory is 2.2 kcal/mol.[7] Since fluorinated enols are strong hydrogen bond donors, this kind of interaction with solvent may contribute to the gap between theory and experiment.

Despite their limitations, the calculations recognize the dramatic relative enol stabilization with respect to their hydrocarbon parents in both systems **1** and **2**. For instance, the keto−enol gap for cyclopentanone and its enol is 15.3 kcal/mol at the HF/6-311G**//3-21G level of theory as compared with 1.1 and 5.0 kcal/mol for systems 1 and 2, respectively.

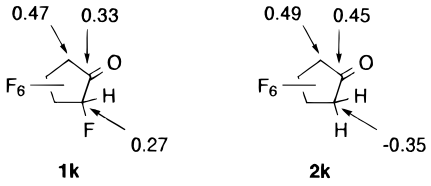
(7) Del Bene, J. E.; Shavitt, I. *J. Mol. Struct.* **1994**, *314*, 9.

Isodesmic reactions for the cyclobutane-derived enols revealed that the relative enol stability arises from ketone destabilization but not enol stabilization relative to their hydrocarbon parents. The generality of this finding has now been tested with similar isodesmic reactions at the HF/6-311G**//3-21G level for systems **1** and **2**. The exothermicity of the isodesmic reactions shown below indicate that cyclopentanone, like cyclobutanone, is severly destabilized by fluorination. Destabilization of ketones by fluorination is well established,[8] but the finding that **1k** is significantly more destabilized than **2k** with respect to cyclopentanone deserves comment.



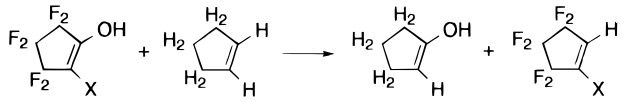
X	ΔE (kcal/mol)
F	-18.7 (**1k**)
H	-12.4 (**2k**)

A calculation of the charge distribution in each ketone afforded insight into the origin of this difference. The charges on carbons shown below were calculated at the HF/6-31G** level; they are based on fits to electrostatic potentials, but the charges based on natural orbitals lead to the same conclusion. A large difference was found between the ketones in the charge at the α-carbons bearing hydrogen. This carbon is positively charged in **1k** but negatively charged in **2k**, so its electrostatic repulsion with the carbonyl carbon in **1k** is replaced by attraction in **2k**.



What is the effect of fluorination on cyclopenten-1-ol? Isodesmic reactions suggest that enols **1e** and **2e** are both destabilized relative to cyclopenten-1-ol at the HF/6-311G**//3-21G level of theory. This finding supports the view that the striking enol stabilities in cyclic, fluorinated keto−enol systems are the result of ketone destabilization without a contribution from enol stabilization. At all levels of theory investigated the enol of system **1** is correctly calculated to be stabler with respect to its ketone than that of system **2**.

(8) See, for example: Smart, B. E. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: Deerfield Beach, FL, 1986; Vol. 3, p 141.



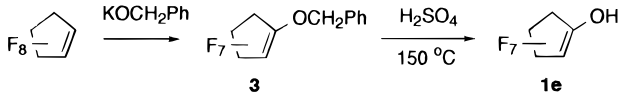
X	ΔE (kcal/mol)
F	-4.8 (**1e**)
H	-1.9 (**2e**)

The geometry of enols has been the focus of several quantum mechanical studies in recent years.[9] In general, the syn planar conformers are the most stable. Particularly intriguing calculations by Dixon and Smart[9a] using a triple-ζ basis set (TZ + P) found the cis,syn conformer for the enol of 2-fluoroacetaldehyde to be 4.2 kcal/mol more stable than the cis,anti conformer. This was attributed, at least in part, to the stabilization of the cis,-syn conformer by the formation of an intramolecular hydrogen bond between the hydroxyl hydrogen and the vinyl fluorine. The main piece of evidence supporting this conclusion was the short H−F distance of 2.37 Å; the sum of the H and F van der Waals radii is 2.67 Å.

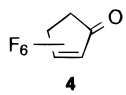
Geometry optimizations at the HF/6-31G** level of theory for enol **1e** also find the syn conformer to be favored, but only by 0.9 kcal/mol. The preference for the syn conformer vanishes in enol **2e** where the isomers are degenerate at the same level of theory. The slight bias for the syn conformer in **1e** may arise in part from internal hydrogen bonding, but the H−F bond distance in the HF/6-31G** optimized structure of *syn*-**1e** is 2.62 Å (just 0.05 Å smaller than the sum of the van der Waals radii). For comparison, the distance between the hydroxyl hydrogen and vinyl hydrogen in **2e** is 2.61 Å. At the same level of theory there was no evidence for intramolecular hydrogen bonding in perfluorocyclobuten-1-ol, **B**.

The geometry for the trans,anti enol of 2-fluoroacetaldehyde found by Dixon and Smart was also interesting, for the O−H bond was rotated 13° out of the plane of the C=C bond. A similar rotation is observed for the anti conformers of **1e** and **2e**; at the HF/6-31G** level of theory the torsion angle *t*(CCOH) is 19° for **1e** and 12° for **2e**. The rotation does not substantially enhance the stability of *anti*-**1e**, however, as the anti planar conformation lies only 0.3 kcal/mol above the structure rotated by 19°.

