Keto–Enol Equilibrium of Methyl Fluorene-9-thionocarboxylate and Acidity Constants of the Enol and the Keto Forms of This and Related Oxygen and Sulfur Esters in Aqueous Solution

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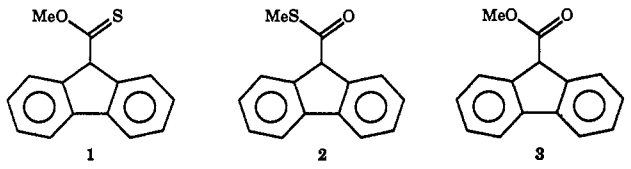
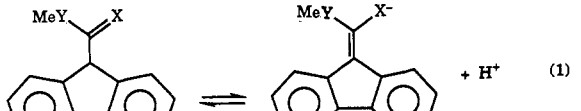
The recent development of new methods for generating enols in solution under conditions where they can be observed and studied directly has produced a wealth of information about the enol isomers of simple aldehydes and ketones.[1] Much less is known about enols of carboxylic acid esters and even less about their sulfur analogs. We report that we have produced the enol of methyl fluorene-9-thionocarboxylate, **1**, in aqueous solution and have determined its keto–enol equilibrium constant as well as acid dissociation constants of the keto and enol forms in that medium. We have also determined acidity constants for the keto



1 2 3

forms of the related esters methyl fluorene-9-thiolcarboxylate, **2**, and methyl fluorene-9-carboxylate, **3**. This constitutes the first evaluation of these quantities for related oxygen and sulfur esters. Comparison of the acidity of **2** and **3** is of special interest because of the generally held belief that thiol esters ionize to carbanions more readily than oxygen esters and that this is the basis of their common occurrence in biological reactions.[3]

The esters **1–3** undergo ionization to their enolate anions in basic aqueous solution, eq 1, as evidenced by UV spectral changes and the manner in which these changes occur and depend upon the acid–base properties of the medium. In acidic solutions these



(1)

esters have UV spectra typical of compounds containing the fluorene moiety, with strong bands in the region λ = 260–270 nm. When the solutions are made basic, these bands are replaced by somewhat stronger absorbances at longer wavelengths, λ = 320–380 nm, characteristic of fluorenyl carbanions. These spectral changes are reversible and are similar to those observed for the carbon-acid ionization of 9-acylfluorenes.[4] They give

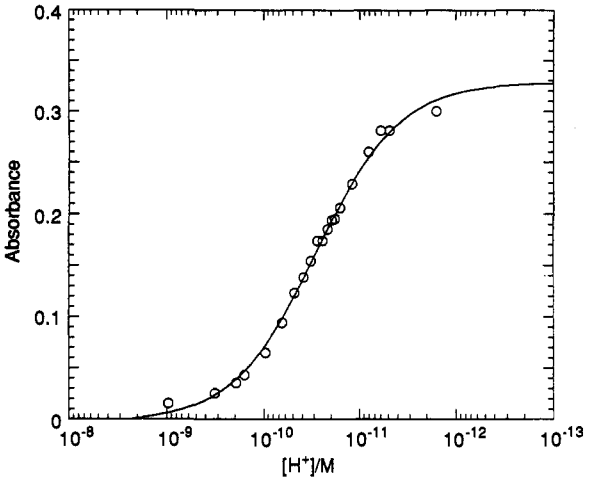


Figure 1. Titration curve for the ionization of methyl fluorene-9-thiolcarboxylate (**2**) in aqueous solution at 25.0 °C, ionic strength = 0.10 M; absorbance measurements at λ = 346 nm.

smooth titration curves, as is illustrated by Figure 1, and least squares fitting using the expected relationship, eq 2,[5] produces

$$A = \frac{A_B Q_a^K + A_A[H^+]}{Q_a^K + [H^+]} \qquad (2)$$

acidity constants whose values are the same for approach to equilibrium from the acidic side as from the basic side; *e.g.*, for **2**, Q_a^K = 10.55 ± 0.03 (acidic side) and pQ_a^K = 10.49 ± 0.03 (basic side). The results, moreover, agree well with acidity constants determined as ratios of rate constants where such determination is possible. Best value (weighted average) acidity constants for all three esters are listed in Table 1. The result for methyl fluorene-9-carboxylate, pQ_a^K = 11.52, is consistent with the value pQ_a^K = 11.65 deduced from rates of hydrolysis of this substance.[7]

