Novel Keto–Enol Systems

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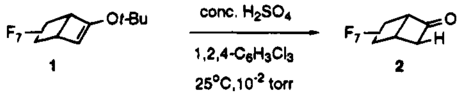
Received July 22, 1994

The enol content of simple ketones at equilibrium is extremely small; e.g., $4.7 \times 10^{-7}\%$ for acetone and $4.2 \times 10^{-5}\%$ for cyclohexanone (H_2O, 25 °C).[1] We wish to report sharply contrasting findings for perfluorinated keto–enol systems.[2]

In the course of a synthesis, we had occasion to prepare bicyclic ketone **2** by acid-induced cleavage of *tert*-butyl enol ether **1**. The ketone was obtained in a cold trap in 78% yield.[3]



1 **2**

Further investigation revealed that the cleavage of **1** initially gave only the enol **3**,[4] which rapidly tautomerized to **2**. Since

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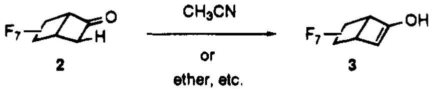
tautomerization was very slow in carbon tetrachloride solution, it was possible to prepare a stable solution of enol by treating a solution of **1** in that solvent containing a little benzene[5] with concentrated sulfuric acid and then separating the layers.

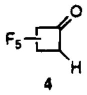
The extremely weak base *N*-methylpyrrolidone (NMP) catalyzes equilibration of the keto and enol forms.[6] When a trace of this catalyst was added to a dilute solution of ketone in carbon tetrachloride, a small amount of enol slowly formed: $K_{3/2} = 0.07 \pm 0.01$. Equilibrium was also approached starting with enol. Use of more than a trace of NMP drives the equilibrium strongly toward enol, as a consequence of hydrogen bonding to the amide. Even acetonitrile is capable of both catalyzing keto–enol equilibration and driving the equilibrium by hydrogen bonding. The potency of **3** as a hydrogen-bond donor is apparent in the fact that $K_{3/2} = 1.94 \pm 0.1$ in carbon tetrachloride containing 1.6% acetonitrile (v/v). Thus, in mildly Lewis basic



2 **3**

solvents such as ether and THF as well as acetonitrile and NMP, the enolization equilibrium lies too far to the right to allow detection of ketone. This is apparently the first example of a simple unhindered, unconjugated keto–enol system in which enol has been demonstrated to be the exclusive form in any medium.[7]

In the 1970s Bekker *et al.* reported the synthesis and chemistry of a series of highly fluorinated enols and the corresponding ketones.[8] These compounds were amazingly stable in what was described as a *kinetic* sense, stoutly resisting equilibration at elevated temperatures and in powerful acids (e.g., triflic, sulfuric). Under conditions which permitted tautomerization, some enols ketonized completely, and there was no case in which an enol was shown to be present in a detectable amount at equilibrium. One of the keto–enol systems they synthesized was the monocyclic counterpart (**4** and **5**) of ours, but no information about the relative energy of the independently synthesized forms was given.[9–11] The Russian workers stated that, as a consequence of resistance to acids and decomposition by bases, "isomerization of either form into the other cannot be thermally or catalytically induced".[11]



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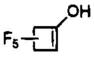

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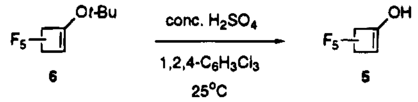
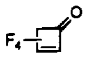
On the chance that the four-membered ring in our system confers special stability on the enol, we wished to study the equilibrium between **4** and **5**. In contrast to the transformation of enol ether **1** into ketone **2**, analogous treatment of enol ether **6** gave exclusively enol **5**.[12] We were unable to find conditions under which **5** gave a detectable quantity of the keto form **4**, and therefore we synthesized **4** via Bekker's route.[11] As was the case for **2** and **3**, acetonitrile and NMP were found to catalyze the equilibration of ketone **4**. When 0.01 equiv of NMP was added to a 0.03 M solution of **4** (1 equiv) in carbon tetrachloride, ^{19}F NMR revealed gradual development of signals for the enol. In addition, however, three other compounds were formed. One was the known enone **7**,[9–11] produced by dehydrofluorination of **5** and/or **4**. The other two were the diastereomeric hemiketals **8** and **9**, generated by addition of enol **5** to ketone **4**. Formation of these compounds impeded



6 **5**



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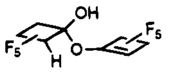

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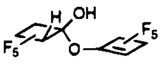

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[1] Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1990**, *112*, 4862.