Syntheses of Enol 1e and Ketone 1k. Enol **1e** was prepared previously by Bekker *et al.* by the following route.[10] In our hands, the high temperature acid-induced

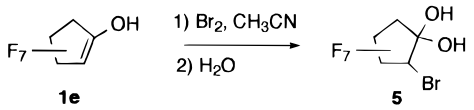


cleavage of benzyl enol ether **3** did not give the enol, but rather the dehydrofluorinated product **4**. To suppress the



decomposition of the enol in this manner, the same reaction was performed at room temperature in 1,2,4-trichlorobenzene as solvent. This modification produced 75−80% yields of enol after trap-to-trap distillation to remove the nonvolatile solvent.

Taking an approach they had employed with success to make other 2*H*-perfluoroketones, the Russian workers were unable to synthesize ketone **1k**. We have developed a route to **1k** starting from its enol. Bromination followed by hydrolysis of **1e** produced *gem*-diol **5**. The ^{19}F

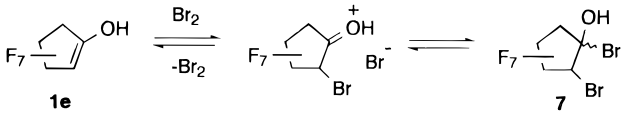


NMR spectrum of this diol displayed three AB quartets for the three sets of geminal fluorine atoms and a multiplet for the fluorine geminal to the bromine. The fluorine vicinal and cis to the bromine was recognizable by the large downfield shift (24 ppm) from its geminal partner.[11]

It seemed likely that the initially formed bromination product was ketone **6**, which hydrated on addition of water. Indeed, ketone independently generated from diol **5** with concentrated sulfuric acid reverted rapidly to **5** when water was introduced.

Monitoring the ^{19}F NMR spectrum of the bromination of **1e** in *dry* acetonitrile did not reveal signals corresponding to ketone **6**, however. Instead, a compound that had two relatively low-field fluorine signals was formed after the addition of excess bromine. The pair of low-field signals suggested a compound with two bromine atoms as in bromohydrin **7**.[12] Evidently, the surrounding halogens destabilize the ketone enough so that loss of HBr to give the ketone is unfavorable in the reaction medium.[13]

Isolation of **7** was impossible, for treating the mixture with limonene or simply reducing the pressure with an aspirator removed bromine and regenerated the enol. A likely mechanism for the bromination/debromination is shown below. Addition of water irreversibly traps the cationic intermediate to give the stable diol **5**.



Reducing the bromine in compound **5** to hydrogen would generate the hydrate of ketone **1k**, but reductions with tributyltin hydride were plagued by poor solubility of the substrate in typical hydride solvents (e.g., benzene or hexanes). Reduction was observed photochemically in

(9) (a) Dixon, D. A.; Smart B. E. *J. Phys. Chem.* **1991**, *95*, 1609. (b) Turecek, F.; Cramer, C. J. *J. Am. Chem. Soc.* **1995**, *117*, 12243.

(10) Bekker, R. A.; Popkova, V. Ya.; Knunyants, I. L. *Izv. Akad. Nauk. SSSR* **1978**, *2*, 493 (Engl. transl. p 430).

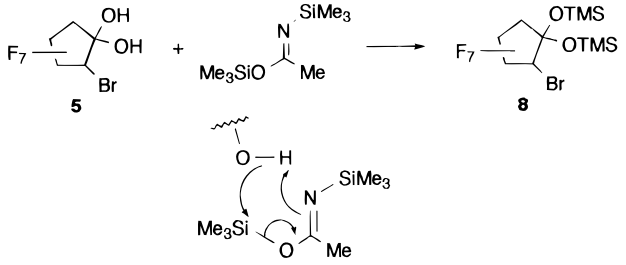
(11) Barlow, M. G.; Haszeldine, R. N.; Morton, W. D.; Woodward, D. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2170−80.

(12) ^{19}F NMR of **7** (CH_3CN): −103.9, −125.8 (subsplit AB q, J = 244 Hz, 2F); −104.3, −127.9 (subsplit AB q, J = 238 Hz, 2F); −118.7, −122.8 (AB q, J = 244 Hz, 2F); −121.2 (m, 1F).

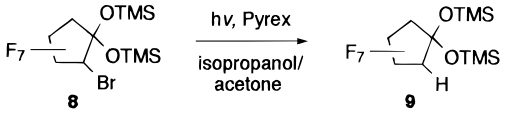
(13) Stable bromohydrins of perfluorocyclobutanone have been isolated (Andreades, S.; England, D. C. *J. Am. Chem. Soc.* **1961**, *83*, 4670).

2-propanol containing acetone,[14] but the product was dehydrated by the hydrogen bromide formed in the reaction. The resulting ketone did not survive, as part of it enolized and part was apparently trapped by 2-propanol.