These carbon-acid ionizations and their reversals are rapid, but some of their rates can be measured by stopped-flow techniques. The thiono ester, **1**, proved to be the most amenable for such study. Ketonization of its enolate ion showed general acid catalysis in acetic acid and biphosphate ion buffers and gave the hydronium ion isotope effect k_{H^+}/k_{D^+} = 3.50 ± 0.09 in dilute perchloric acid solutions. This is classic evidence for rate-determining proton transfer from catalyst to substrate and substantiates the expected β-carbon protonation mechanism for the ketonization reaction.

Rates of ketonization of this substrate are directly proportional to acid concentration at low acidities, but this proportionality drops off in more concentrated acids, and acid catalysis becomes saturated. This phenomenon is barely discernible in H_2O solutions, where the rapidity of the reaction limits measurements to acidities at which it is hardly visible, but, as Figure 2 shows, catalytic saturation is clearly apparent for the slower reaction in D_2O solution. This saturation is produced by conversion of the enolate ion to its less reactive enol form, eq 3. Least squares

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(1) For a comprehensive review, see: *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990.

(2) These esters were prepared by standard methods, and their structures were confirmed by their spectral properties. All three substances were very susceptible to oxidation in aqueous solution, and all measurements were therefore made using degassed solvents.

(3) See, *e.g.*: Abeles, R. H.; Frey, P. A.; Jencks, W. P. *Biochemistry*; Jones and Bartlett: Boston, 1992; pp 52–53.

(4) Harcourt, M. P.; More O'Ferrall, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 822–823; *Bull. Soc. Chim. Fr.* **1988**, 407–414. Harcourt, M. P. Ph.D. Thesis, National University of Ireland, 1987.

(5) Measurements were made at constant stoichiometric substrate concentrations (*ca.* 10^{-4} M); the parameters A_B and A_A are absorbances of the substrate completely in the basic and acidic forms, respectively, and Q_a^K is the acidity constant of the keto isomer.[6]

(6) This is a concentration dissociation constant appropriate to the ionic strength of the measurements, μ = 0.10 M.

(7) Alborz, M.; Douglas, K. T. *J. Chem. Soc., Perkin Trans. 2* **1982**, 331–339.

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Table 1. Summary of Equilibrium and Rate Constants for 9-Substituted Fluorene Derivatives[a]

Quantity/9-Substituent	MeO, S (1)	MeS, O (2)	MeO, O (3)	HO, O[b] (4)	H, O[c] (5)	Me, O[c] (6)
pQ_a^K	7.40	10.51	11.52	11.73	6.19	9.44
pQ_a^E	1.60			2.23	7.41	7.66
pK_E	5.80			9.50	−1.22	2.28
$k'_{H^+}/M^{-1}\,s^{-1}$	1.21×10^5	1.31×10^7	1.19×10^9	1.82×10^8	4.0×10^5	1.1×10^7

[a] 25 °C; aqueous solution; ionic strength = 0.10 M. [b] Reference 12. [c] Reference 4.

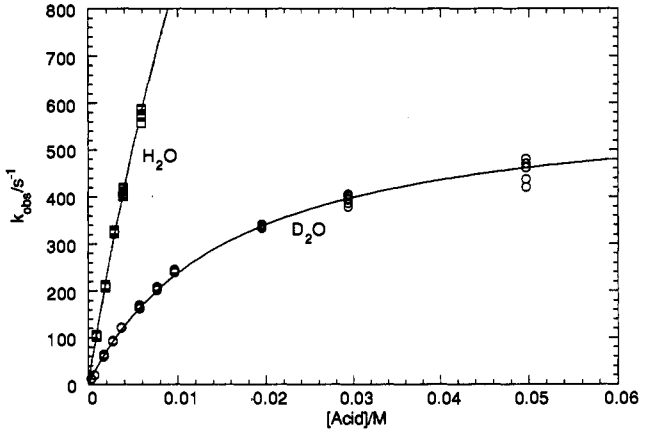
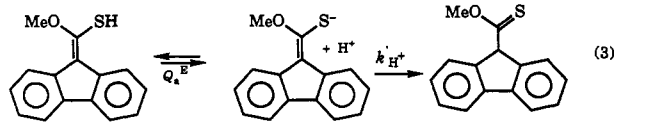


