Tetrahedron Vol 33, pp 2781 to 2784. Pergamon Press 1977. Printed in Great Britain

THE RELATIVE BASICITY OF SULFUR CONTAINING ESTERS

J. R. GRUNWELL* and D. L. FOERST
Department of Chemistry, Miami University, Oxford, OH 45056, U.S.A.

and

F. KAPLAN* and J. SIDDIGUI
Department of Chemistry, University of Cincinnati, Cincinnati, OH, 45221, U.S.A.

(*Received in the USA 26 January 1977; Received in the UK for publication 25 May 1977*)

Abstract—The relative gas phase proton affinities for an amide, ester, and thiolester have been established as $CH_3CONHCH_3 > CH_3COSCH_3 > CH_3COOCH_3$ using ion cyclotron resonance techniques. A dithioester is more basic than the thiolester: $CH_3CSSCH_3 > CH_3COSCH_3$. *d*-Orbitals are unimportant in the electronic structure of thiolesters.

It is important to understand how the electronic structure may control the chemistry of thiolesters because of the crucial part these esters play in metabolism and biosynthesis.[1] Several authors have pointed out that esters are more stable than thiolesters because π-orbital overlap between sulfur $3p_z$ and carbon $2p_z$ atomic orbitals is smaller than the corresponding overlap between oxygen $2p_z$ and carbon $2p_z$ orbitals.[1-3]

The hydrolysis of thiolesters is catalyzed by hydronium ion[4-7] and the rate determining step is addition of water to the CO of the ester.[8] Acid catalysis is more effective for esters than thiolesters,[9] a fact which may be explained by assuming a lower solution basicity for thiolesters than esters. Thiolesters exert a smaller effect than esters on the stretching frequency of the acetylenic C–H bond of phenylacetylene.[10] In addition, the carbonyl stretching frequency for thiolesters is lower than ketones. IR spectroscopists have argued that since $3p_\pi$–$2p_\pi$ bonding is unimportant for the CO carbon sulfur bond of thiolesters then sulfur must withdraw electron density from the CO π-bond into nominally empty d-orbitals through $3d_\pi$–$2p_\pi$ bonding.[10-12] Thus, d_π–p_π bonding will decrease the carbonyl π-bond order thereby lowering the CO stretching frequency and will decrease the amount of electron density associated with oxygen rendering the thiolester less basic.

Since these arguments are based on isolated molecule electronic effects, they are more properly tested by measurements in the gas phase. The purpose of this research was to use a combination of CNDO/2 calculations and ion cyclotron resonance spectroscopy to evaluate the basicity of methyl thiolacetate relative to N-methylacetamide and methyl acetate and the basicity of methyl dithioacetate relative to methyl thiolacetate.

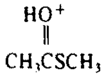
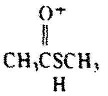
RESULTS AND DISCUSSION

Riveros *et al.* briefly reported that thiolesters have about the same basicity as the corresponding esters.[13] We found the relative gas phase basicities for an amide, ester and thiolester to be $CH_3CONHCH_3 > CH_3COSCH_3 > CH_3COOCH_3$. The basicity order of these CO compounds is analogous to the relative gas phase basicities of other nitrogen, sulfur, and oxygen compounds.[14] There is a reversal in relative basicity in the gas phase as compared to solution for the ester and thiolester. This reversal is similar to that observed for other noncarbonyl oxygen and sulfur compounds.

A comparison of the relative gas phase basicity for π-bonded sulfur and oxygen was done in order to determine if the above mentioned reversal in relative solution and gas phase basicity was unique to divalent σ-bonded oxygen and sulfur. Thiocarbonyl compounds are less basic than the corresponding CO compounds in solution, e.g. the pKa of protonated acetamide[15] is −0.9 while that of protonated thioacetamide[16] is −2.6. We found methyl dithioacetate to be more basic than methyl thiolacetate in the gas phase. This is the first example of the comparison of the gas phase basicities between a thiocarbonyl and the corresponding carbonyl compound.

