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Gas Electron Diffraction Analysis on *S*-Methyl Thioacetate, $CH_3C(O)SCH_3$

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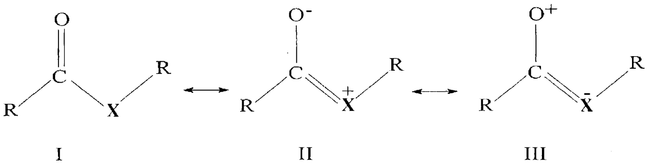
The molecular structure of *S*-methyl thioacetate, $CH_3C(O)SCH_3$, was determined by gas electron diffraction (GED) with the assistance of quantum chemical calculations (B3LYP/6-31G* and MP2/6-31G*). Experimental and theoretical methods result in a structure with syn conformation (C═O double bond syn with respect to the S−C(H$_3$) single bond). The following skeletal geometric parameters were derived from the GED analysis (r_a values with 3σ uncertainties): C═O = 1.214(3), C−C = 1.499(5), S−C(sp^2) = 1.781(6), S−C(sp^3) = 1.805(6) Å, O═C−C = 123.4(8)°, O═C−S = 122.8(5)° and C−S−C = 99.2(9)°.

Introduction

Structural and conformational properties of thioesters of the type RC(O)SR′ are of great interest because of their close relation to many biomolecules. They represent simple model compounds for biomolecules such as coenzyme A. The different reactivity of thioesters as compared to that of oxoesters has attracted considerable interest in the past years. From vibrational spectra and force constant calculations it was concluded that resonance structures II and III (Chart 1) play an important role in oxoesters (X = O) and make only a negligible contribution to the ground-state structure of thioesters (X = S).[1] This would allow acetyl coenzyme A to possess a driving force for acetylation reactions to form oxygen esters or amides with larger resonance stabilizations. A quantitative rationalization of the different reactivity of methyl acetate and methyl thioacetate with nucleophiles has been given by Yang and Drueckhammer on the basis of orbital interactions.[2] According to a natural bond orbital (NBO) analysis, interactions of n_σ and n_π electron lone pairs at the bridging X atom (X = O or S) with antibonding σ^* and π^* orbitals play an important role in the ground state properties of the esters and in the transition state of these reactions. These delocalization interactions are considerably higher in the oxoesters and lead to increase the activation energy of the reaction compared to that in thioesters. Orbital interactions such as conjugation ($n_\pi \rightarrow \pi^*$(C═O)) and anomeric effects ($n_\sigma \rightarrow \sigma^*$(C═O) and $n_\sigma \rightarrow \sigma^*$(C−C)) have also a strong influence on the structural and conformational properties of isolated oxoesters and thioesters. Thus, the comparison of geometric structures of oxo- and thioesters can provide experimental information about the importance of these orbital interactions. The gas-phase structure of methyl acetate, $CH_3C(O)OCH_3$, has been determined by a joint analysis of gas electron diffraction (GED) and microwave spectroscopic (MW) data.[3] In the present study we report the gas-phase structure of the analogous thioester $CH_3C(O)SCH_3$ using GED and quantum chemical calculations. The vibrational spectra and matrix isolation photochemistry of this compound have been reported previously.[4]

CHART 1



Quantum Chemical Calculations

The geometric structures of methyl thioacetate were optimized at different fixed dihedral angles ϕ(O═C−S−C) with the MP2 approximation and B3LYP method using 6-31G* basis sets. The potential curve for internal rotation around the S−C(sp^2) bond possesses minima for planar syn and anti conformations. The anti conformer is considerably higher in energy (ΔE = 5.26 and 4.59 kcal/mol according to MP2 and B3LYP, respectively), and the free energy difference is even higher ($\Delta G°$ = 6.01 kcal/mol according to MP2). The barrier to internal rotation from syn to anti is predicted to be about 12 kcal/mol. Very

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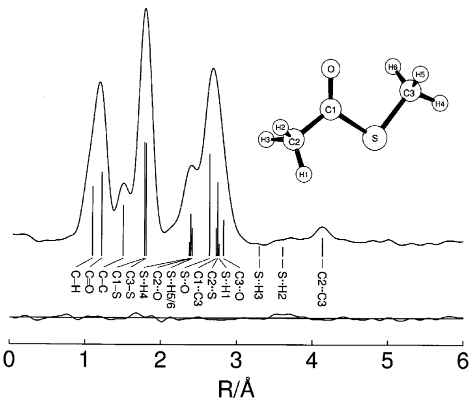