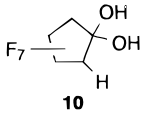
Protection of the hydroxyls of **5** with trimethylsilyl groups was therefore sought. The first attempt with the excellent silating agent trimethylsilyl triflate resulted in no reaction, but treatment with *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) in methylene chloride produced the bis-(trimethylsiloxy) derivative **8** cleanly.[15] Perhaps BSA delivers the trimethylsilyl group through a six-membered cyclic transition state with the formation of a hydrogen bond between the nitrogen lone pair of the acetamide with the hydroxyl group of the diol. The low reactivity of trimethylsilyl triflate can be rationalized by this mechanism, as a weakly basic triflate oxygen will not hydrogen bond to the hydroxyl group nearly as well as the acetamide nitrogen.



Unlike its unprotected precursor, **8** underwent clean photochemical reduction with 2-propanol/acetone. The reduction works equally well by irradiation in benzene or hexane with tributyltin hydride as the hydrogen atom donor.

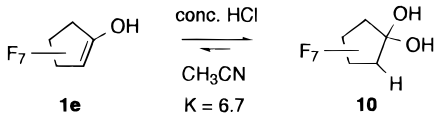


This route to bis(trimethylsiloxy) ether **9** is straightforward, but the hydration of **1e** would in principle give the unprotected diol **10** directly. When the enol was



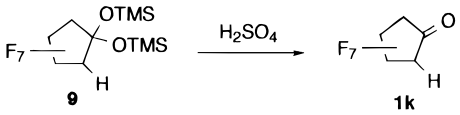
treated with water, however, the only products were those resulting from dehydrofluorination rather than hydration.[16] This problem has been circumvented by performing the hydrolysis with concentrated hydrochloric acid in acetonitrile. This produces diol **10** as the major product, but approximately 10% of the enol remains even at long reaction times.

An equilibrium between **1e** and **10** had apparently been established, but approach from the diol side was required for confirmation. The isolation of **10** free of its enol proved to be extremely difficult, so the enol contaminant was removed by titrating the equilibrium mixture with bromine to irreversibly remove the enol in the form of bromohydrate **5**, as discussed above. After 1.5 h the equilibrium between **1e** and **10** was reestablished.



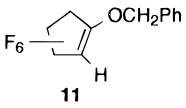
The interconversion must take place via ketone **1k** (and/or its conjugate acid); it is surprising that enolization of the ketone competes at all with hydration in concentrated hydrochloric acid, as the hydration of perfluorinated ketones is very exothermic.[17] This serves to illustrate the strong driving force for enolization in fluorinated keto−enol systems.

Diol **10** was silated with BSA in methylene chloride to give give bis(trimethylsiloxy) ether **9**. Since this route to **9** is shorter than the bromination scheme presented above it is preferred for large-scale preparations. When **9** was treated with sulfuric acid in carbon tetrachloride at room temperature ketone **1k** was generated in 90% yield. The ketone is extremely labile as a neat liquid but



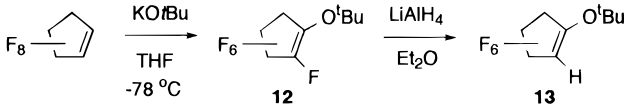
reasonably stable in carbon tetrachloride in the absence of Lewis basic catalysts. The ^{19}F NMR spectrum of **1k** shows three AB quartets for the three sets of geminal fluorine atoms and a high-field doublet at −218.0 ppm for the fluorine geminal to hydrogen. A strong peak at 1817 cm^{-1} in the infrared spectrum reveals the carbonyl moiety.

Syntheses of Enol 2e and Ketone 2k. The sulfuric acid-induced cleavage of benzyl enol ether **11**, which was obtained from perfluoro enol ether **3** and lithium aluminum hydride, was expected to give enol **2e**. This reaction



unfortunately produced a complicated mixture of products, so a new precursor to enol **2e** was needed.

In the course of preparing bicyclic enol **A**,[5a] we discovered that the acid-induced cleavage of its *tert*-butyl enol ether proceeds smoothly provided that a *tert*-butyl cation trap is present. With the hope that the same would be true in system **2**, *tert*-butyl enol ether **13** was prepared as shown below.



Addition of potassium *tert*-butoxide to perfluorocyclopentene produced perfluoro *tert*-butyl enol ether, **12**, via

(14) Paleta, O.; Jezek, R.; Dedek, V. *Coll. Czech. Chem. Commun.* **1983**, *48*, 766. For reviews of photoreduction of the carbon−halogen bond, see: Lodder, G. In *Supplement D: The Chemistry of Halides, Pseudo-halides and Azides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1983; Part 2. Lodder, G.; Cornelisse, J. In *Supplement D2: The Chemistry of Halides, Pseudo-halides and Azides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1995; Part 2.

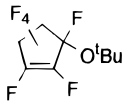
(15) Yalpani, M.; Wilke, G. *Chem. Ber.* **1985**, *118*, 661.

(16) The major product of the hydrolysis was 3-hydroxyperfluorocyclopent-2-enone, as reported earlier (ref 10).

