

Experimental and Computational Thermochemical Study of 2- and 3-Thiopheneacetic Acid Methyl Esters

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Thiophene-based compounds have widespread use in modern drug design, biodiagnostics, electronic and optoelectronic devices, and conductive polymers. The present study reports an experimental and computational thermochemical study on the relative stabilities of 2- and 3-thiopheneacetic acid methyl esters. The enthalpies of combustion and vaporization were measured by a rotating-bomb combustion calorimeter, Calvet microcalorimetry, and correlation gas chromatography, and the gas-phase enthalpies of formation at $T = 298.15$ K were determined. Standard ab initio molecular orbital calculations at the G3 level were performed, and a theoretical study of the molecular and electronic structure of the compounds studied was carried out. Calculated enthalpies of formation, using atomization and isodesmic reactions are in very good agreement with the experimental results.

1. Introduction

Thiophene is a chemically stable compound that is easy to process, and its applications have been a constant matter of investigation. Several books and reviews are available on the chemistry of thiophenes.¹ It is the simplest representative of an aromatic structure bearing sulfur. Thiophene obeys the $4n + 2\pi$ electron rule, and it is generally considered to be aromatic.² Its structure can be assumed to be derived from benzene by the replacement of two annular CH groups by sulfur. The sulfur atom in this five-membered ring acts as an electron-donating heteroatom by contributing two electrons to the aromatic sextet, and thiophene is thus considered to be an electron-rich heterocycle.

Thiophene-based compounds have been investigated extensively and have also found widespread use in modern drug design,³ biodiagnostics,⁴ electronic and optoelectronic devices,⁵ and conductive polymers.⁶ Moreover, condensed thiophenes comprise a significant portion of the organosulfur compounds in petroleum and in other products from fossil fuels, being obtainable as byproducts of petroleum distillation.⁷ Thus, different studies related to their biodegradation⁸ and catalytic dehydrodesulfuration⁹ have been carried out. In this regard, several reviews of various aspects of thiophene coordination and reactivity in transition metal complexes have been reported.¹⁰

Over the past years, we have been involved in a thermochemical study of the energetics of thiophene derivatives.^{11–17}

A development of an understanding of the structural effects on the thermodynamic stabilities reflected in the gas-phase enthalpies of formation of the compounds studied has been of fundamental interest to us. The relationship between substituents on the five-membered ring of thiophene is different from that of similar substituents in benzene. Our work has focused mainly on the energetic differences between isomers containing different functional groups in positions 2 and 3, and the substituent effects in thiophene relative to benzene analogues. In a previous article we reported the thermochemistry of 2- and 3-thiophenecarboxylic acids.¹¹ In general, the $-\text{COOH}$ group of thiophenecarboxylic acids acts much the same way as that in other organic compounds. We showed previously that 3-thiophenecarboxylic acid is slightly more stable, thermodynamically, than 2-thiophenecarboxylic acid with an isomerization enthalpy of 2.6 kJ mol^{-1} . In comparison with benzene and its analogous substituted derivative benzoic acid, we found that the 2-isomer is destabilized by 2.4 kJ mol^{-1} as a result of the through-space interaction between the oxygen of the hydroxyl group and the sulfur atom.¹³ With the result obtained with 3-thiophenecarboxylic acid, -0.2 kJ mol^{-1} , we concluded that there are not significant differences between the substituent effects produced by a carboxyl group in benzene and those produced by the 3-position in thiophene.¹³ Similarly, the relative stability obtained for the substitution of two H atoms by COOH groups in the 2,5-position of thiophene and the 1,4-position of benzene involve the same energetic effects.¹⁵

The purpose of the present work is to study the energetics of the 2- and 3-thiopheneacetic acid methyl esters, whose formula is presented in Figure 1. The approach selected is a combination

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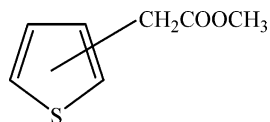


Figure 1. Structural formula of thiopheneacetic acid methyl esters.

of experimental determinations of the enthalpy of formation and high-level ab initio calculations.

2. Experimental Section

2.1. Material and Purity Control. The samples of 2-thiopheneacetic acid methyl ester [CAS 19432-68-9] and 3-thiopheneacetic acid methyl ester [CAS 58414-52-1] were obtained from Fluka and Lancaster, respectively, with a massic purity of greater than 97%. The samples were purified further by repeated distillation under reduced pressure. The purity of both samples was checked by gas-liquid chromatography, using a Hewlett-Packard 4890A gas chromatograph, on a HP5 column, (flame ionization detector (FID) at $T = 473$ K), using a mixture of nitrogen and compressed air as the carrier gas ($p = 3$ psi); the purity was found to be greater than 99.97%.