FIGURE 1. Experimental radial distribution function (top) and difference curve RDF(expt) − RDF(calc) (bottom). Important interatomic distances are indicated by vertical bars.

similar results for the energy differences have been obtained previously with the 6-31+G* basis sets (ΔE = 5.17 and 4.59 kcal/mol according to MP2 and B3LYP, respectively).[4] Vibrational amplitudes were derived from the calculated (MP2/6-31G*) force constants using the program ASYM40.[5] All quantum chemical calculations were performed with the GAUSSIAN 98 program package.[6]

Structure Analysis. The experimental radial distribution function (Figure 1), which was derived by Fourier transformation of the molecular intensities, can be fitted reasonably well only with a syn conformer, in agreement with the quantum chemical calculations. A preliminary structural model was refined by least squares procedures. Since the vibrational frequency for torsion around the C1−S bond is predicted to be 127 cm^{-1} and the barrier to internal rotation around this bond is about 12 kcal/mol, the approximation of small-amplitude vibrations is adequate for this molecule. Large amplitude vibrations around the C1−C2 and S−C3 bonds have a negligible effect on the GED intensities.

A planar heavy atom skeleton was assumed, and the CH_3 groups were constrained to C_{3v} symmetry. The tilt angles between the C_3 axis and the C−C and S−C bond direction, respectively, were fixed to the calculated values. Also the torsional position of the acetyl CH_3 group (ϕ(O1−C1−C2−H1), which is predicted by the MP2 method to be intermediate between eclipsing and staggering the C═O bond, is fixed at the calculated value. Because the two S−C bond lengths, S−C(sp^2) and S−C(sp^3), are rather similar, it was not possible to refine both bond lengths and the corresponding vibrational amplitudes simultaneously. The amplitudes for both bond distances are predicted to be equal. In the least squares procedure the mean S−C distance and the difference Δ(S−C) were refined and the vibrational amplitude was fixed to the calculated value. The systematic error due to this constraint was estimated by varying the amplitude by ±0.003 Å. In this case the difference Δ(S−C) varied by less than the experimental uncertainty in Table 1, which corresponds to 3σ. With these assumptions 10 geometric parameters and four vibrational amplitudes were refined simultaneously. Only two correlation coefficients had values larger than |0.6|: p7/l4 = 0.70 and p8/l4 = −0.63. The final results are collected in Tables 1 (geometric parameters) and 2 (vibrational amplitudes) together with calculated values.

TABLE 1. $CH_3C(O)SCH_3$: Experimental and Calculated Geometric Parameters[a]

	GED		MP2/ 6-31G*	B3LYP/ 6-31G*
r C−H	1.092 (5)	p1	1.091[b]	1.094[b]
r C═O	1.214 (3)	p2	1.223	1.210
r C−C	1.499 (5)	p3	1.511	1.516
r (S−C)mean	1.793 (2)	p4	1.794	1.818
Δr SC = rS−C(sp^3) − rS−C(sp^2)	0.024 (10)	p5	0.0026	0.015
r S−C(sp^2)	1.781 (6)		1.781	1.809
r S−C(sp^3)	1.805 (6)		1.807	1.826
∠ O═C−C	123.4 (8)	p6	123.2	123.3
∠ O═C−S	122.8 (5)	p7	122.3	123.6
∠ C−S−C	99.2 (9)	p8	98.2	100.3
∠ H−C2−H	107.6 (27)	p9	108.5[b]	108.9[b]
∠ H−C3−H	109.5 (21)	p10	109.7[b]	110.1[b]
∠ tilt (C2H3)	2.4[c]		2.4	2.7
∠ tilt (C3H3)	1.3[c]		1.3	1.8
ϕ(O1−C1−C2−H1)	143.1[c]	143.1[c]	143.1	172.1
ϕ(C1−S−C3−H4)	180.0[c]	180.0[c]	178.1	179.2

[a] Values in Å and deg, uncertainties are 3σ values. For atom numbering see Figure 1. [b] Mean value. [c] Not refined

TABLE 2. $CH_3C(O)SCH_3$: Interatomic Distances and Experimental and Calculated Vibrational Amplitudes (Excluding Nonbonded Distances Involving Hydrogen Atoms)[a]

	distance	ampl (GED)		ampl (MP2)
r C−H	1.09	0.076		0.076
r C═O	1.21	0.035 (4)	l1	0.038
r C−C	1.50	0.052 (6)	l2	0.050
r S−C	1.78−1.80	0.051[b]		0.051
r O1···C2	2.40	0.064 (6)	l3	0.061
r O1···S	2.64	0.059 (6)	l3	0.056
r C1···C3	2.74	0.074 (7)	l4	0.072
r S···C2	2.75	0.083 (7)	l4	0.081
r C2···C3	4.14	0.082 (7)	l4	0.080

[a] Values in Å, uncertainties are 3σ values. For atom numbering see Figure 1. [b] Not refined.