[2] Portions of this work were presented by R.A.C. at the 199th National Meeting of the American Chemical Society, Boston, MA, April 22–27, 1990, Abstract FLUO 0022, and by P.E.L. at the 24th ACS Northeast Regional Meeting, Burlington, VT, June 19–22, 1994, Paper 128.

[3] ^{19}F NMR ($CDCl_3$): Φ −111.8, −130.8 (AB q, J = 222 Hz, 2F); −116.0, −125.6 (AB q, J = 229 Hz, 2F); −182.0 (s, 2F); −186.0 ppm (subsplit d, 1F). ^1H NMR ($CDCl_3$): δ 5.4 (d, J = 51 Hz). IR (vapor): 2910 (ν_{CH}), 1838 cm^{-1} ($\nu_{C=O}$).

[4] ^{19}F NMR (CCl_4): Φ −117.4, −126.1 (AB q, J = 212 Hz, 2F); −118.3, −125.8 (AB q, J = 212 Hz, 2F); −126.8 (d, J = 22.6 Hz, 1F); −191.5 (s, 1F); −197.3 ppm (s, 1F). IR (CH_3CN): 3100 (ν_{OH}), 1730 cm^{-1} ($\nu_{C=C}$). MS *m/e*: 222 (M^+), 175 ($C_5HF_6^+$), 156 ($C_5HF_5^+$), 106 ($C_4HF_3^+$, base).

[5] In the absence of benzene, which scavenges *tert*-butyl cations, the reaction is not clean and ketonization is quite rapid. The ketonization catalyst is believed to be bisulfate ion.

[6] The Russian group whose work is described later in the text made frequent use of NMP as a base for catalyzing reactions of perfluoro enols. (a) Bekker, R. A.; Melikyan, G. G.; Lur'e, E. P.; Dyatkin, B. L.; Knunyants, I. L. *Dokl. Akad. Nauk SSSR* **1974**, *217*, 1320; Engl. transl., p 572. (b) Bekker, R. A.; Melikyan, G. G.; Dyatkin, B. L.; Knunyants, I. L. *Zh. Org. Khim.* **1975**, *11*, 1370; Engl. transl., p 1356. (c) Bekker, R. A.; Melikyan, G. G.; Dyatkin, B. L.; Knunyants, I. L. *Zh. Org. Khim.* **1975**, *11*, 2370; Engl. transl., p 2415.(d) Bekker, R. A.; Badanyan, Sh. O.; Melikyan, G. G.; Knunyants, I. L. *Zh. Org. Khim.* **1977**, *13*, 1582; Engl. transl., p 1461.

[7] Remarkable enols stabilized by oxygen and chlorine substituents have recently been described; they approach **3** in stability. Ettlinger, M. G.; Watson, K. J.; Jaroszewski, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 1557.

[8] For a concise summary of this work, which encompasses 19 papers, see: Hart, H.; Rappoport, Z.; Biali, S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1990; pp 502–14.

[9] Bekker, R. A.; Popkova, V. Ya.; Knunyants, I. L. *Dokl. Akad. Nauk SSSR* **1976**, *229*, 870; Engl. transl., p 514.

[10] Bekker, R. A.; Popkova, V. Ya.; Knunyants, I. L. *Dokl. Akad. Nauk SSSR* **1976**, *231*, 864; Engl. transl., p 700.

[11] Bekker, R. A.; Popkova, V. Ya.; Knunyants, I. L. *Dokl. Akad. Nauk SSSR* **1977**, *235*, 103; Engl. transl., p 370.

