Tautomeric Equilibria in Acetoacetic Acid[1]

Karen D. Grande and Stuart M. Rosenfeld*

Department of Chemistry, Wellesley College, Wellesley, Massachusetts 02181

Received October 5, 1979

Tautomeric equilibria in acetoacetic acid have been examined by ^1H NMR and found to be strongly solvent dependent. Values for enol tautomer range from less than 2% in deuterium oxide to 49% in carbon tetrachloride. Chemical shift data suggest that the enol tautomer is internally hydrogen bonded in the less polar solvents and that internal hydrogen bonding is unimportant for the keto tautomer. The acid probably exists in the keto form in the solid state.

Introduction

Studies of structure- and solvent-dependent keto–enol equilibria figure prominently in the history of organic chemistry. The solution-phase structure of ethyl acetoacetate, for example, was hotly debated around the turn of the century,[2] and numerous subsequent studies[3] have addressed the solvent dependence of tautomeric equilibria in this compound. Surprisingly, there are no detailed literature reports of such equilibria in β-keto acids,[4] perhaps in part because of handling difficulties due to the thermal lability[5] of these compounds. The parent of the series, acetoacetic acid (3-oxobutanoic acid), was first isolated as a crystalline solid in 1952,[6] and there is still little or no information available on its spectroscopic properties[7] and structure in solution or in the solid state. The synthetic[8] and biochemical[9,10] significance of the β-keto acids has prompted us to partially fill this void with an ^1H NMR study of the title compound.

Experimental Section

^1H NMR spectra were taken on a Perkin-Elmer R-32 spectrometer at ambient temperature (ca. 35 °C) with tetramethylsilane as internal standard unless otherwise noted. Sample concentrations were 0.03 to 0.05 g/mL. Though samples were prepared immediately before spectra were taken, traces of the decarboxylation product, acetone, were often evident. Percent enol tautomer was determined by direct integration of methyl, methylene, and vinyl absorptions, taking the average of three integrations. ^{13}C NMR spectra were taken on a Bruker WH-90 spectrometer.

Acetoacetic Acid. The procedure of Krueger[6] was found to be inefficient and therefore the following preparation was used. Through a solution of 12 g (0.14 mol) of diketene (Aldrich, redistilled) in 60 mL of CCl_4 at 0–5 °C was bubbled 5.22 g (0.14 mol) of HCl gas, followed by addition of 2.57 g (0.14 mol) of H_2O and subsequent stirring at 0–5 °C for ca. 3 h. The volume was reduced under vacuum. The mixture was cooled and the solid acid was filtered and washed with several portions of cold CCl_4 to give 14.6 g (90%) of white crystalline acetoacetic acid (mp 37–8 °C, uncorrected). ^1H NMR and mass spectra (most intense peaks at m/e 58 and 102) were in accord with the proposed structure. The material is extremely hygroscopic but can be stored under vacuum in a freezer for several weeks with little change.

Table I. Percent Enol in Acetoacetic Acid and in Ethyl Acetoacetate at 35 °C

solvent	percent enol: acetoacetic acid	percent enol: ethyl acetoacetate
carbon tetrachloride	49	31[b]
benzene-d_6	25	16.2[c]
chloroform-d	23.5	8.2[c]
dimethyl-d_6 sulfoxide	10.8	7.7
acetone-d_6	4.7	7.3
hexafluoro-2-propanol	~2	
deuterium oxide	<2[a]	0.4[c]

[a] Run at 0 °C. [b] Reference 12. [c] Reference 13 (these values are for the corresponding protium-containing solvents).

Results

The percent enol tautomer in various solvents is listed in Table I along with data for ethyl acetoacetate. Though these values were not strongly concentration dependent in this concentration range, a concentration study of acetoacetic acid in benzene-d_6 revealed that a decrease in concentration by a factor of four (from 0.17 g/mL to 0.04 g/mL) led to an increase of 4.6% (20.7 to 25.3) in enol concentration. Equilibrium was established within 3 min of mixing, though the time scale was somewhat longer when samples were mixed at −25 °C (CCl_4) and spectra were run at this temperature. In both cases, the keto tautomer was predominant in the preequilibrium spectra.

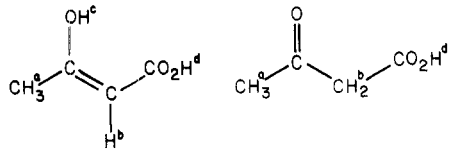
^1H NMR chemical shifts of both keto and enol tautomers are listed in Table II. No splitting was observed in any of these signals, though a splitting of 0.5 Hz would have been easily detected. ^{13}C NMR chemical shifts for the keto tautomer appear in Table III along with values for these shifts in ethyl acetoacetate.