2.2. Experimental Determination of the Enthalpy of Formation in the Gas Phase. The enthalpies of formation in the gas phase of 2- and 3-thiopheneacetic acid methyl esters, $\Delta_f H_m^o(g)$ at $T = 298.15$ K, were determined by combining the experimental values of their standard enthalpies of formation in the condensed state, $\Delta_f H_m^o(cd)$, obtained by combustion calorimetry, and the standard enthalpies of vaporization, $\Delta_f^g H_m^o$ obtained both by Calvet microcalorimetry and correlation gas chromatography.

2.2.1. Combustion Calorimetry. The enthalpies of combustion were measured at the University of Porto using the rotating-bomb calorimeter formerly at the National Physical Laboratory, Teddington, U. K.^{18,19} The calorimeter consists of a tantalum lined bomb of internal volume 0.329 dm³. Water was added to the calorimeter from a weighted acrylic vessel, and, for each experiment, a correction to the energy equivalent was made for the deviation from 3965.0 g of the mass of water added. Calorimetric temperatures were measured to 1×10^{-4} K with a quartz thermometer (Hewlett-Packard HP 2804A) interfaced to a microcomputer programmed to compute the adiabatic temperature change. Ignition temperatures were chosen so that the final temperatures were very close to 298.15 K. The rotation of the bomb was started when the temperature rise of the main period reached about 0.63 of its total value and continued throughout the experiment. The frictional work of bomb rotation was automatically included in the correction for heat exchange, and the work of stirring was included by using the procedure described by Good et al.²⁰ Data acquisition and control of the calorimeter was performed using the program LABTERMO.²¹

The energy equivalent of the calorimeter was determined in the conventional way, without rotation of the bomb, from the combustion of benzoic acid, National Bureau of Standards (NBS) thermochemical standard 39i, having a massic energy of combustion under bomb conditions of $-(26434 \pm 3)$ J·g⁻¹, as described previously.²² The electrical energy for the ignition was determined from the change in potential across a capacitor when 40 V was discharged through a platinum ignition wire. For the cotton thread fuse (empirical formula CH_{1.686}O_{0.843}), the massic energy of combustion is assigned to $\Delta_c u^0 = -16240$ J·g⁻¹,²⁰ a value that was confirmed in our laboratory. Corrections for the nitric acid formation, from traces of N₂ remaining inside the bomb, were based on -59.7 kJ·mol⁻¹ for the molar energy of formation of 0.1 mol·dm⁻³ HNO₃ (aq) from O₂, N₂, and H₂O

(1).²³ From 10 calibration experiments, the energy equivalent of the calorimeter, $\epsilon(\text{calor})/(\text{J}\cdot\text{K}^{-1})$ was found to be $\{20369.0 \pm 2.3 (0.011\%)\}$ for an average mass of water added to the calorimeter of 3965.0 g; the quoted uncertainty is the standard deviation of the mean.

The samples of the thiopheneacetic acid methyl esters were contained in sealed polyester bags made of Melinex (0.025 mm of thickness) with massic energy of combustion $\Delta_c u^0 = -(22902 \pm 5)$ J·g⁻¹,²⁴ a value that was confirmed in our laboratory. The mass of Melinex used in each experiment was corrected for the mass fraction of water ($w = 0.0032$), and the mass of carbon dioxide produced from its combustion was calculated using the factor previously reported.²⁴ Samples were ignited in oxygen at a pressure of 3.04 MPa with a volume of 15 cm³ of water added to the bomb. The amount of nitric acid produced was determined by the Devarda's alloy method.²⁵ The densities of the 2- and 3-thiopheneacetic acid methyl esters were determined by a Paar Precision Density Meter DMA 02D, being 1.182 and 1.185 g·cm⁻³ for the 2- and 3- isomers respectively.

For each compound, $(\partial u/\partial p)_T$ at $T = 298.15$ K was assumed to be -0.2 J·g⁻¹·MPa⁻¹, a typical value for organic compounds.²⁶ The standard state corrections were calculated by the procedures given by Hubbard et al.²⁷ and by Good and Scott.²⁸ The samples, Melinex bags, and cotton fuses were weighed with a precision of $\pm 1 \times 10^{-5}$ g in a Mettler AG 245 balance.

The atomic masses used for the elements were those recommended by the IUPAC in 2005,²⁹ yielding the molar mass of the thiopheneacetic acid methyl esters, 156.205 g·mol⁻¹.