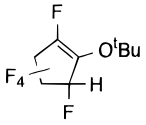
(17) (a) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898. (b) Hine, J.; Flackstean, H. *J. Org. Chem.* **1979**, *42*, 177.

an addition−elimination pathway. A singlet in the ^{19}F NMR spectrum at Φ −152.7 ppm revealed the vinyl fluorine and a double bond stretch at 1713 cm^{-1} in the infrared spectrum provided strong evidence for the enol ether structure.[18] Compound **12** is sensitive to traces of acid and partially decomposed during distillation to enol **1e** and enone **4**. This was true even when the distillation was performed over calcium carbonate to scavenge adventitious acid and at low pressure to keep pot temperatures moderate.

Compound **12** was accompanied by an isomer that comprised *ca.* 10% of the reaction mixture. While the minor isomer has not been fully characterized, we are confident that it possesses the structure of compound **12a**. The minor product simply results from an S_N2' reaction by the alkoxide on perfluorocyclopentene. The structure of **12a** was based primarily on its mass spectrum, particularly the base peak at 193 for the loss of a *tert*-butoxy group to generate the stable allylic cation; the 193 peak is absent in **12** as loss of the *tert*-butoxy group would generate a high energy vinyl cation.



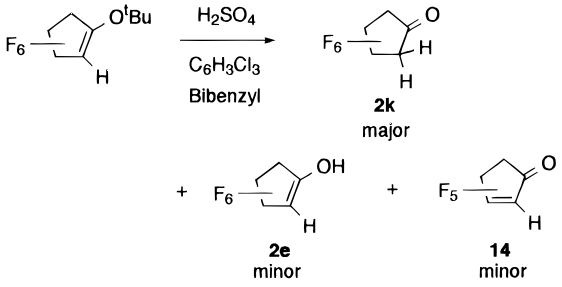
12a



13a

The vinyl fluorine of compound **12** was substituted by hydrogen with lithium aluminum hydride to give enol ether **13**. As in the previous reaction, compound **13** was accompanied by *ca.* 10% of **13a**, which resulted from an S_N2' reaction of hydride on the starting material. The mass spectra of compounds **13** and **13a** were virtually identical, and noticeably absent was a peak at 175 for the loss of the *tert*-butoxy moiety, indicating that both compounds possessed the enol ether structure.

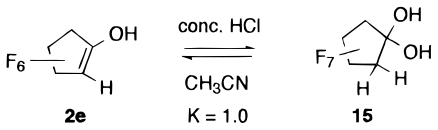
The acid-induced cleavage of **13** was complete in 5 min when it was mixed with sulfuric acid in 1,2,4-trichlorobenzene containing 3 equiv of bibenzyl as a *tert*-butyl cation trap. Trap-to-trap distillation to remove the nonvolatile solvent yielded a mixture of ketone **2k**, enol **2e**, and 5−10% of a third compound identified as the dehydrofluorinated product **14**.



Enone **14** can be identified by three peaks in the ^{19}F NMR spectrum at Φ −104.9, −123.8, and −126.5 in a 1:2:2 ratio. Attempts to remove the enone from the product mixture by distillation or preparative gas chromatography resulted in further decomposition of **2e** and **2k** to **14**. As a result, 5−10% of the enone was usually present in the equilibration studies presented above, but larger amounts did not alter the equilibrium constant.

The mechanism of the acid-induced cleavage of **13** was probed with ^{19}F NMR spectroscopy by shaking the enol ether in an NMR tube containing 2 equiv of sulfuric acid and 3 equiv of benzene in carbon tetrachloride. The initially formed product was clearly enol **2e** as identified by three singlets at Φ −104.4, −120.0, and −130.5, which are very close to those of the structurally similar starting material. After a few minutes the ketone peaks quickly rose from the base line at Φ −116.5, −129.8, and −139.8 ppm. The ^1H NMR spectrum of the enol in carbon tetrachloride consists of a multiplet at 5.35 ppm for the vinyl hydrogen and a singlet at 5.7 ppm for the hydroxyl group. The latter peak shifts downfield to 9.5 ppm in acetonitrile as a consequence of the hydrogen bonding interaction between the enol and the solvent. The two hydrogens of the ketone appear as a subsplit triplet (J = 17 Hz) at 2.82 ppm; the large splitting is presumably from coupling to the vicinal fluorines.

As for system **1**, independent preparation of the keto tautomer was attempted via hydrolysis of the enol in the hope of obtaining ketone **2k** free of of its enol and the enone. Enol **2e** did react with concentrated hydrochloric acid in acetonitrile, but the desired diol comprised only 50% of the equilibrium mixture. Since the two compounds could not be separated, a new route to **2k** was investigated.



2e **15**

Thermal fragmentation of *tert*-butyl enol ethers to ketones and isobutylene is a well-known process.[19] In the case of enol ether **13**, the elimination would produce ketone **2k** directly. Indeed, when **13** was subjected to flash vacuum pyrolysis in a quartz tube at 500 °C, compound **2k** was the major product, but the reaction mixture also contained 30−35% of enol **2e** and 5−10% of enone **14**.

