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A COMPARATIVE QUANTUM CHEMICAL STUDY OF METHYL ACETATE AND *S*-METHYL THIOACETATE

TOWARD AN UNDERSTANDING OF THE BIOCHEMICAL REACTIVITY OF ESTERS OF COENZYME A

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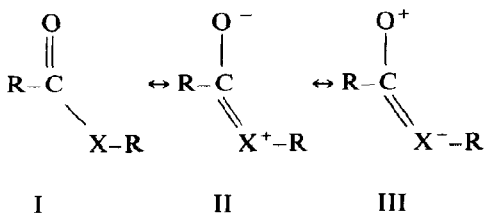
The electronic structures of methyl acetate and *S*-methyl thioacetate and the corresponding anions have been investigated using the INDO-MO method. Equilibrium geometries, gas-phase anion proton affinities and barriers to internal rotation have been computed. Analysis of the effect of the d-type functions on sulfur on the static and dynamic properties of the thioester and its anion reveal no role for $(p-d)_\pi$ conjugative effects. The results of this work indicate that the unique properties of thioester, and hence esters of coenzyme A, may be attributed to the lack of resonance, rather than to a sulfur d-orbital expansion

1. Introduction

The biochemical importance of coenzyme A and the finding that acyl derivatives of the coenzyme are thioesters [1] have led to a continuing interest in thioesters. These molecules have high reactivity toward alkaline hydrolysis [2], and high acidity of the hydrogen atoms adjacent to the carbonyl group compared with oxygen esters [3].

The hydrogen bond acceptor basicity of the carbonyl oxygen of thioesters is significantly lower than that of amide and oxygen esters [4]. Baker and Harris [4] proposed an explanation for these properties that invoked resonance structures I–III, in which X is sulfur.



I II III

Structure III implies $(2p-3d)_\pi$ bonding that is impossible when X is nitrogen or oxygen. The proposal of Baker and Harris is, however, inconsistent with Wadsö's [5] finding that the resonance energies of thioesters are smaller than those of oxygen esters by some 13 kcal mol^{-1}. In addition, a comparison of carbonyl stretching force constants of ketones, thioesters and oxygen esters [6] infers no significant contribution of structure II or III to the ground state of thioesters. Yet, the driving force for the high reactivity of thioesters toward alkaline hydrolysis and the high acidity of the hydrogen atoms adjacent to the carbonyl group are not fully understood.

This work presents a comparative quantum-chemical study of the electronic structure, proton affinities and barrier to internal rotation for methyl acetate, *S*-methyl thioacetate and the corresponding anions. The principal objectives of the compu-

Abbreviations: INDO, intermediate neglect of differential overlap; HOMO, highest occupied molecular orbital

tations are to calculate: (1) reliable geometrical data for the esters; (2) barriers to internal rotation about the C(O)–O and C(O)–S bonds; and (3) proton affinities for the ester anions. Objectives 2 and 3 are aimed at a much better understanding of bonding characterstics, electronic structure, and d-orbital involvement in the thioesters, which provides yet another useful entry in understanding the chemical and physical characteristics of the esters of coenzyme A.

2. Method of calculation

All calculations were performed within the framework of the INDO-MO method, details of which have been given elsewhere [7].

Geometry optimizations of methyl acetate and its anion begun using the structural parameters obtained from an electron-diffraction study [8]. The geometrical parameters for *S*-methyl thioacetate and its anion were taken from the data reported for *S*-methyl thioformate [9] and thioacetic acid [10].