2.2.2. Calvet Microcalorimetric Measurements. The standard molar enthalpies of vaporization of both thiopheneacetic acid methyl esters were measured by the vacuum drop microcalorimetric technique described by Skinner et al.³⁰ for the determination of enthalpies of sublimation, which has been previously tested for liquid vaporizations in our laboratory.³¹ The measurements were performed with a Calvet high-temperature microcalorimeter (Setaram HT 1000) with the vacuum promoted by a rotary vacuum pump and a vapor diffusion pump. The apparatus and technique have been already described in the literature.³² Samples of about 6–8 mg of each compound, contained in thin glass capillary tubes sealed at one end, were dropped from room temperature into the hot reaction vessel in the microcalorimeter held at a predefined temperature $T = 350$ K, and then removed from the hot zone by vacuum vaporization. The samples of compounds and the glass capillary tubes were weighed on a Mettler CH-8608 analytical balance, with a sensitivity of (1×10^{-6}) g. The thermal corrections for the glass capillary tubes were determined in separate experiments, and were minimized, as far as possible, by dropping tubes of nearly equal mass, to within ± 10 mg, into each of the twin calorimeter cells. The microcalorimeter was calibrated in situ performing vaporization experiments with *n*-undecane, following the same procedure as the one described above for the compounds. The calibration constant of the calorimeter, k_{cal} , was obtained as the average of six independent calibration experiments with *n*-undecane, using its reported standard molar enthalpy of vaporization, at $T = 298.15$ K, $\Delta_f^g H_m^o = (56.580 \pm 0.566)$ kJ·mol⁻¹,³³ and at $T = 350$ K, $k_{\text{cal}} = (0.9969 \pm 0.0026)$.

The observed enthalpies of vaporization were corrected to $T = 298.15$ K, using the value of $\Delta_{298.15\text{K}}^{350\text{K}} H_m^o(g)$ estimated by the Benson Group Method,³⁴ using values from Stull et al.³⁵

2.2.3. Correlation Gas Chromatography. The enthalpies of vaporization of methyl, 2- and 3-thiopheneacetic acid methyl esters were also measured by correlation gas chromatography using the procedure previously described.³⁶ A Hewlett-Packard

model 5890 series II gas chromatograph equipped with a split/splitless capillary injection port, an FID, and a 30 m SPB-5 capillary column was used. The retention times, t , were recorded to three significant figures following the decimal point on an HP 3356 series II integrator. The solvent used was methylene chloride. Methane was bubbled into the solution just prior to injection and was used as the nonretained reference to determine the dead volume of the column. Column temperatures were controlled by the instrument and monitored using a Fluke 51 K/J thermometer. All correlation gas chromatography experiments were performed in duplicate to confirm reproducibility. The results of only one experiment are reported below.

2.2.4. Computational Details. Standard ab initio molecular orbital calculations³⁷ were performed with the Gaussian 03 series of programs.³⁸ The energies of the compounds studied were calculated using Gaussian-3 theory, at the G3 level.³⁹ G3 corresponds effectively to calculations at the QCISD(T)/G3large level, with G3large being a modification of the 6-311+G(3df,2p) basis set, including more polarization functions for the second row (3d2f), less on the first row (2df), and other changes to improve uniformity. In addition, some core polarization functions are added.³⁹ In this method, single-point energy calculations are carried out on MP2(full)/6-31G(d) optimized geometries, incorporating scaled HF/6-31G(d) zero-point vibrational energies, a so-called higher-level correction to accommodate remaining deficiencies, and spin-orbit correction for atomic species only.³⁹

We have also reoptimized the geometries at the MP2(full)/6-31G(3df,2p) level to obtain more reliable molecular structures for the compounds studied.

The charge distribution was analyzed using a population partition technique, the natural bond orbital (NBO) analysis of Reed and Weinhold.^{40–42} The NBO analysis was performed using the NBO program⁴³ implemented in the Gaussian 03 package.³⁸

3. Results and Discussion

3.1. Experimental Results. Table 1 lists typical combustion results for each compound in which $\Delta m(\text{H}_2\text{O})$ is the deviation of the mass added to the calorimeter from 3965.0 g, the mass assigned to $\epsilon(\text{calor})$, and ΔU_{Σ} is the correction to the standard state. The remaining quantities are as previously described.²² Detailed results of each combustion experiment for both thiopheneacetic acid methyl esters are given in tables S1 and S2 of the Supporting Information. The internal energy for the isothermal bomb process, $\Delta U(\text{IBP})$, was calculated according to eq 1:

$$\Delta U(\text{IBP}) = -\{\epsilon(\text{calor}) + c_p(\text{H}_2\text{O}, l)\Delta m(\text{H}_2\text{O})\} \Delta T_{\text{ad}} + (T_i - 298.15)\epsilon_i + (298.15 - T_i - \Delta T_{\text{ad}})\epsilon_f + \Delta U(\text{ign}) \quad (1)$$

where ΔT_{ad} is the calorimeter temperature change corrected for the heat exchange and the work of stirring.

