J. Am. Chem. Soc. **1998,** *120,* 11830−11831

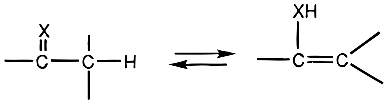
2,4,6-Trimethylthioacetophenone and Its Enol. The First Quantitative Characterization of a Simple Thiocarbonyl System in Aqueous Solution

A. J. Kresge* and Q. Meng

Department of Chemistry, University of Toronto
Toronto, Ontario M5S 3H6, Canada

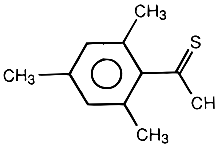
Received July 30, 1998

It is known that thiocarbonyl compounds have a much stronger tendency to undergo tautomeric change to their enol isomers, eq 1, X = S, than is the case in the corresponding oxygen systems,

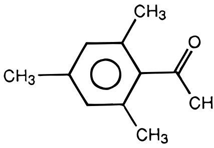


(1)

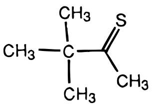
eq 1, X = O,[1] and since thiols are stronger acids than alcohols, thioenols are also expected to be more acidic than their oxygen analogues. However, little quantitative information concerning such differences for simple carbonyl systems is available.[2] We wish to report that we have now determined keto−enol equilibrium and acid dissociation constants, as well as rate constants for interconversion of the various species, for 2,4,6-trimethylthioacetophenone, **1**, in aqueous solution. This is the first



1



2



3

quantitative characterization of a simple thiocarbonyl system in this solvent, and together with published information on the oxygen analogue 2,4,6-trimethylacetophenone, **2**,[3] it provides the first quantitative comparison of oxygen and sulfur carbonyls in the same medium.

We initially sought to examine *tert*-butyl methyl thioketone, **3**, but we soon discovered that this substance undergoes facile hydrolysis in aqueous solution at rates comparable to those of keto−enol interconversion. Since hydrolysis probably occurs through nucleophilic attack of water at the thiocarbonyl carbon, we reasoned that this complication might be removed by introducing steric hindrance to such attack in a substrate such as **1** and that this substance would consequently be more amenable to detailed study. That proved to be the case.

We prepared 2,4,6-trimethylthioacetophenone by treating the oxygen ketone, **2**, with Lawesson's reagent.[4] The product obtained proved to be a mixture of keto and enol tautomers whose ^{1}H NMR spectrum in $CDCl_3$ solution indicated a keto−enol ratio of 5:1.[5]

Treatment of an equilibrated aqueous solution of this mixture with Ellman's reagent, a substance commonly used for quantitative estimation of thiol groups,[6] gave an instantaneous uptake of some reagent followed by a slower consumption of an additional amount, with the slower consumption reaching a limiting value in an exponential fashion. The initial fast uptake may be attributed to reaction of thioenol already present in the solution at equilibrium, and the subsequent slower consumption may be assigned to formation of additional enol by isomerization of the keto form. This shows that significant amounts of enol exist in equilibruim with the keto isomer in aqueous solution. The amplitude of the initial uptake, moreover, increased at the expense of the amplitude of the slower consumption with increasing basicity of the medium. This indicates further that more enol species (enol + enolate) exist at equilibruium in the more basic solutions, and that the keto isomer is undergoing appreciable ionization as a carbon acid in the pH range investigated (pH 6−8).

This interpretation of these phenomena leads to eq 2 in which

$$\frac{\text{amplitude of initial uptake}}{\text{amplitude of subsequent uptake}} = R = \frac{[\mathrm{EH}] + [\mathrm{E}^-]}{[\mathrm{KH}]} \qquad (2)$$

EH, E$^-$, and KH represent enol, enolate, and keto forms, respectively. Introducing definitions of the keto−enol equilibrium constant, $K_E = [EH]/[KH]$, and the ionization constant of the keto form as a carbon acid, $Q_a^K = [E^-][H^+]/[KH]$, then gives eq 3,

$$R = K_E + Q_a^K/[H^+] \qquad (3)$$

which predicts that R should be a linear function of $1/[H^+]$. The data obtained conformed to this relationship well, and least-squares analysis produced the following results: $K_E = (1.15 \pm 0.05) \times 10^{-1}$, $pK_E = 0.94 \pm 0.02$, and $Q_a^K = (1.19 \pm 0.05) \times 10^{-8}$ M, $pQ_a^K = 7.93 \pm 0.02$.[7] Use of the further relationship $Q_a^E = K_E/Q_a^K$, in which Q_a^E is the ionization constant of the enol ionizing as a sulfur acid, also gives the additional result $Q_a^E = (1.03 \pm 0.06) \times 10^7$ M, $pQ_a^E = 6.99 \pm 0.02$.[7]

