Energetic Studies and Phase Diagram of Thioxanthene

Vera L. S. Freitas,[†] **Manuel J. S. Monte,**[†] **Luís M. N. B. F. Santos,**[†] **José R. B. Gomes,**[‡] **and Maria D. M. C. Ribeiro da Silva***[,†]

Centro de Investigação em Química, Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, P-4169-007 Porto, Portugal, and CICECO, Departamento de Química, Universidade de Aveiro, Campus Universitário de Santiago, P-3810-193 Aveiro, Portugal

Received: July 7, 2009; Revised Manuscript Received: September 9, 2009

The molecular stability of thioxanthene, a key species from which very important compounds with industrial relevance are derived, has been studied by a combination of several experimental techniques and computational approaches. The standard ($p° = 0.1$ MPa) molar enthalpy of formation of crystalline thioxanthene (117.4 ± 4.1 kJ·mol^{-1}) was determined from the experimental standard molar energy of combustion, in oxygen, measured by rotating-bomb combustion calorimetry at $T = 298.15$ K. The enthalpy of sublimation was determined by a direct method, using the vacuum drop microcalorimetric technique, and also by an indirect method, using a static apparatus, where the vapor pressures at different temperatures were measured. The latter technique was used for both crystalline and undercooled liquid samples, and the phase diagram of thioxanthene near the triple point was obtained (triple point coordinates $T = 402.71$ K and $p = 144.7$ Pa). From the two methods, a mean value for the standard ($p° = 0.1$ MPa) molar enthalpy of sublimation, at $T = 298.15$ K (101.3 ± 0.8 kJ·mol^{-1}), was derived. From the latter value and from the enthalpy of formation of the solid, the standard ($p° = 0.1$ MPa) enthalpy of formation of gaseous thioxanthene was calculated as 218.7 ± 4.2 kJ·mol^{-1}. Standard *ab initio* molecular orbital calculations were performed using the G3(MP2)//B3LYP composite procedure and several homodesmotic reactions in order to derive the standard molar enthalpy of formation of thioxanthene. The *ab initio* results are in excellent agreement with the experimental data.

1. Introduction

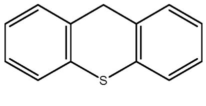
Thioxanthene is a heteropolycyclic compound with three fused hexagonal rings (Scheme 1). The terminal cycles are highly aromatic, and the aromaticity is lost in the central ring due to the presence of a methylene group in the *para* position relative to the heteroatom. The thioxanthene scaffold is present in numerous pharmaceutically important compounds. For example, some of its derivatives, like chlorprothixene, thiothixene, flupentixol, cloropentixol, and zuclopenthixol, are effective in the systematic treatment of psychoses. They are also used in the therapy of schizophrenia and other idiopathic psychotic illnesses.[1–3] These drugs have other clinically useful properties, including antiemetic, antinausea, and antihistamine effects, and also have the ability to potentiate analgesics, sedatives, and general anesthetic actions. Hycanthone and lucanthone, both thioxanthene derivatives, are well-known drugs in the treatment of schistosomicides, a parasitic disease, and the latter compound is also used in chemotherapy. Due to the wide range and important applications of the derivatives of thioxanthene, knowledge of their thermodynamic properties is highly valuable.

In the present work, parallel experimental and computational studies were performed. The experimental studies were based on calorimetric measurements, from which the enthalpy of formation in the crystalline phase and the enthalpy of sublimation of thioxanthene were derived. Additional vapor pressure measurements of both crystalline and liquid phases at different temperatures using a static method enabled the determination of the enthalpies and Gibbs energies of sublimation and of vaporization; the temperature and pressure of the triple point as well as the enthalpy of fusion at the triple point were also measured. From these results, the standard ($p° = 0.1$ MPa) molar enthalpy of formation in the gaseous phase, at $T = 298.15$ K, was derived. The calculations, performed with the G3(MP2)//B3LYP approach, were employed to gain further knowledge of the molecular and electronic structures of thioxanthene and were also used to compute its gas-phase enthalpy of formation at $T = 298.15$ K and gaseous heat capacities at different temperatures.

2. Experimental Methods

Materials. The compound thioxanthene ($C_{13}H_{10}S$, CAS 261-31-4) was obtained commercially from Acros Organics with a purity of 98%. The compound was purified by repeated sublimations under reduced pressure. The purity of the final sample was checked by gas chromatography, using an Agilent 4890 apparatus equipped with an HP-5 column, cross-linked, 5% diphenyl and 95% dimethylpolysiloxane (15 m × 0.530 mm i.d. × 1.5 μm film thickness), confirming a purity of

SCHEME 1: Molecular Structure of Thioxanthene



---

* Corresponding author. E-mail: mdsilva@fc.up.pt. Fax: +351 220 402 522. Phone: +351 220 402 538.

[†] Universidade do Porto.

[‡] Universidade de Aveiro.

10.1021/jp906413y CCC: $40.75

99.95%. No phase transitions were detected using differential scanning calorimetry, between 298 K and the temperature of fusion of the compound.

The compounds used in the calibrations of the calorimetric systems were benzoic acid [CAS 65-85-0], Standard Reference Material (SRM), supplied by National Bureau Standard (NBS), and naphthalene [CAS 91-20-3], scintillation grade 99+%, obtained from Aldrich Chemical Co.