[12] The Russian group prepared the enol by distillation of the benzyl enol ether from concentrated sulfuric acid (ref 9).

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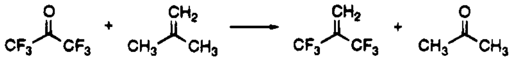
enolization, allowing time for a small amount of dehydrofluorination to occur. This problem was circumvented by carrying out the reaction at higher dilution. With 0.01 equiv of NMP in a 0.0013 M solution of **4** in carbon tetrachloride, enolization was clean and quantitative. Thus, *the enol is much stabler thermodynamically than its ketone even in a solvent of extremely low Lewis basicity*. No medium has been found in which ketone is detectable at equilibrium.

Ab initio quantum mechanical calculations[13] show **4** to be stabler than **5** by 3.1 kcal/mol,[14] and **2** to be stabler than **3** by 7.9 kcal/mol. Even with allowances for entropy and solvent versus gas phase differences, calculations at this level of theory certainly do not do justice to the relative stability of the perfluoro enols.[15] On the other hand, they do correctly predict the monocyclic enol to be substantially stabler compared to ketone than the bicyclic one.[16] Calculations for a series of keto–enol systems further indicate that the four-membered ring in the two systems discussed above does *not* bias keto–enol equilibrium in favor of enol. We therefore predict that the remarkable thermodynamic stability found for enols **3** and **5** relative to their ketones will turn out to be characteristic of other highly fluorinated keto–enol systems.[17]

As to the reason(s) for this, perfluorination is known to destabilize ketones. This effect is reflected in the voracity with which perfluoro ketones undergo hydration and other addition reactions;[18] it is illustrated by the following isodesmic reaction, whose ΔH_r is calculated to be -18.2 kcal/mol.[13]



The effect can be understood in terms of competition for electron density between the electron-deficient carbonyl carbon and electron-withdrawing groups. One might inquire whether perfluorination has the additional consequence of stabilizing the enol. The answer appears to be negative, as indicated by the ΔH_r for the isodesmic transformation below: -6.9 kcal/mol.[13]

We will explore the generality of the phenomena discussed here and investigate further the chemistry of perfluorinated keto–enol systems.

Acknowledgment. The authors wish to thank the Air Force Office of Scientific Research and the National Science Foundation for support of this research. We are grateful to James Gino and John Azariah for preliminary synthetic work. D.M.L. thanks Professor David A. Evans for his generous hospitality, which included access to his computing facilities, during a sabbatical at Harvard.

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(13) The calculations were carried out with geometry optimization at the 6-31G** level using the Spartan package of programs (Hehre, W., Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92717).

(14) At this level of theory, cyclobutanone itself is stabler than its enol by 19.6 kcal/mol. On the basis of thermochemical group equivalents, this energy difference was estimated to be 18.7 kcal/mol (Brickhouse, M. D.; Squires, R. R. *J. Phys. Org. Chem.* **1989**, *2*, 389).

(15) The calculated energetic advantage of the keto form diminishes as the quality of the theory improves. At the AM1, STO-3G, 6-31G* and 6-31G** levels, **4** is stabler than **5** by 19.2, 13.0, 6.2, and 3.1 kcal/mol, respectively (geometry optimized in each case).

(16) They also indicate considerably less stability for pentafluoroacetone enol relative to its ketone than in the case of **2**/**3**, consistent with literature evidence that the keto form is stabler even in Lewis basic solvents (refs 6a,b).

(17) The Moscow workers reported that perfluorocyclohex-1-enol undergoes ketonization (and competing dehydrofluorination) in water. Bekker, R. A.; Popkova, V. Ya.; Knunyants, I. L. *Dokl. Akad. Nauk SSSR* **1977**, *233*, 591; Engl. transl., p 187. Bekker, R. A.; Popkova, V. Ya. *Izv. Akad. Nauk SSSR* **1978**, 2775; Engl. transl., p 2476. Since the ketone surely hydrated in this medium and the hydration equilibrium lies far to the right for saturated perfluoro ketones, this report does not demonstrate that the keto form is stabler than the enol.

(18) 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.