Before explaining these results the site of protonation of CO compounds should be discussed. It is generally accepted that in solution protonation occurs at CO oxygen for amides, esters and thiolesters.[17] In addition, Olah has demonstrated oxygen protonation for thiolesters in magic acid.[18] However, a reversal of protonation site may occur in the gas phase. Using a semi-empirical SCFMO method, Yonezawa predicted electrophilic attack at the sulfur of methyl thiolacetate because the HOMO is of the π type localized largely on sulfur.[19] We have performed CNDO/2 calculations on carbonyl oxygen and sulfur protonated methyl thiolacetate and found carbonyl oxygen protonation is more stable regardless of d-orbital participation (Table 1).

Table 1. Stability of protonated methyl thiolacetate

	$-E_T(au)$
 $CH_3\overset{\overset{HO^+}{\|}}{C}SCH_3$	55.3684 55.6388†
 $CH_3\overset{\overset{O^+}{\|}}{C}\underset{H}{S}CH_3$	55.2377 55.5430†

†With d-orbitals.

If one were to compare ethylmethyl sulfide with methyl thiolacetate, replacement of the Et group with an OAc group would be expected to decrease the basicity of sulfur because the OAc group is more electron withdrawing than the Et group. Our experimental result shows that ethylmethyl sulfide is more basic than methyl thiolacetate. However, this does not ensure protonation on sulfur rather than oxygen since it is known that although amides are less basic than amines,[21] amides protonate on the carbonyl oxygen in the gas phase.[22]

CNDO/2 calculations of N-methyl acetamide, methyl acetate and methyl thiolacetate with and without d-orbitals in the basis set show that the amount of negative charge on the carbonyl oxygen decreases in the order amide, ester, and thiolester regardless of d-orbital participation (Table 2). The CO carbon–oxygen bond was set at the double bond 1.22 Å and single bond distance 1.36 Å in order to estimate the effect of lengthening the bond on the charge distribution. The relative negative charge correlates with the solution basicity rather than the gas phase basicity. The population of $2p_z$ and $2p_y$ orbitals show the same trend. The $2p_y$ orbital is the one which is protonated. If the correlation between relative basicity and decreasing negative charge is not fortuitous, then d-orbitals are not necessary for the description of the electronic structure of thiolesters since the carbonyl oxygen negative charge and $2p_y$ orbital population are smallest for thiolesters regardless of d-orbital participation.

Pople and Hehre have shown that the gas phase experimental or calculated relative basicity does not correlate necessarily with the electron density associated with the atom to be protonated.[23] If the species being protonated is neutral, then the relative distribution of positive charge in the protonated molecule also must play a significant part in controlling the basicity. The difference between the electronic properties of the neutral and protonated species ought to correlate with the relative basicity unless several factors are working against one another. Examination of Table 2 shows that there are no correlations between gas phase basicities and the charge differences between protonated and neutral molecules.

The delocalization of positive charge on the protonated CO compounds occurs primarily by polarization of the π electrons. The CO oxygen p_z orbital acquires between 0.4 and 0.5 electrons upon protonation of N-methyl acetamide, methyl acetate or methyl thiolacetate. The two primary sources for the electron density are the CO carbon and the heteroatom bonded to the CO. The N atom of amides donates more π electrons than the CO carbon while for esters and thiolesters the oxygen and S atoms donate fewer π electrons than the CO carbon. The S atom of thiolesters donates slightly fewer π electrons than the O atom of the corresponding ester while the thiolester CO carbon donates more π electrons than the ester CO carbon. Thus p_π–p_π stabilization occurs in the order amides > esters > thiolesters.

Sulfur is much more polarizable than oxygen or nitrogen.[24] Among amides, esters and thiolesters, the CO carbon of thiolesters has the least π electron density and the S atom of protonated methyl thiolacetate is positively charged while the O and N atoms of protonated ester and amide are negatively charged. The charge difference between protonated and unprotonated forms, $\Delta\rho_x$, is much larger for thiolesters than amides or esters. Thus there is a significant polarization of the CO carbon sulfur σ-bond in the direction of the CO so that a thiolester CO carbon has less positive charge than the corresponding ester or amide in the protonated form. This polarization tends to compensate for relative lack of stabilization from $3p_\pi$–$2p_\pi$ bonding in thiolesters as compared with that from $2p_\pi$–$2p_\pi$ bonding in esters and amides.