The lithium salt of acetoacetic acid[11-14] in D_2O showed no signals assignable to the enolic tautomer, suggesting that the enol represents less than 2% of the equilibrium mixture under these conditions.

(1) Portions of this work were presented by K.G. at the 19th Annual Undergraduate Research Symposium, Boston College, May 10, 1979.
(2) Ihde, A. *J. Chem. Educ.* **1959**, *36*, 330.
(3) See, for example: Gero, A. *J. Org. Chem.* **1954**, *19*, 1960.
(4) Among the exceptions to this statement is a semiquantitative description of such equilibria in benzoylacetic acid which demonstrates the solvent dependence confirmed and further examined in the present study: Logue, M. W.; Pollack, R. M.; Vitullo, V. P. *J. Am. Chem. Soc.* **1975**, *97*, 6868.
(5) Hay, R. W.; Bond, M. A. *Aust. J. Chem.* **1967**, *20*, 1823.
(6) Krueger, R. C. *J. Am. Chem. Soc.* **1952**, *74*, 5536.
(7) One erroneous report of the acetoacetic acid ^1H NMR spectrum has appeared: Ainsworth, C.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 73.
(8) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 510.
(9) See, for example: Warren, S.; Zerner, B.; Westheimer, F. H. *Biochemistry* **1966**, *5*, 813.
(10) Breusch, F. L. *Adv. Enzymol.* **1948**, *8*, 343.
(11) Hall, L. M. *Anal. Biochem.* **1962**, *3*, 75.
(12) Hobson, R. F. *Org. Magn. Reson.* **1974**, *6*, 129.
(13) Meyer, K. H. *Justus Liebigs Ann. Chem.* **1911**, *380*, 212.
(14) Abraham, R. J.; Loftus, P. "Proton and Carbon-13 NMR Spectroscopy"; Heyden: Philadelphia, 1978; p 170.

0022-3263/80/1945-1626$01.00/0

Table II. ^{1}H NMR Chemical Shifts (δ Values) for Enol and Keto Tautomers in Various Solvents[b]



solvent		
carbon tetrachloride	a, 2.00	a, 2.27
	b, 5.00	b, 3.42
	c, 11.71	d, 11.38 (br)
	d, 11.38 (br)	
benzene-d_6	a, 1.48	a, 1.65
	b, 4.84	b, 2.92
	c, 12.10 (variable shape)	d, 11.80 (variable shape)
	d, 11.80 (variable shape)	
chloroform-d	a, 2.00	a, 2.30
	b, 5.00	b, 3.54
	c, 11.80 (br)	d, 10.30 (br)
	d, 10.30 (br)	
acetone-d_6	a, 2.00	a, 2.20
	b, 5.05	b, 3.50
	c, 6.0 (br)	d, 6.0 (br)
	d, 6.0 (br)	
dimethyl-d_6 sulfoxide	a, 1.89	a, 2.15
	b, 5.02	b, 3.45
	c, 12.57 (br)	d, 12.57 (br)
	d, 12.57 (br)	
hexafluoro-2-propanol	a, -	a, 2.33
	b, -	b, 3.62
	c, -	d, -
	d, -	
deuterium oxide[a]	a, -	a, 2.27
	b, -	b, 3.66
	c, -	d, -
	d, -	

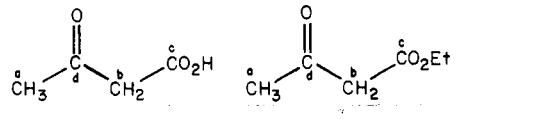
[a] (Trimethylsilyl)-1-propanesulfonic acid was used as internal standard and spectra were run at 3 °C to avoid the rapid decarboxylation evident at 35 °C. The keto methylene peak (δ 3.66) disappeared within minutes due to incorporation of deuterium, presumably via chemical exchange between the enol tautomer and solvent. [b] All signals are singlets.

Discussion

Our a priori expectations were that the keto tautomer of acetoacetic acid would be favored more strongly in nonpolar solvents than that of ethyl acetoacetate, since the former has a potential internal hydrogen bond not available to the ester. It also seemed unlikely that a solvent dependence as large as that observed for ethyl acetoacetate would be found. The solvent dependence of the tautomeric equilibrium in ethyl acetoacetate is generally explained[15] as resulting from stabilization of the more polar keto tautomer by polar solvents. Hydrogen bonding in the keto tautomer of acetoacetic acid was expected to substantially diminish this effect.