For each compound, the products of combustion in the experiments consist of a gaseous phase and an aqueous mixture of sulfuric acid for which the thermodynamic properties are known. The values of $\Delta_c u^0$ refer to the reactions represented by eq 2:

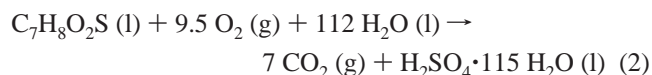


Table 2 lists, for each compound, the individual values of $\Delta_c u^0$, together with the mean and the standard deviation of the

TABLE 1: Typical Combustion Results at $T = 298.15$ K ($p^\circ = 0.1$ MPa) for the Substituted Thiopheneacetic Acid Methyl Esters^a

	2-thiopheneacetic acid methyl ester	3-thiopheneacetic acid methyl ester
$m(\text{cpd})/\text{g}$	0.81844	0.70808
$m'(\text{fuse})/\text{g}$	0.00329	0.00258
$m''(\text{Melinex})/\text{g}$	0.04358	0.04115
T_i/K	297.0199	297.1255
T_f/K	298.1824	298.1324
$\Delta T_{\text{ad}}/\text{K}$	1.12209	0.97449
$\epsilon_i/\text{J}\cdot\text{K}^{-1}$	74.49	74.35
$\epsilon_f/\text{J}\cdot\text{K}^{-1}$	73.82	73.62
$\epsilon(\text{calor})/\text{J}\cdot\text{K}^{-1}$	20370.67	20366.49
$\Delta m(\text{H}_2\text{O})/\text{g}$	-0.4	0.6
$-\Delta U(\text{IBP})/\text{J}$	22940.29	19918.38
$\Delta U(\text{fuse})/\text{J}$	53.43	41.90
$\Delta U(\text{Melinex})/\text{J}$	998.09	942.35
$\Delta U(\text{HNO}_3)/\text{J}$	39.04	22.69
$\Delta U(\text{ign})/\text{J}$	1.11	1.10
$\Delta U_{\Sigma}/\text{J}$	31.98	29.23
$-\Delta_c u^0/\text{J}\cdot\text{g}^{-1}$	26657.73	26666.77

^a $m(\text{cpd})$ is the mass of compound burnt in each experiment; $m'(\text{fuse})$ is the mass of the fuse (cotton) used in each experiment; $m''(\text{Melinex})$ is the mass of Melinex used in each experiment; T_i is the initial temperature rise; T_f is the final temperature rise; ΔT_{ad} is the corrected temperature rise; ϵ_i is the energy equivalent of the contents in the initial state; ϵ_f is the energy equivalent of the contents in the final state; $\epsilon(\text{calor})$ is the energy equivalent of the calorimeter corrected for the deviation of mass of water added to the calorimeter; $\Delta m(\text{H}_2\text{O})$ is the deviation of mass of water added to the calorimeter from 3965.0 g; $\Delta U(\text{IBP})$ is the energy change for the isothermal combustion reaction under actual bomb conditions; $\Delta U(\text{fuse})$ is the energy of combustion of the fuse (cotton); $\Delta U(\text{Melinex})$ is the energy of combustion of the Melinex; $\Delta U(\text{HNO}_3)$ is the energy correction for the nitric acid formation; $\Delta U(\text{ign})$ is the electric energy for the ignition; ΔU_{Σ} is the standard state correction; $\Delta_c u^0$ is the standard massic energy of combustion. ^b $\Delta U(\text{IBP})$ includes $\Delta U(\text{ign})$.

TABLE 2: Individual Values of Standard ($p^\circ = 0.1$ MPa) Massic Energies of Combustion, $\Delta_c u^0$, of the Compounds, at $T = 298.15$ K

2-thiopheneacetic acid methyl ester	3-thiopheneacetic acid methyl ester
$-\Delta_c u^0/\text{J}\cdot\text{g}^{-1}$	
26646.89	26667.69
26639.47	26658.69
26657.73	26669.73
26640.81	26666.77
26661.32	26658.43
26667.82	26667.03
$-\langle \Delta_c u^0 \rangle / (\text{J}\cdot\text{g}^{-1})$	
$(26652.3 \pm 4.8)^a$	$(26664.7 \pm 2.0)^a$

^a Mean value and standard deviation of the mean.