The UV spectrum of an equilibrated acidic aqueous solution of the present ketone plus enol consists of end absorption with a shoulder at $\lambda \cong 225$ nm, which shifts to $\lambda \cong 250$ nm when the solution is made basic. This change may be attributed to ionization of the enol. Absorbances measured at a constant total substrate concentration in solutions of different acidity gave a smooth titration curve governed by an apparent acid ionization constant, $Q_a^{eq} = [E^-][H^+]/([E] + [K])$, and the data obtained produced the result $Q_a^{eq} = (8.98 \pm 1.15) \times 10^{-9}$ M, $pQ_a^{eq} = 8.05 \pm 0.06$.[7] This equilibrium constant may also be expressed in terms of K_E and Q_a^K as $Q_a^{eq} = Q_a^K/(1 + K_E)$, and use of the values of these constants obtained in the experiments described above employing Ellman's reagent gives $Q_a^{eq} = (1.07 \pm 0.04) \times 10^{-8}$ M, $pQ_a^{eq} = 7.97 \pm 0.02$.[7] These two independent determinations of Q_a^{eq} agree with one another very well, and that lends confidence to our interpretation of the phenomena observed.

We also performed kinetic measurements of the rate of approach to keto−enol equilibrium in the present system, using perchloric acid, sodium hydroxide, and buffer solutions. The experiments in buffers were done by using series of solutions of constant buffer ratio but varying total buffer concentration, and extrapolation of these data to zero buffer gave intercepts,

---

(1) See, for example: Duus, F. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, pp 385−388.

(2) Some recent studies providing limited information are described in: (a) Selzer, T.; Rappoport, Z. *J. Org. Chem.* **1996**, *61*, 5462−5467. (b) Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Popik, V. V.; Rappoport, Z.; Selzer, T. *Can. J. Chem.* **1998**, *76*, 657−661.

(3) Kresge, A. J.; Schepp, N. P. *J. Chem. Soc., Chem. Commun.* **1989**, 1548−1549.

(4) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061−5087.

(5) Satisfactory ^{13}C NMR and high-resolution mass spectra were also obtained.

(6) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70−77. Riddles, P. W.; Blakeley, R. L.; Zerner, B. In *Methods in Enzymology*; Hirs, C. H. W., Timasheff, S. N., Eds.; Academic Press: New York, 1983; Vol, 91, pp 49−60.

(7) This is a *concentration* equilibrium constant applicable at the ionic strength of the present measurements, 0.10 M.

10.1021/ja9826993 CCC: $15.00

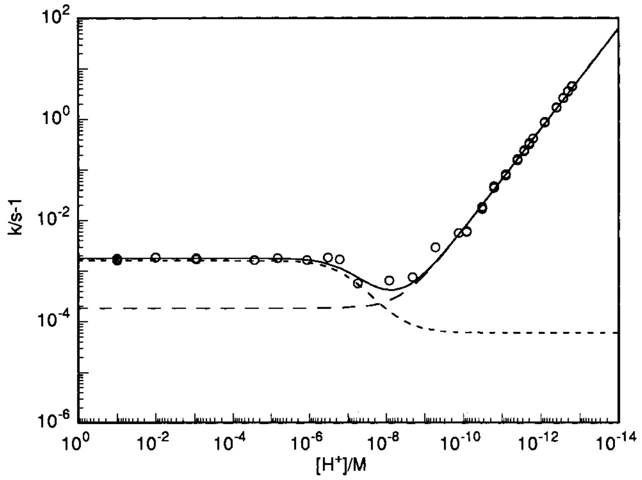
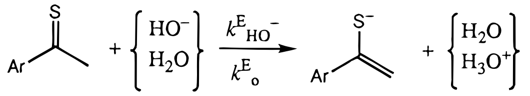
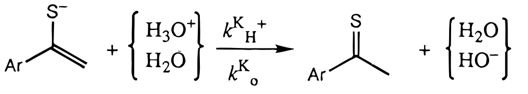


Figure 1. Rate profile for keto−enol interconversion in the 2,4,6-trimethylthioacetophenone system; (circles and solid line) rate of approach to equilibrium, (dashed line) rate of enolization, and (dotted line) rate of ketonization.