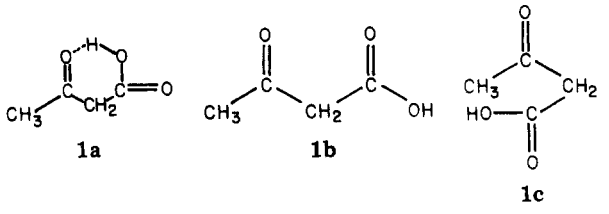
Clearly, the data in Table I do not support this reasoning. The qualitative similarities in equilibrium constants for acetoacetic acid and its ethyl ester are striking and suggest that the keto form of the acid does not benefit from a strong internal hydrogen bond. The chemical shifts of the carboxyl proton, the weighted average of enol and keto carboxyl proton shifts due to chemical exchange,

Table III. ^{13}C NMR Chemical Shifts (δ Values) of Acetoacetic Acid and Ethyl Acetoacetate[14] in Chloroform-d



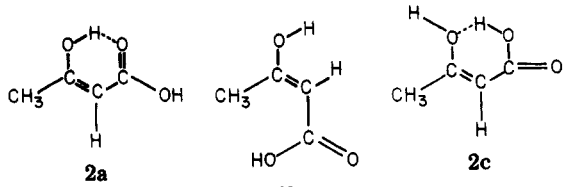
a, 29.2	a, 29.9
b, 48.2	b, 50.0
c, 170.7	c, 167.2
d, 201.7	d, 200.5

Scheme I



1a 1b 1c

Scheme II



2a 2b 2c

appear to support this conclusion. The general trend of decreasing enol concentration with increasing solvent polarity requires that the keto form be the more polar tautomer. The decrease in enol concentration in the more concentrated samples in benzene-d_6 probably results from the higher polarity of the bulk medium due to higher concentration of the polar acid.

The ^{1}H NMR chemical shifts for both tautomers are generally constant over the range of solvents. Dramatic shifts to higher field in benzene-d_6 are proably due to shielding effects[16] exerted by this solvent which is known to associate strongly with β-keto esters.[17] The lack of large changes in the keto tautomer chemical shifts (methyl and methylene) with substantial changes in solvent polarity and hydrogen-bonding ability suggests that the hydrogen-bonded conformer **1a** (Scheme I) is not predominant under any conditions, since this conformer would be destabilized relative to the others (**1b** and **1c**) by strong hydrogen-bonding solvents, such as hexafluoro-2-propanol, leading to changes in chemical shift. Perhaps dimeric association affords extra stabilization to **1b** or **1c** but not to the internally hydrogen-bonded **1a**. In accord with this suggestion, we find that small upfield shifts (3.5 to 5.5 Hz) for keto methyl and methylene peaks accompany a tenfold reduction in the concentration of the acid in $CDCl_3$. Similar concentration-dependent upfield shifts in ethyl acetoacetate have been attributed previously to the destruction of intermolecular hydrogen bonds upon dilution.[17]

The enol tautomer almost certainly exists as the internally hydrogen-bonded conformer **2a** (Scheme II) in the less polar solvents. The enol hydroxyl proton shifts reflect this state of affairs, being at lower field than expected for

(15) Wheland, John. "Advanced Organic Chemistry", 3rd ed.; Wiley: New York, 1949.

(16) Karabatsos, G. J.; Taller, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 3624.
(17) Rogers, M. T.; Burdett, J. L. *Can. J. Chem.* **1965**, *43*, 1516.

a non-hydrogen-bonded enol.[18-20] A 20-fold reduction in acid concentration in $CDCl_3$ causes a change of less than 6 Hz (downfield) in the position of this resonance. The trans-enol **2b** is presumably much less stable and unlikely to be important under these conditions.[22,23] Conformer **2c** is probably not favored since the π-base strength of the carbonyl oxygen exceeds that of the other carboxyl oxygen or enol oxygen, and, further, the carboxyl proton shifts would be moved downfield by this internal hydrogen bond and the enolic proton shifts would presumably be substantially upfield of their observed position. Other conformers lacking an internal hydrogen bond are not likely to be important under equilibrium conditions as has been observed in 3-keto esters.[24] Therefore the enol tautomer is best represented as **2a**. Enol hydroxyl proton shifts do not change from carbon tetrachloride to chloroform-*d*, but these shifts are determined in part by chemical exchange which may serve to obscure small changes in shift.

Separate enol and carboxyl proton resonances were not observed in the more polar solvents. The lack of detectable splitting in the enol methyl and vinyl signals stands in contrast to the observation of a splitting of 0.74 Hz for the analogous protons in methyl acetoacetate.[22]

The broad-band-decoupled ^{13}C NMR spectrum (Table III) of acetoacetic acid in chloroform-*d* is unexceptional, showing the complete keto tautomer spectrum and one peak presumably due to the enol (δ 88.1, olefinic CH carbon). Assignments are in accord with those observed for both methyl[22] and ethyl[14] esters of the acid.