Discussion

Only the syn conformation of $CH_3C(O)SCH_3$ is observed in the GED experiment. To investigate the existence and relative stability of different conformers, the IR spectrum of matrix-isolated molecules and the effects of subsequent broad-band UV−visible photolysis have been investigated.[4] No evidence of a second conformation could be confirmed by these experiments. Various effects that stabilize the syn conformer or destabilize the anti form of oxo- and thioesters have been discussed by Pawar et

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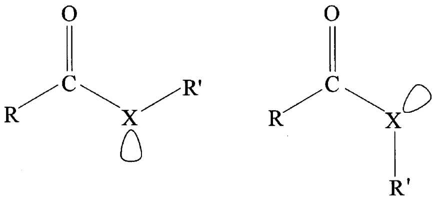
CHART 2



syn (Z) anti (E)

al.[7] Dipole−dipole interactions destabilize the anti form of methyl thioacetate. According to MP2 calculations the dipole moments(μ(anti) = 4.7 D and μ(syn) = 1.5 D) differ strongly. Anomeric interactions between the n_σ lone pair of sulfur with trans standing σ* bonds, i.e., n_σ (S) → σ*(C═O) in the syn conformer and n_σ (S) → σ*(C−C) in the anti form (see Chart 2) are very similar (4.9 and 4.4 kcal/mol, respectively) and lead only to a slight preference of the syn conformation.

Surprisingly, conjugation between the p-shaped sulfur lone pair n_π and the (C═O) π bond, n_π (S) → π*(C═O), favors the syn form strongly over the anti conformation (45.1 and 42.1 kcal/mol, respectively). In addition to these electronic effects, steric strain destabilizes the anti form, as can be seen from calculated C−S−C angles (98.2° for syn and 104.5° for anti). Thus, electronic and steric effects lead to a strong preference of the syn form with a calculated (MP2) energy difference of 5.26 kcal/mol between the two conformations.

This energy difference between the two conformations almost vanishes in thioformic acid, HC(O)SH. According to MW this compound exists in the gas phase as a mixture of both forms, with the syn conformer favored slightly.[8] Low-temperature NMR spectroscopy of thioformic acid in CD_2Cl_2 solution resulted in 52.5% anti conformer, corresponding to $\Delta G° = -0.03$ kcal/mol.[9] A similar NMR experiment for S-methyl thioformate, $HC(O)SCH_3$, resulted in a free energy difference of 1.57 kcal/mol.[7] Only the syn conformer was observed in a MW study of the gas phase.[10]

Comparison of geometric parameters of methyl acetate and methyl thioacetate reveals that orbital interactions are rather different in these two esters. Both interactions, conjugation n_π (X) → π*(C═O) and anomeric effect n_σ (X) → σ*(C═O), which can be represented by resonance structure II in Chart 1, lead to shortening of the X−C(sp^2) bond, relative to the X−C(sp^3) bond. In methyl acetate the O−C(sp^2) distance (1.360(6) Å) is shorter by 0.082(9) Å than the O−C(sp^3) bond (1.442(6) Å), whereas the two S−C bond lengths in methyl thioacetate differ by only 0.024(10) Å. Thus, experimental X−C bond lengths indicate that orbital interactions represented by the resonance structure II are weaker in the thioester. This is confirmed by an NBO analysis of the MP2 wave function, which results in interaction energies of 61.9 kcal/mol in methyl acetate and 49.9 kcal/mol in methyl thioacetate. The S−C(sp^2) bond distance in methyl thioacetate (1.781(6) Å) is equal to that in dimethyl dithiocarbonate $(CH_3S)_2CO$, (1.777(3) Å,[11]) and the S−C(sp^3) bond distance (1.805(6) Å) to that in dimethyl sulfide, $(CH_3)_2S$, (1.807(2) Å,[12]). Table 3 compares the skeletal geometric parameters of $CH_3C(O)SCH_3$ with those of $CF_3C(O)SCH_3$ [13] and $CF_3C(O)SCF_3$.[14] CH_3/CF_3 substitution at the carbon atom causes slight shortening of the C═O bond, lengthening of the C−C bond, and considerable shortening of the S−C(sp^2) bond from 1.781(6) to 1.743(14) Å in trifluoromethyl thioacetate, leading to a larger difference between the two S−C distances of 0.064(22) Å. Furthermore, the O═C−C angle decreases by about 6° and the O═C−S angle increases by about the same amount, i.e., the C═O bond is bent toward the CF_3 group.