TABLE 3: Derived Standard ($p^\circ = 0.1$ MPa) Molar Values of Substituted Thiopheneacetic Acid Methyl Esters in the Condensed Phase, at $T = 298.15$ K

compound	$-\Delta_c U_m^0(l)$ ($\text{kJ}\cdot\text{mol}^{-1}$)	$-\Delta_c H_m^0(l)$ ($\text{kJ}\cdot\text{mol}^{-1}$)	$-\Delta_f H_m^0(l)$ ($\text{kJ}\cdot\text{mol}^{-1}$)
2-thiopheneacetic acid methyl ester (l)	4163.2 ± 2.2	4169.4 ± 2.2	330.4 ± 2.4
3-thiopheneacetic acid methyl ester (l)	4165.2 ± 1.7	4171.4 ± 1.7	328.5 ± 2.0

mean. Table 3 lists the derived standard molar values for the energies and enthalpies of combustion, $\Delta_c U_m^0$, $\Delta_c H_m^0$, respectively, as well as the standard molar enthalpies of formation, $\Delta_f H_m^0$, of the liquid compounds, at $T = 298.15$ K. In accordance with normal thermochemical practice, the uncertainties

TABLE 4: Standard ($p^\circ = 0.1$ MPa) Molar Enthalpies of Vaporization, $\Delta_1^g H_m^\circ$, for the Two Substituted Thiopheneacetic Acid Methyl Esters, at $T = 298.15$ K, Determined by Calvet Microcalorimetry

compound	number of experiments	T (K)	$\Delta_{1,298.15\text{K}}^{g,T} H_m$ (kJ·mol ⁻¹)	$\Delta_{1,298.15\text{K}}^T H_m^\circ(\text{g})$ (kJ·mol ⁻¹)	$\Delta_1^g H_m^\circ(298.15\text{K})$ (kJ·mol ⁻¹)
2-thiopheneacetic acid methyl ester (l)	5	349.7	71.4 ± 0.3	9.55	61.9 ± 1.4
3-thiopheneacetic acid methyl ester (l)	5	349.8	70.5 ± 0.2	9.57	60.9 ± 1.3

TABLE 5: Retention Times at Different Temperatures

T/K	379.4	374.3	369.3	364.3	359.3	354.2	349.1
	t/min						
methane	1.675	1.659	1.640	1.622	1.607	1.595	1.577
3-chloro-2-butanone	1.987	2.008	2.032	2.068	2.114	2.176	2.247
ethyl 2-chloropropionate	2.432	2.53	2.648	2.799	2.986	3.229	3.525
isopropyl chloroacetate	2.494	2.605	2.704	2.915	3.129	3.407	3.753
2-thiopheneacetic acid methyl ester	7.550	8.760	10.283	12.274	14.773	18.078	22.453
3-thiopheneacetic acid methyl ester	7.892	9.183	10.810	12.950	15.620	19.153	23.893
4-chloroacetophenone	9.739	11.422	13.535	16.341	19.803	24.380	30.566

TABLE 6: Summary of Calculated Values Obtained by Correlation Gas Chromatography

	slope	intercept	$\Delta_{\text{sln}}^g H_m(364\text{K})$ (kJ/mol)	$\Delta_1^g H_m^\circ(298.15\text{K})$ (kJ/mol) (lit)	$\Delta_1^g H_m^\circ(298.15\text{K})$ (kJ/mol) (calc)
3-chloro-2-butanone	-3350.0	10.002	27.9	40.5	38.9
ethyl 2-chloropropionate	-4136.2	11.189	34.4	46.2	47.2
isopropyl chloroacetate	-4275.9	11.479	35.5	46.0	48.6
2-thiopheneacetic acid methyl ester	-5545.0	12.854	46.1		61.1 ± 7.3
3-thiopheneacetic acid methyl ester	-5586.5	12.907	46.4		61.5 ± 7.3
4-chloroacetophenone	-5591.8	12.661	46.5	62.7	62.6

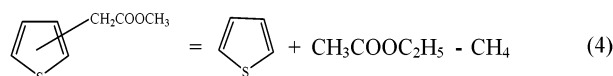
$$\Delta_1^g H_m^\circ(298.15\text{K}) = (1.224 \pm 0.158) \Delta_{\text{sln}}^g H_m(364\text{K}) + (4.68 \pm 5.79) r^2 = 0.968 \text{ (eq 6)}$$

assigned to the standard molar enthalpies of combustion and formation are twice the overall standard deviation of the mean and include the uncertainties in calibration and in the auxiliary quantities used. To derive $\Delta_f H_m^\circ(\text{l})$ from $\Delta_c H_m^\circ(\text{l})$, the standard molar enthalpies of formation of $\text{H}_2\text{O}(\text{l})$, $\text{CO}_2(\text{g})$, and H_2SO_4 in 115 $\text{H}_2\text{O}(\text{l})$ at $T = 298.15$ K, $-(285.830 \pm 0.042)$,⁴⁴ $-(393.51 \pm 0.13)$,⁴⁴ and $-(887.81 \pm 0.01)$ kJ·mol⁻¹,²³ respectively, were used.