It seems likely that the ketone is the initially formed product, but a small amount dehydrofluorination occurs to give enone **14** in the hot tube. The hydrogen fluoride generated *in situ* then catalyzes the cleavage of the *tert*-butyl enol ether to give a substantial amount of enol **2e** in the reaction mixture. An attempt to scavenge the hydrogen fluoride by performing the pyrolysis over a bed of calcium carbonate failed as enone **14** was the only isolated product. No further attempts have been made to isolate ketone **2k** free of its enol.

Conclusions

Recent work from this laboratory showed that highly fluorinated cyclobutane-derived enols were thermodynamically stable with respect to their ketones in a variety of media. The present work demonstrates that strained four-membered rings are not uniquely responsible for this striking inversion of the usual stability relationship, for it is found as well in cyclopentane-derived keto−enol systems. Enol **1e** is the only detectable tautomer at equilibrium in all media. Enol **2e**, in which the vinyl fluorine of **1e** has been replaced with a hydrogen, is the only detectable form at equilibrium in Lewis basic

(18) Benzyl enol ether **3** has a C=C stretching band at 1725 cm^{-1} (ref 10).

(19) McEwen, I.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1982,** 1179. Daly, N. J.; Wentrup, C. *Aust. J. Chem.* **1968**, *21*, 1535.

solvents by virtue of its strength as a hydrogen bond donor, but is only present to the extent of 13% in carbon tetrachloride. Quantum mechanical calculations suggest that the difference in the two systems is attributable to greater ketone destabilization of **1k** than **2k** relative to cyclopentanone. We are currently in the process of extending this study of keto−enol relationships to highly fluorinated acyclic systems. The contrasting results will be reported shortly.

Experimental Section

^{19}F NMR spectra were recorded at 282.2 MHz. Trichlorofluoromethane was used as an internal standard, and all chemical shifts are reported on the Φ scale (ppm from internal trichlorofluoromethane, upfield negative). The ^{1}H NMR spectra were recorded at 300 MHz. Tetramethylsilane was used as an internal standard and chemical shifts are reported on the δ scale.

Carbon tetrachloride was distilled from phosphorus pentoxide and acetonitrile from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from potassium benzophenone ketyl. Perfluorocyclopentene was prepared from octachlorocyclopentene according to literature methods.[20] Where noted, Pyrex reaction vessels and NMR tubes were silated with refluxing *N*,*O*-bis(trimethylsilyl)acetamide, followed by several acetone rinses. The glassware was then dried in an oven for a minimum of 6 h at 140 °C.

Analytical gas chromatograms were obtained on a 25 m methyl silicone capillary column with flame ionization detector. The standard program was as follows: carrier pressure 25 p.s.i.; injector 150 °C; detector 200 °C; column temperature is noted in text. Isolation of pure compounds was done by preparative GC using a thermal conductivity detector. The column used was 25 ft × 1/4 in., 20% QF-1 on 80/100 mesh Chromosorb-W HP. The standard program was as follows: injector 190 °C; detector 210 °C; column temperature is noted in text. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377. Isolated yields were corrected for purity.

The quantum mechanical calculations were performed on Gaussian 92, Revision C.3.[21] Vibrational frequencies were calculated at the HF/6-31G** level of theory and were scaled by 0.893.[22] The electrostatic point charges were calculated with the Spartan package of programs.[23]

Perfluorocyclopenten-1-ol (1e). To a dry 50 mL round-bottom flask containing 15 mL of 1,2,4-trichlorobenzene and a stir bar was added 3.2 g (0.01 mol) of 1-benzoxyperfluorocyclopentene.[10] The reaction vessel was attached to the vacuum line, and two U-traps cooled to −13 °C (ethylene glycol/CO_2(s)) and −78 °C (2-propanol/CO_2(s)) were attached in series. Concentrated sulfuric acid (10 mL, 0.1 mol) was added, and the heterogeneous liquids were stirred vigorously for 15 min. All volatile products were removed under reduced pressure (30 mTorr) and collected in the U-traps. The −13 °C U-trap contained only 1,2,4-trichlorobenzene, and the −78 °C U-trap contained 1.7 g (77% yield) of enol **1e** (95%) and enone **4** (5%). The ^{19}F and ^{1}H NMR spectra of both compounds were consistent with those reported elsewhere.[10]

2-Bromoperfluorocyclopentane-1,1-diol (5). Freshly prepared enol **1e** (5.5 g, 26 mmol) was statically transferred at 15 mTorr to a 25 mL round-bottom flask containing 10 mL of dry acetonitrile. With the vessel cooled in an ice bath, bromine (2 mL, 39 mmol) was added at once followed by 5 mL of water. The residual bromine was quenched with 10 mL of a saturated solution of sodium thiosulfate, and the product was extracted with 3−15 mL portions of diethyl ether. The solvents were removed first on a rotary evaporator and then with a vacuum pump at 1 Torr. Analysis of the ^{1}H NMR spectrum revealed 0.6 equiv of acetonitrile complexed to the hydroxyl groups. Otherwise, the compound was shown to be pure by ^{19}F NMR spectroscopy: 7.6 g (88% yield) of a light yellow oil. ^{19}F NMR (CD_2Cl_2): Φ −107.1 (d of d, J = 245, 16 Hz, 1F); −121.2 (d of d, J = 236, 17 Hz, 1F); −122.0, −125.6 (AB q, J = 247 Hz, 2F); −131.2 (d, J = 245, 1F); −132.0 (d, J = 236 Hz, 1F); −132.9 (m, 1F). ^{1}H NMR (CD_2Cl_2): δ 3.8 (bs, 2H); 2.01 (s, 2H). IR (thin film, cm^{-1}): 3000−3600 (br), 1320, 1289, 1217, 1187, 1120, 1077, 1023, 958, 835, 805.