Table 2. Total charge and π-electron densities of protonated and neutral acetyl compounds

X^e	ρ_O	$\rho_O(H)$	$\Delta\rho_O{}^g$	ρ_C	$\rho_C(H)$	$\Delta\rho_C$	ρ_X	$\rho_X(H)$	$\Delta\rho_X$	P_yO
CH_3NH^a	−368	−165	+203	+364	+453	+ 89	−194	−117	+ 77	1.9385
CH_3NH^b	–	−203	+165	–	+431	+ 67	–	− 79	+115	–
CH_3O^a	−321.	−142	+179	+393	+528	+131	−231	−131	+100	1.9356
CH_3O^b	–	−286	+135	–	+471	+ 78	–	−197	+124	–
$CH_3S^{a,c}$	−260	−102	+158	+291	+355	+ 64	−121	+ 97	+218	1.9090
$CH_3S^{b,c}$	–	−146	+114	–	+336	+ 45	–	+132	+253	–
$CH_3S^{a,d}$	−228	− 88	+140	+238	+316	+ 78	−122	+ 94	+216	1.9248
$CH_3S^{b,d}$	–	−127	+101	–	+316	+ 78	–	+124	+246	–

X^f	P_zO	$P_zO(H)$	ΔP_zO^h	P_zC	$P_zC(H)$	ΔP_zC	P_zX	$P_zX(H)$	ΔP_zX
CH_3NH^a	1.4132	1.7536	−340	0.7958	0.6711	+125	1.7955	1.6251	+170
CH_3NH^b	–	1.8473	−434	–	0.6572	+139	–	1.5561	+240
CH_3O^a	1.3289	1.6863	−357	0.8005	0.5837	+217	1.8817	1.7943	+ 87
CH_3O^b	–	1.7910	−462	–	0.5378	+263	–	1.7522	+130
$CH_3S^{a,c}$	1.2810	1.6501	−359	0.8073	0.5547	+254	1.9373	1.8726	+ 65
$CH_3S^{b,c}$	–	1.7702	−489	–	0.5016	+306	–	1.8240	+113
$CH_3S^{a,d}$	1.2332	1.6492	−416	0.8217	0.5820	+240	2.0221	1.9104	+112
$CH_3S^{b,d}$	–	1.7774	−544	–	0.5526	+269	–	1.8291	+193

a) C–O carbonyl distance is 1.22Å
b) C–O carbonyl distance is 1.36 Å
c) no d-orbitals
d) with d-orbitals
e) total charge densities
f) π electron populations
g) $\Delta\rho = \rho(H) - \rho$
h) $\Delta P_z = P_z - P_z(H)$

The inclusion of d-orbitals in the basis set for thiolesters has only a minor effect on the charge distribution. With d-orbitals, the S atom donates a little more π electron density to the CO group but the CO carbon sulfur σ polarization is a little smaller.

The ionization potential for methyl thiolacetate is not known and an estimate is needed for calculation of the H atom affinity. For acetic acid, thiolacetic acid, and acetamide the ionization potentials[25] are 10.36, 10.00 and 9.77 eV respectively while for dimethylether, dimethyl sulfide and dimethyl amine they are 10.00, 8.7 and 8.24 eV, respectively. The average of the ionization potentials for dimethyl ether and acetic acid is 10.2 eV, a value which is close to the ionization potential for methyl acetate 10.27 eV. Similarly, the average for dimethyl amine and acetamide is 9.0 eV and the value for N-methylacetamide is 8.9 eV. Thus the ionization potential for methyl thiolacetate estimated from the average of thiolacetic acid and dimethyl sulfide is 9.35 eV. Since the ionization potentials of thiolacetic acid and dimethyl sulfide are between those of the corresponding oxygen and nitrogen compounds, this method of estimation guarantees that the ionization potential of methyl thiolacetate will lie between the potential for N-methylacetamide and methyl acetate.