which, together with the perchloric acid and sodium hydroxide results, provide the rate profile shown in Figure 1. Analysis of this profile in terms of enolization effected by proton transfer from ketone to hydroxide ion ($k^E_{HO^-}$) and water (k^E_o), eq 4, and ketonization effected by protonation of enolate ion by hydronium ion ($k^K_{H^+}$) and water (k^K_o), eq 5, leads to the following results: $k^E_{HO^-} = (4.00 \pm 0.10) \times 10^1$ M^{-1} s^{-1}, $k^E_o = (1.82 \pm 0.08) \times 10^{-4}$ s^{-1}, $k^K_{H^+} = (1.33 \pm 0.32) \times 10^4$ M^{-1} s^{-1}, $k^K_o = (5.97 \pm 0.24) \times 10^{-5}$ s^{-1}, and $Q_a^E = (1.20 \pm 0.32) \times 10^{-7}$ M, p$Q_a^E = 6.92 \pm 0.11$.[7] The latter value agrees well with other determinations of this quantity described above. These rate constants were used to construct the various lines shown in Figure 1.



(4)



(5)

Buffer catalysis was strong in all of the buffer solutions examined, and analysis of results obtained at different buffer ratios showed the form of catalysis to be both general acid and general base. This is as expected, for the rate constants measured were specific rates of approach to equilibrium, which are sums of enolization plus ketonization rate constants; enolization will be a general base-catalyzed reaction and ketonization will be a general acid-catalyzed process.[8]

Table 1. Comparison of 2,4,6-Trimethylacetophenone and 2,4,6-Trimethylthioacetophenone Keto−Enol Systems

	2,4,6-trimethyl-acetophenone[a]	2,4,6-trimethylthio-acetophenone
pK_E	6.92	0.94
pQ_a^E [b]	10.69	6.99
pQ_a^K [b]	17.61	7.93

[a] Reference 3. [b] Reference 7.

Further support for interpretation of the rate profile in terms of the individual reactions shown in eqs 4 and 5 is provided by isotope effects. The breakdown of observed rate constants into contributions from enolization and ketonization presented in Figure 1 indicates that enolization dominates in the basic region, and consideration of the relative values of k^E_o and $k^E_{HO^-}$[HO$^-$] shows that this reaction will occur through hydroxide-ion catalysis in dilute sodium hydroxide solutions. The solvent isotope effect on such a process can be expected to be inverse ($k_H/k_D < 1$) since a solvated hydroxide ion is consumed and the hydrogen−oxygen bonds of the solvent water molecules thus liberated are strengthened.[9] Comparison of rates of reaction in H$_2$O and D$_2$O gave $k^E_{HO^-}/k^E_{DO^-} = 0.83 \pm 0.01$, consistent with this expectation. The substrate isotope effect, on the other hand, should be in the normal direction ($k_H/k_D > 1$) and probably of considerable magnitude, and the measured value, $k_H/k_D = 5.89 \pm 0.04$, is again consistent with expectation.

The presently determined keto−enol equilibrium and acid dissociation constants are compared with their counterparts for the corresponding oxygen system in Table 1. It may be seen that K_E for the sulfur ketone is very much greater than that for its oxygen analogue, by 6 orders of magnitude; this difference is nicely consistent with the prediction $K_E(S)/K_E(O) \geq 10^6$ made recently for a different oxygen−sulfur simple ketone pair.[2a] The greater enol content of thioketones has been attributed to the relative weakness of the sulfur−oxygen π-bond.[2a] The data of Table 1 also show the sulfur enol to be a considerably stronger acid than its oxygen analogue. This is consistent with the greater acidity of thiophenol (pK_a = 6.49)[10] over phenol (pK_a = 10.00),[11] and it agrees as well with the only other comparison of acid strengths of sulfur and oxygen enols, in which triphenylethenethiol, pQ_a^E = 8.49, was found to be a stronger acid than its oxygen analogue by ΔpQ_a^E = 2.88.[2b] These differences in K_E and Q_a^E combine to make 2,4,6-trimethylthioacetophenone a stronger carbon acid than its oxygen counterpart by a remarkably large 10 orders of magnitude.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

JA9826993

---

[8] Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1990; pp 390−480.

[9] Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177−273.

[10] Biggs, A. I. *Trans. Faraday Soc.* **1956**, *52*, 35−39.

[11] Liotta, C. L.; Perdue, E. M.; Hopkins, H. P., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7981−7985.