TABLE 3. Skeletal Geometric Parameters of $CH_3C(O)SCH_3$, $CF_3C(O)SCH_3$, and $CF_3C(O)SCF_3$

	$CH_3C(O)SCH_3$	$CF_3C(O)SCH_3$ [a]	$CF_3C(O)SCF_3$ [b]
r C═O	1.214(3)	1.206(6)	1.202(6)
r C−C	1.499(5)	1.527(5)	1.525(10)
r S−C(sp^2)	1.781(6)	1.743(14)	1.780(3)
r S−C(sp^3)	1.805(6)	1.807(16)	1.820(3)
∠ O═C−C	123.4(8)	116.8(21)	118.7(21)
∠ O═C−S	122.8(5)	127.2(19)	127.1(15)
∠ C−S−C	99.2(9)	97.5(13)	99.8(13)

[a] Reference 13. [b] Reference 14.

Additional CH_3/CF_3 substitution at the sulfur lengthens again the S−C(sp^2) bond and causes no further changes of geometric parameters in perfluoromethyl thioacetate larger than the experimental uncertainties.

Many organic chemistry and biochemistry books dealing with enzymatic reactions of coenzyme A attribute its acetyl transfer ability to the lower degree of electron delocalization or resonance of a lone electron pair of the bridging sulfur with the C═O group of an thioester in relation to the similar interaction in an oxoester.[15−17] Moreover, from a thermodynamic point of view the hydrolysis of a thioester is more favored than that of the corresponding ester: $\Delta G°$ at pH = 7 amounts to −7.5 kcal mol^{-1} (1 cal = 4.18 J) for the hydrolysis of coenzyme A.

Whether the discussed structural difference supported by thermodynamic data may explain huge differences of about 2000-fold more reactivity of a thioester compound compared with its equivalent oxoester in the reaction with an alquil cyanoacetate[18] represents an open question. Moreover, the general reactivity tendency is just the opposite when thioesters and oxoesters hydrolyze in basic solutions.[19]

Our previous reported structural study on $CF_3C(O)$-$SOC(O)CF_3$, a molecule specially suited to compare

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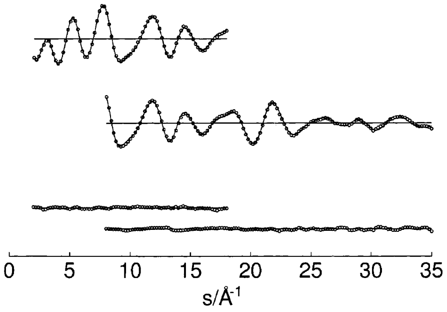

FIGURE 2. Averaged experimental molecular intensities for long (top) and short (bottom) nozzle-to-plate distances and residuals.

thioester and oxoester properties, shows that the deviation from 0° of the O═C−S−O and the O═C−O−S torsional angles would indicate a more extended double bond character of the C−O than of the C−S single bond. The opposite trend is obtained by analyzing the rotational energy barriers around the C−S and C−O single bonds. Values of 13.2 and 10.6 kcal mol^{-1} were calculated forthe height of the barrier around the C−S and C−O single bonds, respectively, with B3LYP/6-31G* approximation.[20]

More experimental effort is necessary to elucidate the described ambiguity. However, a plausible way to explain these rather controversial results has been reported by Drueckhammer[2] et al. Using theoretical tools the authors explain the compared reactivity of oxoesters and thioesters toward nucleophiles, evaluating losses of delocalization energies for the oxoester and thioester in going from the reactants to the transition state.

Experimental Section

The compound was purchased and purified by repeated distillation in a vacuum line. The purity was checked by FTIR and ^{13}C and ^{1}H NMR spectroscopy.

GED intensities were recorded with a Gasdiffraktograph[21] at 25 and 50 cm nozzle-to-plate distances and with an accelerating voltage of about 60 kV. The sample reservoir was kept at −5 °C, and the inlet system and gas nozzle were at room temperature. The photographic plates were analyzed with the usual methods,[22] and averaged molecular intensities in the s-ranges 2−18 and 8−35 Å^{-1} in steps of $\Delta s = 0.2$ Å^{-1} are shown in Figure 2 ($s = (4\pi/\lambda) \sin \theta/2$; λ is electron wavelength and θ is scattering angle).

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Supporting Information Available: Details of quantum chemical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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