The proton affinities for N-methyl acetamide and methyl acetate are reported to be 209 and 195 ± 2 kcal/mole, respectively.[26,27] Since the thiolester is bracketed between the amide and ester, and the proton exchange reactions between dimethyl sulfide (P.A. = 197)[28] and methyl acetate and dimethyl sulfide and methyl thiolacetate are approximately themoneutral, the proton affinity of methyl thiolacetate must be within 2 kcal of that for methyl acetate. Thus the proton affinity for methyl thiolacetate is estimated to be 197 ± 2 kcal/mole. Using the relationship[28] $HA(B^+) = PA(B) + IP(H) - IP(H)$ the H atom affinity for ionized methyl thiolacetate is calculated to 100 kcal/mole, a value which is close to those reported for other CO compounds which protonate at the CO oxygen.[28] For example, the H atom affinity for ionized methyl ethyl ketone is 102 kcal/mole.[22] For compounds which protonate at sulfur, such as methyl mercaptan and dimethyl sulfide, the H atom affinities of the molecular ions are considerably lower, 89 kcal/mole and 83 kcal/mole respectively.[14]

The answer to the question of why thiolesters are less basic than esters in solution does not lie in the intrinsic argument involving d-orbital participation advanced by Baker and Harris[10] since the gas phase basicity is reversed. The reason must be that protonated thiolesters are less well solvated than protonated esters, a conclusion which was also reached by Arnett when comparing other sulfur and oxygen analogues.[14] Poor solvation of methyl dithioacetate relative to methyl thiolacetate probably also accounts for this pair of reversed solution and gas phase basicities.

EXPERIMENTAL

Mass spectra were obtained on a Hitachi Perkin Elmer RMU-6 single focusing mass spectrometer (70 eV). Ion cyclotron resonance spectra were run on a Varian ICR-9 spectrometer. Double resonance experiments were performed at a pressure of 3×10^{-5} torr and pertinent results are given below.

Methyl thiolacetate. Methyl thiolacetate was prepared according to the literature procedure from methane thiol and acetyl chloride: b.p. 94–96°/760 mm (lit.[29] 95–96/760 mm); mass spectrum *m/e* (rel intensity) 90(11), 74(3), 59(6), 48(3), 47(11), 46(6), 45(22), 44(3), 43(100), 41(3).

Methyl dithioacetate. The dithioester was prepared according to the literature procedure[30] from iodomethane and magnesium dithioacetate prepared by the addition of CS_2 to an etheral soln of MeMgBr: b.p. 38–39°/24 mm (lit.[31] 80–81°/95 mm); mass spectrum *m/e* (rel intensity) 106(30), 92(5), 76(8), 61(8), 60(5), 59(100), 58(27), 57(13), 47(8), 46(7), 45(18).

Double resonance results

Mixture 1. Methyl acetate and methyl thiolacetate: (a) *m/e* obs. 91 (protonated methyl thiolacetate), *m/e* irrad. 75 (protonated methyl acetate), ΔI_{91}-decrease; (b) *m/e* obs. 75, *m/e* irrad. 91, ΔI_{75}-no change.

Mixture 2. Methyl thiolacetate and N-methyl acetamide; (a) *m/e* obs. 91 (protonated methyl thiolacetate), *m/e* irrad. 74 (protonated N-methyl acetamide), ΔI_{91}-no change; (b) *m/e* obs. 74, *m/e* irrad. 91 ΔI_{74}-decrease.

Mixture 3. Methyl thiolacetate and dimethylsulfide; (a) *m/e* obs. 91 (protonated methyl thiolacetate), *m/e* irrad. 63, (protonated dimethylsulfide), ΔI_{91}-decrease; (b) *m/e* obs. 63, *m/e* irrad. 91, ΔI_{63}-decrease.

Mixture 4. Methyl acetate and dimethylsulfide; (a) *m/e* obs. 75 (protonated methyl acetate), *m/e* irrad. 63 (protonated dimethylsulfide), ΔI_{75}-decrease; (b) *m/e* obs. 63, *m/e* irrad. 75, ΔI_{63}-decrease.

Mixture 5. Methyl thiolacetate and methylethylsulfide; (a) *m/e* obs. 91 (protonated methyl thiolacetate), *m/e* irrad. 77, (protonated methylethylsulfide), ΔI_{91}-decrease; (b) *m/e* obs. 77, *m/e* irrad. 91, ΔI_{77}-no change.