Figure 2. Relationship between acid concentration and rate of ketonization of the enolate ion of methyl fluorene-9-thionocarboxylate (**1**) in aqueous solution at 25.0 °C.

fitting of the rate expression which applies to such a situation, eq 4, produced the enol acidity constant Q_a^E,[6] and hydronium ion



(3)

$$k_{obs} = \frac{k'_{H^+}Q_a^E[H^+]}{Q_a^E + [H^+]} \qquad (4)$$

catalytic coefficient, k_{H^+}, listed in Table 1, plus a value of Q_a^E for D_2O solution which, when compared with the H_2O result, gave the isotope effect $Q_a^E(H_2O)/Q_a^E(D_2O) = 1.63 \pm 0.33$; the latter is a reasonable value for an acid of this strength.[8] Combination of the H_2O result with the keto acidity constant according to the relationship $Q_a^K/Q_a^E = K_E$ gave the keto–enol equilibrium constant, K_E, listed in Table 1.

The thiol ester **2** and the all oxygen analog, **3**, were considerably more reactive than **1**, and rates of ketonization of their enolate ions could not be measured at acidities sufficiently strong to observe catalytic saturation; enol acidity constants for these substrates were consequently not determined. But rates of ketonization could be measured in weakly acidic buffer solutions. The reactions again showed general acid catalysis, and extrapolation of the data to zero buffer concentration gave intercepts from which the hydronium ion catalytic coefficients listed in Table 1 were determined.

The present results show methyl fluorene-9-thionocarboxylate, **1**, to be a remarkably strong carbon acid. Much of its acid strength must be due to the presence of a fluorene nucleus, whose five-membered ring achieves fulvenoid aromaticity in the ionization reaction product. This effect is evident in the acidity constants of 9-formylfluorene, **5**, and 9-acetylfluorene, **6**,[4] which are listed in Table 1 and show each of these substances to be 10 pK units more acidic than its simple aliphatic analog, acetaldehyde (pQ_a^K = 16.73).[9] and acetone (pQ_a^K = 19.27),[9] respectively, and there is a similar difference between the acidity constants of the thiol ester **2** and pK_a = 20.4–21.5 recently determined for ethyl thiolacetate.[10] The thiono group in **1**, however, must exert a sizable acid-strengthening effect as well, for this substance is 4 pK units more acidic than its oxygen analog **3**.

The influence of the thiono group may also be seen in the remarkably large keto–enol equilibrium constant of **1**. A direct comparison with the oxygen ester **3** is unfortunately not possible, but, if the carboxylic acid **4** may be used as a surrogate (their pQ_a^K values are closely similar), the thiono-group effect on K_E can be put at 4 orders of magnitude. Replacing oxygen with sulfur is known to raise the enol content of simple ketones markedly,[11] but no quantitative estimate of that effect seems to be available.

The thiol ester **2** is more acidic than the oxygen ester **3**, as expected, but the difference is only 1 pK unit. This is rather small for what is commonly believed to be a major effect. Its magnitude is, of course, attenuated here by the strong acidifying influence of the fluorene nucleus, but it seems unlikely that removing the fluorene group would convert this small pQ_a^K difference into a very large one, and it would very probably also not make this effect stronger than the presently dominant thiono group effect.

Acknowledgment. We are grateful to the Natural Sciences Research Council of Canada, the U.S. National Institutes of Health, and Conselho Nacional de Pesquisa of Brazil for financial support of this research.

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(10) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 10297–10302.

(11) See, *e.g.*: Duus, F. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: New York, 1979; pp 385–388.

(12) Andraos, J. Ph.D. Thesis, University of Toronto, 1992.