2-Bromoperfluorocyclopentanone (6). To an NMR tube containing 50 mg of diol **5** and 0.5 mL of chloroform-*d* was added 0.1 mL of concentrated sulfuric acid. The tube was shaken vigorously for 20 min, and the ^{19}F NMR spectrum indicated that formation of ketone **6** was complete. ^{19}F NMR ($CDCl_3$): Φ −119.9, −122.6 (AB q, J = 296 Hz, 2F); −122.7 (d, J = 258 Hz, 1F); −124.3, −128.9 (AB q, J = 250 Hz, 2F); −137.3 (d, J = 258 Hz, 1F); −149.4 (m, 1F). IR ($CDCl_3$, cm^{-1}): 1805, 1338, 1313, 1259, 1189, 1100, 1033, 1009, 980, 834.

2-Bromo-1,1-bis(trimethylsiloxy)perfluorocyclopentane (8). To a dry 25 mL round-bottom flask equipped with a Teflon stir bar were added 3 mL of *N*,*O*-bis(trimethylsilyl)acetamide (12 mmol) and 10 mL of methylene chloride. At ambient temperature, 1.0 g (3.3 mmol) of diol **5** dissolved in 5 mL of methylene chloride was added dropwise to the reaction vessel. After 15 min the reaction mixture was washed with one 10 mL portion of water, and the methylene chloride layer was dried over $MgSO_4$. The solution was concentrated, and the resulting liquid was passed through a silica gel column to remove residual silating agent, with methylene chloride as the eluting solvent. After removal of the solvent *in vacuo*, the residue was distilled at 60−62 °C/1.5 Torr to give **8** as a clear, colorless liquid (1.1 g, 74% yield). ^{19}F NMR ($CDCl_3$): Φ −106.3 (d, J = 244 Hz, 1F); −118.0 (d, J = 235 Hz, 1F); −121.2, −126.5 (AB q, J = 250 Hz, 2F); −130.4 (d, J = 244 Hz, 1F); −130.4 (m, 1F); −132.5 (d, J = 235 Hz, 1F). ^{1}H NMR ($CDCl_3$): δ 0.30 (s, 9H); 0.24 (s, 9H). MS *m*/*e*: 345, 343 ($C_8H_{10}BrF_6OSi^+$), 147 ($C_5H_{15}OSi^+$); 73 (Me_3Si^+). Anal. Calcd for $C_{11}H_{18}F_7Si_2O_2Br$: C, 29.27; H, 4.01; F, 29.47. Found: C, 29.18; H, 4.07; F, 29.53.

2*H*-Perfluorocyclopentane-1,1-diol (10). Enol **1e** (4.3 g, 0.020 mol) was statically transferred at 25 °C/30 mTorr to a 100 mL round-bottom flask containing 50 mL of acetonitrile. The contents of the reaction vessel were thawed, and then 10 mL of concentrated hydrochloric acid was added. After 2 h of stirring at 25 °C, the reaction mixture was diluted with 20 mL of distilled water. The organic layer was extracted with 3−25 mL portions of diethyl ether and dried over magnesium sulfate. Diethyl ether was removed on a rotary evaporator at 20 Torr to leave a milky white liquid. The reaction mixture contained 35% of **10**, 5% of **1e**, and 60% of acetonitrile by ^{19}F and ^{1}H NMR spectroscopy. To remove acetonitrile, 50 mL of 1,2-dichloroethane was added, and the mixture was distilled at 10 Torr to yield 2.7 g (50% yield) of residual liquid containing 85% of **10**, 5% of **1e**, and 10% of acetonitrile. ^{19}F NMR (CD_2Cl_2): Φ −116.2 (d, J = 263 Hz, 1F); −127.2 (d, J = 263 Hz, 1F); −127.3, −129.8 (AB q, J = 255 Hz, 2F); −131.0, −133.0 (AB q, J = 251 Hz, 2F); −214.1 (d, J = 45 Hz, 1F). ^{1}H NMR (CD_2Cl_2): δ 3.7 (s, 1H); 3.9 (s, 1H); 4.9 (d of multiplet, J = 45.2 Hz, 1H).