Mixture 6. Methyl thiolacetate and methyl dithiolacetate; (a) *m/e* obs. 91 (protonated methyl thiolacetate), *m/e* irrad. 107 (protonated methyl dithiolacetate), ΔI_{91}-decrease; (b) *m/e* obs. 107, *m/e* irrad. 91, ΔI_{107}-no change.

REFERENCES

[1] H. R. Mahler and E. H. Cordes, *Biological Chemistry*, 2nd Edn, Chap. 2, p. 39, and Chap. 8, p. 388, Harper & Row, New York (1971).

[2] W. P. Jencks, *Catalysis in Chemistry and Enzymology*, Chap. 10, p. 518, McGraw-Hill, New York (1969).

[3] S. A. Bernhard, *The Structure and Function of Enzymes*, Chap. 7, p. 220, Benjamin, New York (1968).

[4] J. R. Schaefgen, *J. Am. Chem. Soc.* **70**, 1308 (1948).

[5] P. N. Rylander and D. S. Tarbell, *Ibid.* **72**, 3021 (1950).

[6] B. K. Morse and D. S. Tarbell, *Ibid.* **74**, 416 (1952).

[7] F. H. Noda, S. A. Kurby and H. A. Tardy, *Ibid.* **75**, 913 (1953).

[8] R. Hershfield and G. L. Schmir, *Ibid.* **94**, 1263 (1972).

[9] T. C. Bruice, *Organic Sulfur Compounds* (Edited by N. Kharasch) Vol. 1, Chap. 35, p. 429. Pergamon Press, New York (1961).

[10] A. W. Baker and G. H. Harris, *J. Am. Chem. Soc.* **82**, 1923 (1960).

[11] R. A. Nyquist and W. J. Potts, *Spectrochim. Acta* **14**, 514 (1959).

[12] L. J. Bellamy and R. J. Pace, *Ibid.* **19**, 1831 (1963).

[13] P. C. Isolandi, J. M. Riveros and P. W. Tiedemann, *Trans. Far. Soc.* II, **34**, 1023 (1973).

[14] E. M. Arnett, *Acc. Chem. Res.* **6**, 404 (1973).

[15] M. Liler, *J. Chem. Soc.* B, 385 (1969).

[16] C. Tissier and M. Tissier, *Bull. Soc. Chim. Fr.* 2109 (1972).

[17] G. A. Olah, A. M. White and D. H. O'Brien, *Chem. Rev.* **70**, 561 (1970).

[18] G. A. Olah, A. T. Ku and A. M. White, *J. Org. Chem.* **34**, 1827 (1969).

[19] H. Yamabe, H. Kato and T. Yonezawa, *Bull. Chem. Soc. Japan* **44**, 604 (1971).

[20] J. A. Pople and D. L. Beveridge, *Approximate Molecular Orbital Theory*, McGraw-Hill, New York (1970).

[21] D. H. Aue, H. M. Webb and M. T. Bowers, *J. Am. Chem. Soc.* **98**, 311 (1976).

[22] E. G. Melby, Ph.D. Dissertation, University of Cincinnati (1971).

[23] W. J. Hehre and J. A. Pople, *Tetrahedron Letters*, 2959 (1970).

[24] J. Thorhallson, C. Fisk and S. Fraga, *Theoret. Chim. Acta* **10**, 388 (1968).

[25] J. L. Franklin, J. G. Dillard, H. Rosenstock, J. T. Herron, K. Draxl and F. H. Field, *Ionization Potentials, Appearance Potentials and Heat of Formation of Gaseous Positive Ions*. NSRDS-NBS26 (1969).

[26] R. W. Taft, *Proton Transfer Reactions* (Edited by E. F. Caldin and V. Gold) Chapmen & Hall, London (1975).

[27] R. Yamdagni and P. Kerbarle. *J. Am. Chem. Soc.* **98**, 1320 (1976).

[28] J. L. Beauchamp, *Annu. Rev. Phys. Chem.* **22**, 527 (1971).

[29] A. W. Ralston and J. A. Wilkinson, *J. Am. Chem. Soc.* **50**, 2166 (1928).

[30] J. Meyer, P. Vermeer and L. Brandsma, *Rec. Trav. Chim.* **92**, 601 (1973).

[31] J. Houben and K. M. Schultze, *Ber. Dtsch. Chem. bis* **43**, 2481 (1910).