Detailed results of the measurements of the enthalpies of vaporization determined by Calvet microcalorimetry are given in Table 4. From five independent determinations for each compound at $T = 350$ K, the average values of the observed enthalpies of vaporization, $\Delta_{1,298.15\text{K}}^{g,350\text{K}} H_m$, were corrected to $T = 298.15$ K, using the value of $\Delta_{298.15\text{K}}^{350\text{K}} H_m^\circ(\text{g})$, by means of eq 3:

$$\Delta_1^g H_m^\circ(T = 298.15\text{K}) = \Delta_{1,298.15\text{K}}^{g,350\text{K}} H_m - \Delta_{298.15\text{K}}^{350\text{K}} H_m^\circ(\text{g}) \quad (3)$$

using the enthalpic correction to the reference temperature $T = 298.15$ K, $\Delta_{298.15\text{K}}^{350\text{K}} H_m^\circ(\text{g})$, estimated by a group additivity method, that is,



based on the values of Stull et al.³⁵

The vaporization enthalpies of both 2- and 3-thiopheneacetic acid methyl esters were also measured by correlation gas chromatography. A plot of $\ln(t_o/t_a)$, where t_a represents the time each analyte spends on the column and t_o is a reference time ($t_o = 1$ min), against reciprocal temperature, $(T/\text{K})^{-1}$, results in a straight line whose slope is $\Delta_{\text{sln}}^g H_m/R$. Multiplication of the slope by the gas constant results in the enthalpy of transfer from

TABLE 7: Standard ($p^\circ = 0.1$ MPa) Molar Enthalpies of Formation, in Both Condensed and Gaseous Phases, and Standard Molar Enthalpies of Vaporization, at $T = 298.15$ K

compound	$-\Delta_f H_m^\circ(\text{l})$ (kJ·mol ⁻¹)	$\Delta_1^g H_m^\circ(298.15\text{K})$ (kJ·mol ⁻¹)	$-\Delta_f H_m^\circ(\text{g})$ (kJ·mol ⁻¹)
2-thiopheneacetic acid methyl ester (l)	330.4 ± 2.4	61.9 ± 1.4	268.5 ± 2.8
3-thiopheneacetic acid methyl ester (l)	328.5 ± 2.0	60.9 ± 1.3	267.6 ± 2.4

the stationary phase of the column to the gas phase. Enthalpies of transfer were measured experimentally and then correlated to known vaporization enthalpies measured by some other means. The vaporization enthalpy of the target is obtained from the correlation equation. Selection of the reference compounds is crucial in the evaluation. Generally, reference compounds are chosen with the same type and number of functional groups as the target compound. Some flexibility is possible in certain cases where it has been demonstrated empirically that substitution of a different functional group still provides suitable correlations.⁴⁵

In this case, we could not find any reference compounds in the literature with the same functional group combination as that found in the target compounds. Therefore we used as standards compounds containing functional groups with numerical contributions similar to those present in the target compound, in accordance with the group contribution scheme of reference 46. Chloroesters and chloroketones were chosen as reference compounds. The analysis of the values used as standards in the correlation gas chromatography calculations are given as Table S3 of the Supporting Information.

The retention times for only one duplicate set of runs are reported in Table 5. Plots of $\ln(t_o/t_a)$ versus $1/T$ resulted in straight lines characterized by the slopes and intercepts reported in Table 6. The correlation coefficient, r^2 , exceeded 0.99

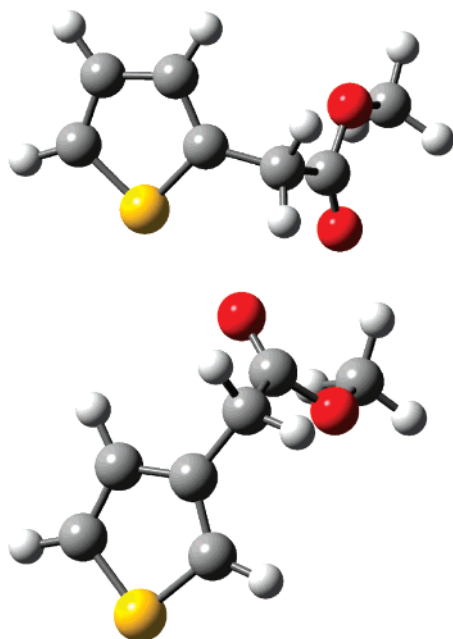


Figure 2. Calculated molecular structures, optimized at the MP2(full)/6-31G(3df,2p) level.