Spectra run at ambient temperatures and at −25 °C in CCl_4 at short intervals immediately upon mixing suggest that acetoacetic acid exists in the keto form in the solid state when crystallized from carbon tetrachloride. This inference appears to be the first comment on the structure of a lower member of this series in the solid state.[25]

Acknowledgment. We thank Jeffrey Bennet for valuable assistance in the preparation of acetoacetic acid. Partial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No. Acetoacetic acid, 541-50-4; diketene, 674-82-8; ethyl acetoacetate, 141-97-9; 3-hydroxybut-2-enoic acid, 73018-20-9; ethyl 3-hydroxybut-2-enoic acid, 1522-29-8.

(18) The potential enediol tautomer from enolization involving the carboxyl group can be excluded from consideration since it is likely to be less stable than the enol derived from the keto function. The lack of detectable enol in malonic acid[19] supports this statement. Further, the enol olefinic CH resonance in the ^{13}C NMR spectrum of acetoacetic acid is within 2 ppm of the analogous resonance in methyl[20] and ethyl[14] acetoacetate enol. If the enediol were present to a significant degree, interconversion with the proposed enol tautomer would occur on a ca. 10^{-16}-s time scale by analogy with related systems[20] and NMR shifts would therefore be a weighted average of the shifts for the two individual tautomeres.

(19) Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co.; Milwaukee, WI; Vol. 2, No. 150D.

(20) Brown, R. S.; Tse, A.; Nakashima, T.; Haddon, R. C. *J. Am. Chem. Soc.* **1979**, *101*, 3157.

(21) The enol hydroxyl proton of methyl acetoacetate in toluene-d_8 appears at δ 12.60.[22]

(22) Matusch, R. *Angew. Chem.* **1975**, *87*, 283.

(23) The trans enol of methyl acetoacetate has been studied by ^1H NMR and was shown to have a methyl proton chemical shift 0.6 ppm downfield of the corresponding peak in the cis isomer (ref 22). We find no unassigned peaks in the expected region of the spectrum.

(24) Veirov, D.; Bercovici, T.; Fischer, E.; Mazur, Y.; Yogev, A. *J. Am. Chem. Soc.* **1977**, *99*, 2723 and references therein.

(25) A previous report lists X-ray crystal spacings for the C_8–C_{24} homologues of acetoacetic acid.[26]

(26) E. Stenhage *Ark. Kemi* **1957**, *3*, 381.

Cycloocta[*def*]fluorene: A Planar Cyclooctatetraene Derivative.[1] Paratropicity of Hydrocarbon and Anion

Itamar Willner[2a] and Mordecai Rabinovitz*[2b]

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

Received August 22, 1979

The synthesis of cycloocta[*def*]fluorene (**1**) from cyclopenta[*def*]phenanthrene (**5**) is described. Hydrocarbon **1** shows paratropic antiaromatic character as deduced from the ^1H NMR spectra and its low acidity ($pK_a = 27$). The antiaromatic character of **1** is attributed to the presence of a planar cyclooctatetraene (COT) moiety. The deprotonation and the formation of cycloocta[*def*]fluorenyl anion (**13**) are presented. The anion **13** exhibits paratropic character which may originate in peripheral delocalization of 16 π electrons.

The thermodynamic characteristics of conjugated molecules are the basis for the concepts of aromaticity and antiaromaticity.[3] While aromaticity ascribes enhanced stabilization of cyclic delocalized molecules relative to their respective acyclic systems, antiaromaticity infers the

(1) For preliminary reports, see: (a) Willner, I.; Gutman, L. A.; Rabinovitz, M. *J. Am. Chem. Soc.* **1977**, *99*, 4167. (b) Willner, I.; Rabinovitz, M. *Tetrahedron Lett.* **1976**, 1223.

(2) (a) Taken in part from the Ph.D. Thesis of I. Willner. (b) To whom correspondence should be addressed.

(3) For general reviews, see: *Chem. Soc. Spec. Publ.* **1967**, *No. 21*. Bergmann, E. D., Pullman, B., Eds.; "Aromaticity, Pseudoaromaticity, Antiaromaticity"; Jerusalem Academic Press: Jerusalem, 1971. Garratt, P. J. "Aromaticity"; McGraw-Hill: London, 1971. Agranat, I. "MTP International Review of Science"; Butterworths: London, 1973; Vol. 3, Chapters 5 and 8; 1976, Vol. 3, Chapter 11. Breslow, R. *Chem. Eng. News* **1965**, *43*, 90; *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 565.

0022-3263/80/1945-1628$01.00/0