2*H*-1,1-Bis(trimethylsiloxy)perfluorocyclopentane (9). From 10. A dry 25 mL three-neck round-bottom flask equipped with a magnetic stir bar and dropping funnel was charged with 1.0 g (5 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide and 10 mL of dry methylene chloride. A solution of 85% pure diol **10** (0.5 g, 2 mmol) in methylene chloride was added dropwise with stirring at ambient temperature. After an additional 30 min of stirring, the reaction mixture was passed through a silica gel column with methylene chloride as the eluting solvent to remove unreacted silating agent. The methylene chloride was removed on a rotary evaporator to leave 0.6 g of 95% pure **9** (77% yield) as a clear, colorless liquid.

(20) Maynard, J. T. *J. Org. Chem.* **1962**, *218*, 112.

(21) Gaussian 92, Revision C.3: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schelegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc.; Pittsburgh, PA, 1992.

(22) Hehre, W. J.; Radom, L.; Schleyer, P.v.R.; Pople, J. S. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(23) Spartan: Hehre, W., Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92717.

The compound was obtained analytically pure by preparative gas chromatography (170 °C, t_R = 4.8 min): ^{19}F NMR ($CDCl_3$): Φ −114.1 (d, J = 257 Hz, 1F); −125.3, −129.2 (AB q, J = 249 Hz, 2F); −126.1 (d, J = 257 Hz, 1F); −129.1, −132.1 (AB q, J = 241 Hz, 2F); −204.8 (d, J = 51 Hz, 1F). ^{1}H NMR ($CDCl_3$): δ 0.25 (s, 9H); 0.26 (s, 9H); 4.60 (d of multiplet, J = 50.5 Hz, 1H). IR (CCl_4, cm^{-1}): 2963, 2903, 1345, 1325, 1302, 1214, 1188, 1199. MS m/e: 372 (M^+), 147 ($C_5H_{15}OSi_2^+$), 73 ($SiMe_3^+$, base). Anal. Calcd for $C_{11}H_{19}F_7O_2Si_2$: C, 35.48; H, 5.14; F, 35.71. Found: C, 35.66; H, 5.09; F, 35.49.

From 8. A solution of 50 mg (0.11 mmol) of compound **8** and 38 mg (0.13 mmol) of tri-*n*-butyltin hydride in 0.5 mL of benzene-d_6 was irradiated in a Pyrex NMR tube for 30 min with a 450 W medium-pressure Canrad-Hanovia lamp. Analysis by ^{19}F NMR spectroscopy revealed complete and clean conversion to compound **9**.

2*H*-Perfluorocyclopentanone (1k). To a 5 mL round-bottom flask containing 80 mg of compound **9** (0.20 mmol) and 0.6 mL of carbon tetrachloride was added 0.1 mL of concentrated sulfuric acid (2.0 mmol). The contents were stirred for 30 min, and then all volatiles were removed at 30 mTorr to a U-trap cooled to −78 °C. The contents of the U-trap were statically transferred (25 °C/30 mTorr) to a flame-dried NMR tube. After the tube had been thawed carefully under a nitrogen atmosphere, 1 μL (8.7×10^{-3} mmol) of hexafluorobenzene was added. Integration of the ketone-to-hexafluorobenzene signals in the ^{19}F NMR spectrum revealed 0.18 mmol of ketone **1k** (90% yield). ^{19}F NMR (CCl_4): Φ −125.3, −128.1 (AB q, J = 298 Hz, 2F); −130.9 (d, J = 266 Hz, 1F), ; −131.1, −132.2 (AB q, J = 258 Hz, 2F); −142.5 (d, J = 266 Hz, 1F); −218.0 (d, J = 48 Hz, 1F). ^{1}H NMR (CD_2Cl_2): δ 5.4 (d of multiplet, J = 48.3 Hz). IR (gas phase, cm^{-1}): 2932, 1817, 1357, 1316, 1262, 1185, 1156, 1032, 1000, 955, 720.

Equilibration of 1k and 1e. To the sample of 0.18 mmol of ketone **1k** in carbon tetrachloride prepared above was added 18 μL (1.8×10^{-3} mmol) of a 0.1 M solution of NMP in carbon tetrachloride. The equilibration was monitored by ^{19}F NMR spectroscopy until all ketone had converted to enol **1e**.

1-*tert*-Butoxyperfluorocyclopentene (12). To a dry 250 mL three-neck round-bottom flask containing 50 mL of dry THF and 9.5 mL (71 mmol) of perfluorocyclopentene was added dropwise 71 mL of 1 M (71 mmol) potassium *tert*-butoxide in THF at −78 °C under N_2 atmosphere. After 1.5 h of stirring at that temperature the reaction mixture was quenched with 50 mL of water. The organic fraction was extracted with three 25 mL portions of pentane and dried over magnesium sulfate. A dynamic transfer at 25 °C/30 mTorr left behind all colored material, and the solvent was removed at 20 Torr on a rotary evaporator. Capillary gas chromatography (50 °C) revealed the reaction product to contain 60% of **12** (t_R = 2.3 min), 5% of **12a** (t_R = 2.0 min), and 35% of THF (t_R = 1.6 min). This product composition is sufficiently pure to be used in the preparation of compound **13**.