3. Results and Discussion

3.1. Equilibrium geometries

The internal parameters subjected to geometry optimization for methyl acetate and *S*-methyl thioacetate (and the corresponding anions) are shown in fig. 1. Optimization consisted of computation of the first (gradient) and second (force constant) derivatives of the potential energy with respect to each of the specified geometrical variables. The procedure is automatically performed in the INDO program described previously [11]. For methyl acetate the calculated gradient ($\boldsymbol{g}$) and force constant matrix ($\boldsymbol{A}$), in the chosen seven-dimensional space have been combined to obtain a new set of variables which should correspond to the equilibrium geometry required. The calculated geometry has been used to start another optimization run, and yielded a norm of the energy gradient (0.0016 a.u.) almost equal to the default value of 0.001 a.u. The final geometries of methyl acetate and its anion $^{-}CH_2C(O)OCH_3$ are given in table 1.

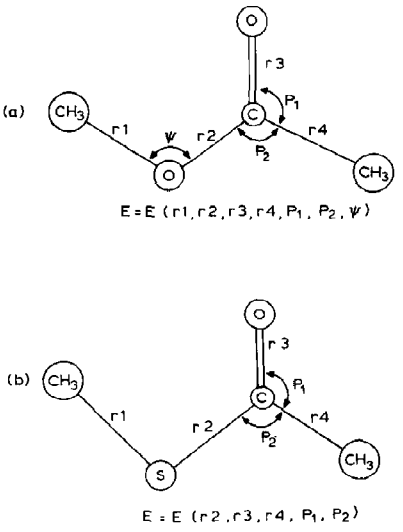


Fig. 1. Internal parameters subjected to geometry optimization: (a) in $CH_3C(O)OCH_3$ and $^{-}CH_2C(O)OCH_3$, (b) in $CH_3C(O)SCH_3$ and $^{-}CH_2C(O)SCH_3$

In the case of *S*-methyl thioacetate the convergence of the optimization procedure was slower and in fact showed oscillation about the absolute minimum. Inclusion of d-functions (on sulfur) does not improve the convergence. The optimized geometries of *S*-methyl thioacetate and its anion $^{-}CH_2C(O)SCH_3$ in the sp and spd basis are listed in table 2

The correspondence between the calculated and experimental geometrical variables is satisfactory. However, the figures in tables 1 and 2 show some significant trends which may be summarized as follows.

(i) There is a general tendency of the calculation to understimate the C=O bond length. This tendency is slightly greater for anions.

(ii) For the thioester and its anion, inclusion of -the d-functions in the basis set does not alter the computed geometry significantly.

(iii) The computation yields bond angles in good agreement with those determined experimentally. This observation is true for the sp and spd basis set calculations, an observation which indicates that the angular dependence of the structural parameters of the thioester and its anion are well accommodated by the sp basis.

Table 1

Optimized geometry of $CH_3C(O)OCH_3$ and $^-CH_2C(O)OCH_3$ as computed with the sp basis set on oxygen

Geometric parameter	Computed values		Experimental values [a]
	$CH_3C(O)OCH_3$	$^-CH_2C(O)OCH_3$	
Bond length (Å)			
C–O	1.45	1.46	1.46
C(O)–O	1.34	1.41	1.36
C=O	1.20	1.14	1.22
C–C	1.46	1.46	1.52
C–H [b]	1.09	1.09	1.09
Bond angle (°)			
C–C=O	123.60	124.90	120.00
C–C–O	111.60	110.40	116.00
O–C=O	124.80	124.60	124.00
C–O–C	113.60	116.40	113.00
HCC, HCH, HCO [b]	109.50	109.50	109.50

[a] Data taken from ref. 8.
[b] Not optimized.

(iv) The fact that the C(O)–S bond length calculated with sp and spd basis sets is almost equal both in $CH_3C(O)SCH_3$ and $^-CH_2C(O)SCH_3$ suggests the absence of $(p–d)_\pi$ conjugative effects, in this bond, in the ground state of the molecule and its anion, because such effects are expected to be manifested by a decrease in the bond length. In addition, the optimized C(O)–S bond lengths computed with the spd basis set are equal in $CH_3C(O)SCH_3$ and $^-CH_2C(O)SCH_3$, which means that α-carbanion formation in thioesters does not enhance the sulfur d-orbital expansion.