TABLE 8: G3-Calculated Energies at 0 K, and Enthalpies at 298 K, for 2- and 3-Thiopheneacetic Acid Methyl Esters^a

compound	G3	
	E_0	H_{298}
2-thiopheneacetic acid methyl ester	-819.762745	-819.751657
3-thiopheneacetic acid methyl ester	-819.763924	-819.752898

^a All values are in hartrees.

in all cases. The correlation between enthalpies of transfer, $\Delta_{\text{sln}}^{\text{g}} H_{\text{m}}(T_{\text{m}})$, measured at the mean temperature, T_{m} , and vaporization enthalpies at $T = 298.15$ K resulted in eq 6, given beneath Table 6. This resulted in the vaporization enthalpies reported in the last column of that Table. The uncertainty reported in this column reflects twice the standard deviations associated with the slope of the correlation equation.

As it can be seen by comparison of the values in Tables 4 and 6, the experimental values of the enthalpy of vaporization obtained by correlation gas chromatography and by the adaptation to vaporization³¹ of the vacuum sublimation drop microcalorimetric technique^{30,32} are fully consistent. These results confirm that the reference compounds used, chloroesters and chloroketones, can act as suitable standards for the isomeric methyl, thiopheneacetates. However, since the data calculated by correlation gas chromatography are strongly dependent on the quality of the standards used, larger uncertainties have been obtained in this instance. Therefore, in the present study we have used the values determined by Calvet microcalorimetry to derive the enthalpy of formation in the gas phase.

Combining the derived standard molar enthalpies of formation in the condensed phase and the standard molar enthalpies of

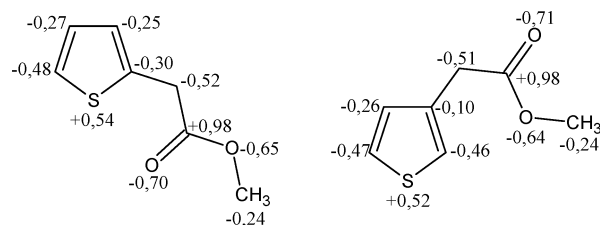


Figure 3. NBO atomic charges for 2- and 3-thiopheneacetic acid methyl esters calculated at the MP2(full)/6-31G(3df,2p) level.

vaporization yields the standard molar enthalpies of formation in the gaseous phase of 2- and 3-thiopheneacetic acid methyl esters, summarized in Table 7.

To our knowledge, there are no experimental results for the enthalpies of combustion, vaporization, and formation in the literature of the title compounds for comparison with our results.

3.2. Molecular and Electronic Structures. To our knowledge, the molecular structures of 2- and 3-thiopheneacetic acid methyl esters have not been determined either in the gaseous or solid state. The calculated molecular structures, optimized at the MP2(full)/6-31G(3df,2p) level of theory, are shown in Figure 2. Bond distances and bond angles are collected in Table S4 of the Supporting Information.

We carried out a population analysis using the NBO analysis,^{40–42} to obtain the natural atomic charges (the nuclear charges minus the summed natural populations of the natural atomic orbitals on the atoms) that characterize the ground electronic state of the compounds studied. As it can be seen in Figure 3, partial negative charge is located at the oxygen atoms and at the C atoms of the thiophene rings and CH₂ groups, whereas partial positive charge is located at the sulfur atom and at the C atom of the CO group.

The NBO analysis also describes the bonding in terms of the natural hybrid orbitals. In the compounds studied, the hybridization of the sulfur atom is sp^4 , with more than 78% of p character, whereas the hybridization of the carbonyl oxygen atom is $sp^{1.3}$ (ca. 57% of p character), and that of the hydroxyl oxygen atom is close to sp^2 with ca. 67% of p character to form the C–O bonds. Sulfur and oxygen atoms have sp and p lone pairs that may delocalize into the vicinal antibonding orbitals.

Several studies on compounds involving atoms with different types of lone pairs (O, S, Se) have shown that the effect of the charge delocalization should not be analyzed only on the basis of $p_X \rightarrow \sigma^*_{CX}$ hyperconjugation because orbital interactions involving sp lone pairs, that is, $sp_X \rightarrow \sigma^*_{CX}$, are not negligible.⁴⁷ This behavior is observed in the compounds studied, and it was also observed in our previous studies on 2- and 3-thiophenecarboxylic acids¹¹ and 2,5-thiophenedicarboxylic acid.¹⁵

3.3. Theoretical Determination of the Enthalpies of Formation. G3-calculated energies at 0 K and enthalpies at 298 K for 2- and 3-thiopheneacetic acid methyl esters, are given in Table 8.