Ethers **12** and **12a** were freed of THF by gravity column chromatography on silica gel with pentane as the eluting solvent to give 8.8 g (47% yield) of clear, colorless liquid after removal of the pentane. ^{19}F NMR of **12** ($CDCl_3$): Φ −116.3 (s, 2F); −117.7 (s, 2F); −131.3 (s, 2F); −152.7 (s, 1F). ^{1}H NMR of **12** ($CDCl_3$): δ 1.4 (s). IR (thin film, cm^{-1}): 2990, 1713, 1365, 1292, 1250, 1144, 1012, 978. MS of **12** m/e: 251 ($C_8H_6F_7O^+$), 57 ($C_4H_9^+$, base). MS of **12a** m/e: 251 ($C_8H_6F_7O^+$), 193 ($C_5F_7^+$, base), 57 ($C_4H_9^+$).

2*H*-1-*tert*-Butoxyperfluorocyclopentene (13). A 100 mL round-bottom flask equipped with a stir bar and water condenser was charged with 9.4 g (32 mmol) of 90% pure **12** and 25 mL of dry tetrahydrofuran. Lithium aluminum hydride (1.2 g, 32 mmol) was added cautiously in 0.2 g increments at 0 °C, and the contents were stirred for 1 h. With the vessel cooled in an ice bath, the excess lithium aluminum hydride was quenched by dropwise addition of 5% hydrochloric acid until evolution of hydrogen ceased. The product was extracted with 3 × 15 mL of ether; the extract was washed with 15 mL of saturated brine and dried over $MgSO_4$. After gravity filtration, ether and THF were removed at aspirator pressure to leave a liquid containing 90% of **13** and 10% of **13a**. The two isomers were separated by gravity column chromatography on silica gel (pentane) with **13a** eluting just before **13**. A total of 4.2 g of **13** (53% yield) was isolated after removal of the solvent. ^{19}F NMR of **13** ($CDCl_3$): Φ −102.7 (s, 2F); −119.6 (s, 2F); −131.9 (s, 2F). ^{1}H NMR of **13** ($CDCl_3$): δ 1.53 (s, 9H); 5.32 (s, 1H). IR of **13** (thin film, cm^{-1}): 2992, 1651, 1372, 1344, 1265, 1250, 1100, 1020, 958. MS of **13** m/e: 233 ($C_8H_7F_6O^+$), 57 ($C_4H_9^+$, base). Anal. Calcd for $C_9H_{10}F_6O$: C, 43.56; H 4.06; F, 45.93. Found: C, 43.86; H, 4.23; F 45.77. MS of **13a** m/e: 233 ($C_8H_7F_6O^+$), 57 ($C_4H_9^+$, base).

2*H*-Perfluorocyclopenten-1-ol (2e) and 2,2*H*-Perfluorocyclopentanone (2k). Enol ether **13** (34 mg, 13 mmol) and 80 mg of bibenzyl (39 mmol) were added to a silated 5 mL side-arm flask containing 2 mL of 1,2,4-trichlorobenzene. Concentrated sulfuric acid (0.015 mL, 26 mmol) was added to the reaction vessel with efficient magnetic stirring. After 1 min the volatile products were passed though two U-traps connected in series at a pressure of 10 mTorr. The first trap, cooled to −13 °C (ethylene glycol/CO_2(s)), collected the solvent and bibenzyl. The second trap, cooled to −78 °C, contained the more volatile **2e**, **2k**, and enone **14**. The contents of the latter U-trap were statically transferred to an NMR tube containing dry chloroform-*d*. Integration of the signals in the ^{19}F NMR spectrum showed the reaction product to consist 70% of **2k**, 25% of **2e**, and 5% of **14**. ^{19}F NMR of **2e** ($CDCl_3$): Φ −104.4 (s, 2F); −120.0 (s, 2F), −130.5 (s, 2F). ^{1}H NMR of **2e** ($CDCl_3$): δ 5.35 (s, 1H), 5.70 (s, 1H). ^{19}F NMR of **2k** ($CDCl_3$): Φ −116.5 (s, 2F); −129.8 (s, 2F), −139.8 (s, 2F). ^{1}H NMR of **2k** ($CDCl_3$): δ 2.82 (d of d).

Equilibration of 2k and 2e. A mixture of **2k**, **2e**, and **14** as prepared above was statically transferred at 25 °C (30 mTorr) to a cold NMR tube (−196 °C) containing 0.5 mL of carbon tetrachloride and 2 μL (1.7×10^{-2} mmol) of hexafluorobenzene as an internal standard. After the tube had been carefully warmed, integration of the ketone, enol, and hexafluorobenzene signals revealed 1.0×10^{-1} mmol of enol-plus-ketone. A 10 μL aliquot of a 0.1 M solution of 1-methyl-2-pyrrolidone (1.0×10^{-3} mmol) in carbon tetrachloride was added to the NMR tube via syringe. The ^{19}F NMR spectrum was recorded every 2 h until a constant **2k**/**2e** (87/13) ratio was established.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for support of this research.

Supporting Information Available: The final optimized geometries (6-31G**) in Cartesian coordinates for ketones **1k**, **2k** and enols **1e**, **2e** (syn and anti) (3 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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