3.2. Barrier to internal rotation

The energies of methyl acetate, *S*-methyl thioacetate, and the corresponding anions have

Table 2

Optimized geometry of $CH_3C(O)SCH_3$ and $^-CH_2C(O)SCH_3$ as computed with sp and spd basis sets on sulfur

Geometric parameter	Computed values				Experimental values [a]
	sp basis set		spd basis set		
	$CH_3C(O)SCH_3$	$^-CH_2C(O)SCH_3$	$CH_3C(O)SCH_3$	$^-CH_2C(O)SCH_3$	
Bond lengths (Å)					
C(O)–S	1.73	1.76	1.76	1.76	1.78
C=O	1.19	1.18	1.16	1.18	1.24
C–C	1.48	1.47	1.47	1.47	1.54
C–S [b]	1.80	1.80	1.80	1.80	1.80
C–H [b]	1.09	1.09	1.09	1.09	1.09
Bond angle (°)					
C–C=O	126.20	126.90	124.10	123.60	125.00
C–C–S	110.40	110.89	109.50	110.03	110.00
S–C=O	123.40	122.10	126.40	126.40	125.00
C–S–C [b]	100.00	100.00	100.00	100.00	100.00
HCH, HCC, HCS [b]	109.50	109.50	109.50	109.50	109.50

[a] Data taken from refs. 9 and 10.
[b] Not optimized.

been calculated as a function of the torsional angle, θ, about the C(O)–X (X = O or S) bond. The barrier to internal rotations thus calculated (within the rigid rotor approximation) are given in table 3. The calculated barriers are in qualitative agreement with experimental barries reported for similar molecules [12]. The tendency of a thioester and its anion to have lower barriers to internal rotation about the C(O)–S bond is directly related to the lower tendency of sulfur to form $(p-p)_\pi$ bonding as compared to oxygen. The presence of d-functions on sulfur increases the barrier height by only about 1.5% in both cases (thioester and its anion), i.e. $(p-d)_\pi$ conjugation is of minor importance in thioesters.

3.3. Charge density distribution

Figs. 2 and 3 present the net charges on each atom and the π-bond orders for the oxygen ester and its anion and for the thioester and its anion, respectively. Inspectively. Inspection of figs. 2 and 3 reveals the following.

(i) A carbonyl group adjacent to oxygen in the oxygen ester (and its anion) is much more polar than that adjacent to sulfur in the thioester (and its anion). In the oxygen esters, where significant resonance effects are known to be present in the C(O)–X group of a type represented by structure II, this polarity with a high negative charge on the carbonyl oxygen is expected. Thus, replacing oxygen by sulfur reduces the net negative charge on the carbonyl oxygen atom by 40%, i.e., structure II makes no signficant contribution either to the ground state of the thioester or to that of its anion. It is interesting to note that this charge is not accumulated on the sulfur atom. Inclusion of d-functions on sulfur facilitates this transfer of charge, away from the carbonyl oxygen, and leads to accumulation of a greater negative density on the sulfur atom.

(ii) The π-bond order in the C(O)–O bond region is almost twice that in the C(O)–S bond region, whether or not d-functions are included. In fact, the d-functions on sulfur have no influence on the π-bond order in the C(O)–S bond region. This point is also evident on recognizing that the p–π orbital of sulfur is all bonding (95.7%) whereas, the d–π orbitals are only 1% involved in π-bonding. This negligible π-bonding capacity indicates that, in the thioester and its anion, there is no role for $(2p-3d)_\pi$ bonding involving the sulfur atoms.

(iii) The relative magnitudes of the π-bond orders and the charge distribution in the H_3C–C, C(O)–O and C(O)–S regions suggest two different interaction and delocalization schemes for the thioesters and oxygen esters. Thus, in the case of the thioester, the H_3C–C=O interaction is pronounced, whereas the C(O)–O interaction is predominant in the case of the oxygen ester. Therefore, one may conclude that in the case of the α-Carbanion of thioesters the carbonyl oxygen acts as an electron sink much better than that of oxygen esters.