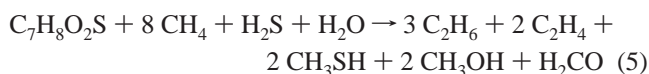
The standard procedure to obtain enthalpies of formation in Gaussian- n theories is through atomization reactions,^{48,49} but

TABLE 9: Comparison of G3-Calculated Enthalpies of Formation, Using Isodesmic Reactions 5, 6, and 7 for the Three Most Stable Conformers of Thiopheneacetic Acid Methyl Esters with Experimental Values^a

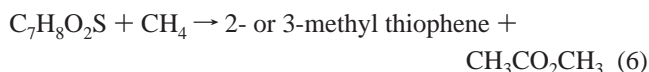
compound	G3				experimental
	atomization reaction	bond separation reaction (eq 5)	isodesmic reaction (eq 6)	mean value	
2-thiopheneacetic acid methyl ester	-262.8	-266.2	-261.6	-263.5	-268.5
3-thiopheneacetic acid methyl ester	-266.1	-269.4	-265.8	-267.1	-267.6

^a All values are in kJ mol^{-1} .

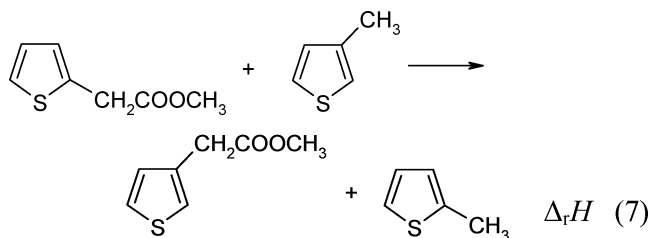
there has been some suggestion^{50–54} that there is an accumulation of errors in the application of this method to larger molecules. Glukhovtsev and Laiter⁵⁰ showed that more accurate heats of formation can be derived using isodesmic or homodesmotic reactions⁵⁵ rather than atomization energies. As Raghavachari et al.⁵⁶ pointed out, one of the deficiencies of the isodesmic reaction approach is that many different isodesmic reactions can be set up for the same molecule yielding different results. These authors have proposed to use a standard set of isodesmic reactions, the “bond separation reactions”,³⁷ where all formal bonds between non-hydrogen atoms are separated into the simplest parent molecules containing these same kinds of linkages, to derive the theoretical enthalpies of formation. The bond separation isodesmic reaction for the compounds studied in this work, C₇H₈O₂S, is



We also obtained the enthalpies of formation of the compounds studied using another isodesmic reaction with methyl thiophenes as references:



The calculated values for the enthalpies of formation of 2- and 3-thiopheneacetic acid methyl esters at the G3 level of theory, using atomization, bond separation isodesmic reaction (eq 5), and isodesmic reaction (eq 6), are shown in Table 9. As it can be seen in this table, there is very good agreement between the theoretical and experimental values. The G3-calculated isomerization enthalpy, 2-isomer ↔ 3-isomer, -3.3 kJ mol^{-1} , is in reasonable agreement with the experimental difference, $0.9 \pm 2.1 \text{ kJ mol}^{-1}$. Since the combustion experiments and the methodology to determine the enthalpy of formation in the condensed state are the same for the pair of isomers (the equivalence of the calorimeter, calibration, and auxiliary substances used, $\Delta_f H_m^0(\text{H}_2\text{O}, 298.15 \text{ K})$, $\Delta_f H_m^0(\text{CO}_2, 298.15 \text{ K})$, etc.), we expect that many of the errors associated with these variables are largely cancelled when isomers are compared. This can also be confirmed by reaction 7:



Using experimental literature values for the enthalpies of formation of 2- and 3-methylthiophenes,⁵⁷ (83.5 ± 0.9) and (82.6 ± 0.9) $\text{kJ}\cdot\text{mol}^{-1}$, together with the enthalpies of $-(268.5 \pm 2.8)$ and $-(267.6 \pm 2.4)$ $\text{kJ}\cdot\text{mol}^{-1}$ evaluated in this study for the 2- and 3-substituted methyl esters, respectively, results in a reaction enthalpy of $(1.8 \pm 3.9) \text{ kJ}\cdot\text{mol}^{-1}$. The theoretical value calculated at the G3 level is $-3.2 \text{ kJ}\cdot\text{mol}^{-1}$, in good agreement with the experiment. Even so, the experimental energy differences between the two isomers are too close to call. These results are consistent with the expectation that, in the absence of substantial steric effects, alkyl substituents, less capable of resonance interactions, are likely to have a smaller effect on relative stabilities than that observed for carboxyl groups.

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Supporting Information Available: Tables S1 and S2 listing the details of all combustion calorimetry experiments, at $T = 298.15 \text{ K}$, for 2- and 3-thiopheneacetic acid methyl esters, Table S3 with a summary of the available literature values of the vaporization enthalpy standards for the correlation gas chromatography calculations, and Table S4 with the calculated molecular structures, optimized at the MP2(full)/6-31G(3df,2p) level. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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