3.4. The proton affinities of $^-CH_2C(O)OCH_3$ and $^-CH_2C(O)SCH_3$

The proton affinity of an anion A^- or the proton detachment energy of an acid AH, may be

Table 3

Total energies of oxygen ester and thioester and the corresponding anions as a function of rotation about the C(O)–X (X=O or S) bond and the computed barrier energies ($E^\ddagger$)

Species	Basis on the heteroatom	Total energy (eV)		$E^\ddagger$ (kcal mol^{-1})
		$\theta = 0°$	$\theta = 90°$	
$CH_3C(O)OCH_3$	sp	−1477.5002	−1476.2377	29.10
$^-CH_2C(O)OCH_3$	sp	−1468.2954	−1467.4481	19.53
$CH_3C(O)SCH_3$	sp	−1307.4788	−1306.8766	13.88
	spd	−1311.1911	−1310.5811	14.06
$^-CH_2C(O)SCH_3$	sp	−1298.4770	−1297.8149	15.26
	spd	−1302.0285	−1301.3569	15.48

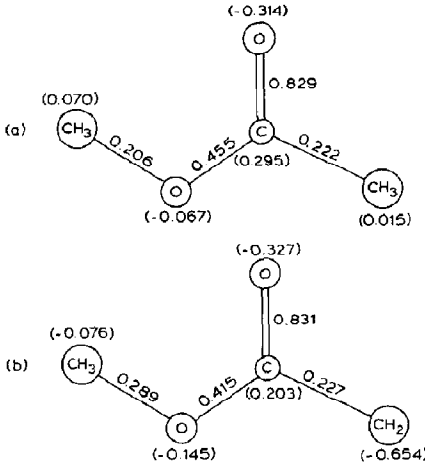


Fig. 2. Charge distribution and the π-bond orders in (a) $CH_3C(O)OCH_3$(sp), and (b) $^-CH_2C(O)OCH_3$(sp).

defined as $-\Delta H_{298}$ for the gas phase reaction

$$A^- + H^+ \rightleftharpoons AH \qquad (1)$$

The proton detachment energy (PDE) may be written as

$$PDE = -\Delta E_0^{el} - \Delta ZPE - \int_0^{298} \Delta C_p dT \qquad (2)$$

where ΔE_0^{el} is the electronic energy difference $E(A^-) - E(AH)$, ΔZPE the zero-point energy difference ZPE(AH) − ZPE(A^-), and ΔC_p the difference of constant-pressure molar heat capacities $C_p(H^+) + C_p(A^-) - C_p(AH)$. If A^- and AH possess the same number of rotational degrees of freedom, and if vibrational and electronic contributions to $C_p(A^-) - C_p(AH)$ are neglected, then the last term in eq. 2 reduces to the H^+ contribution of $+5RT/2$ or 6.2 kcal mol^{-1} at 298 K. ΔZPE values are typically 25–40 kcal mol^{-1} and which reduce the computed anion proton affinities.

In table 4, the computed proton affinities ($-\Delta E_0^{el}$ contribution only) are listed for the anions studied. For the thioester anion, the proton affinities calculated using the sp and spd basis sets are included.

Inspection table 4 indicates that the proton affinity of the thioester anion is lower than that of the oxygen ester anion by about 20 kcal mol^{-1}.

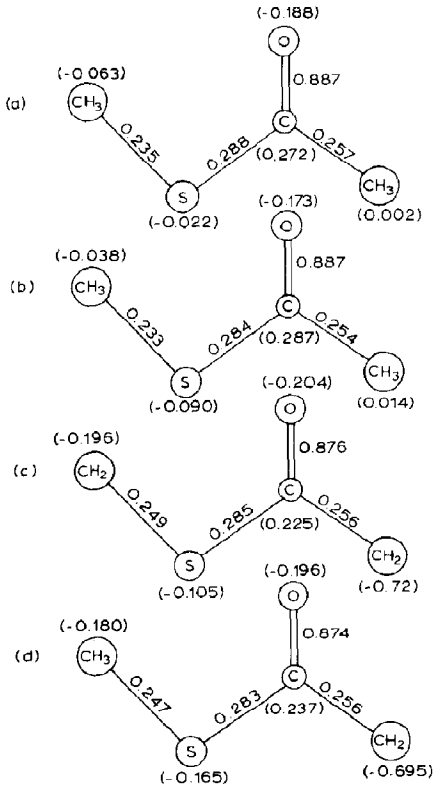


Fig. 3. Charge distribution and the π-bond orders in (a) $CH_3C(O)SCH_3$(sp), (b) $CH_3C(O)SCH_3$(spd), (c) $^-CH_2C(O)SCH_3$(sp) and (d) $^-CH_2C(O)SCH_3$(spd).

Hence, the gas-phase acidity of the H–C bond in the carbonyl methyl group in the thioester is greater than that of the same bond in the oxygen ester.

The inclusion of d-functions in the basis set

TABLE 4

The computed proton affinities of $^-CH_2C(O)OCH_3$ and $^-CH_2C(O)SCH_3$ as a function of basis set

Species	Basis on the hetero-atom	Total energy (eV)	Proton affinity (kJ mol^{-1})
$CH_3C(O)OCH_3$	sp	−1477.5002	
$^-CH_2C(O)OCH_3$	sp	−1468.2954	887.722
$CH_3C(O)SCH_3$	sp	−1307.4788	
	spd	−1311.1911	
$^-CH_2C(O)SCH_3$	sp	−1298.4770	868.342
	spd	−1302.0285	883.863

does not alter the conclusion drawn in the last paragraph. These d-functions did lower the energies of the thioester and its anion, the extent of lowering amounting to 3.5 eV per sulfur atom, which is typical for INDO calculations. However, the extent of lowering is almost exactly the same for the thioester and its anion. This indicates that the d-functions have the expected mathematical effect, yet without chemical significance, as far as proton affinities are concerned. This rules out the importance of d-orbital conjugation in connection with enhanced acidities, a conclusion which elaborates upon the work of Bernardi et al. [13] on carbanions of methanol and methyl mercaptan.

It is important to establish by a criterion other than that of anion proton affinities whether the use of d-functions to augment the standard INDO sp basis set is necessary for providing an adequate description of the electronic stability of the anion considered. Koopman's theorem of electron detachment energies (EDE) provides such a criterion. For ab initio computations using the DZ basis set, it has been shown [14] that, unless diffuse and/or polarization functions are employed, EDEs of anions computed would correspond to HOMOs which are actually unbound (−Ve EDEs). In our computation, the EDEs of the thioester anions are 5.48 and 5.55 eV for the sp and spd basis, respectively. Such a result indicates that the INDO sp basis set provides an adequate description of the electronic stability of the thioester anion studied.

It is clear from the present investigation that some inherent differences between sulfur and oxygen atoms are being reflected in the properties of thioesters and oxygen esters. Two such differences are the lower electronegativity of sulfur and the lower tendency of sulfur to form $(p-p)_\pi$ bonding compared to oxygen. Consequently, the effect of these two differences is to make the contributions of structures II and III to the ground state of a thioester and its anion negligible, and thus allow acetyl-CoA to possess a driving force for acetylation reactions to form oxygen esters or amides with large resonance stabilization. The formation of α-carbanions is facilitated because the carbonyl oxygen is a much better electron sink than that in oxygen esters; i.e., the α-carbanion in sulfur esters is stabilized by delocalization of its negative charge between the α-carbon and acyl oxygen atom. This is a result of the lack of a resonance rather than sulfur d-orbital conjugation. This result is in excellent agreement with a previous conclusion derived from less direct investigation of force constant calculations [6].

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