Finally, the specific density considered for crystalline thioxanthene[4] was 1.326 $g \cdot cm^{-3}$ and the relative atomic masses used were those recommended by the IUPAC commission in 2005.[5]

Rotating-Bomb Calorimetry. The combustion experiments were performed with an isoperibol calorimeter equipped with a twin valve rotating bomb (with an internal volume of 0.258 dm^3), formerly developed by Professor Stig Sunner at the University of Lund,[6] Sweden, and installed in our department. Detailed descriptions of the apparatus and of the procedure were already published in the literature,[7] and thus, only some important remarks related to the experiments will be given here. The accurate numerical calculation of the corrected temperature rise in the isoperibol calorimetry was carried out by means of the Labtermo program.[8,9]

The energy equivalent of the calorimeter ε(calor) was determined using benzoic acid NBS SRM 39j, having a massic energy of combustion, $\Delta_c u$, under standard bomb conditions of $-(26434 \pm 3)$ $J \cdot g^{-1}$. Calibration experiments were carried out in oxygen at a pressure of 3.04 MPa (previously flushed) with 1.00 cm^3 of deionized water added to the bomb, without rotation of the bomb. From six experiments, $\varepsilon(\text{calor}) = (25157.4 \pm 1.1)$ $J \cdot K^{-1}$ (the uncertainty quoted is the standard deviation of the mean) for an average mass of water added to the calorimeter of 5217.0 g.

The procedure followed for the combustion of the organosulfur compound was that described by Waddington et al.[10] For each experiment, a volume of 10.00 cm^3 of water was added to the bomb, and the bomb was charged to a pressure of 3.04 MPa with oxygen without flushing, ensuring sufficient amounts of nitrogen oxides to oxidize the sulfur quantitatively to sulfur trioxide. The energy of reaction was always referred to the final temperature of $T_f = 298.15$ K. Rotation of the bomb was started when the temperature rise in the main period reached about 63% of its final value and continued until the end of the experiment, ensuring a homogeneous solution of H_2SO_4(aq) in the bomb at the conclusion of the measurements. After the calorimetric measurements, the combustion products were checked for unburned carbon and other products of incomplete combustion, and in all cases, these undesired species were not detected. The nitric acid formed due to the presence of nitrogen residues in the oxygen, used in the fulfillment of the bomb, was determined by Devarda's alloy method.[11] Due to the relatively large amount of water used to ensure homogeneous H_2SO_4(aq) in the thioxanthene combustions, no carbon dioxide analyses were performed.

The corrections for nitric acid formation were made on -59.7 $kJ \cdot mol^{-1}$ for the molar energy of formation of 0.1 $mol \cdot dm^{-3}$ HNO_3(aq) from N_2(g), O_2(g), and H_2O(l).[12] For the cotton thread fuse of empirical formula $CH_{1.686}O_{0.843}$, $-\Delta_c u° = 16240$ $J \cdot g^{-1}$,[13] a value that was previously confirmed in our laboratory. The value for the pressure coefficient of specific energy $(\partial u/\partial p)_T$ was assumed to be -0.2 $J \cdot g^{-1} \cdot MPa^{-1}$, at $T = 298.15$ K, a typical value for most organic compounds.[14]

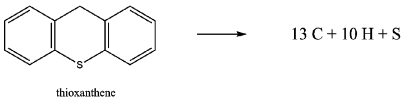
Calvet Microcalorimetry. The standard ($p° = 0.1$ MPa) molar enthalpy of sublimation of thioxanthene was measured by the vacuum drop microcalorimetric technique described by Skinner et al.[15] The measurements were performed with a Calvet high-temperature microcalorimeter (Setaram HT1000) with the vacuum promoted by a rotary vacuum pump and a vapor diffusion pump. The details of the apparatus and of the technique are in the literature.[16] Samples of about 2−4 mg of thioxanthene, contained in thin glass capillary tubes sealed at one end, were dropped from room temperature into the hot reaction vessel in the calorimeter held at a predefined temperature, $T = 376.0$ K, and then removed from the hot zone by vacuum. The thermal corrections for the glass capillary tubes were determined in separate experiments, and were minimized by dropping tubes of nearly equal mass, to within 1 ± 10^{-4} g, into each of the twin calorimetric cells. The microcalorimeter was calibrated *in situ* by performing sublimation experiments with naphthalene and following a procedure identical to that described above for thioxanthene.

The calibration constant of the calorimeter, k_{cal}, was obtained as the average of six independent calibration experiments with naphthalene, using its reported standard ($p° = 0.1$ MPa) molar enthalpy of sublimation at $T = 298.15$ K, $\Delta_{cr}^{g}H_m^\circ = 72.51 \pm 0.12$ $kJ \cdot mol^{-1}$.[17] At $T = 376$ K, $k_{cal} = 1.000 \pm 0.007$.

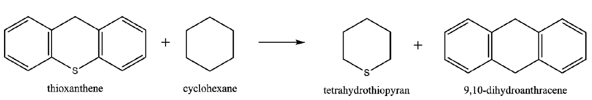
Vapor Pressure Measurements. The vapor pressures of both liquid and crystalline phases of thioxanthene were measured in the temperature range 337.87−446.75 K using a static apparatus fully described and tested before.[18] This apparatus uses MKS capacitance diaphragm absolute gauges, operating at a self-controlled constant temperature—Baratron 631A01TBEH ($T_{gauge} = 423$ K) for measuring pressures in the range 0.4−133 Pa and in the temperature range 253−423 K (from now on named gauge 1) and Baratron 631A11TBFP ($T_{gauge} = 473$ K) capable of measuring pressures in the range 3−1330 Pa and in the temperature range 253−473 K (from now on named gauge 2).

The temperatures of the condensed sample were measured using a platinum resistance thermometer Pt100 class 1/10 (in a four wire connection). This thermometer was calibrated by comparison with a SPRT (25 Ω; Tinsley, 5187A). The uncertainty of the temperature measurements is estimated to be less than ±0.01 K. To avoid condensation of the vapor, the tubing between the condensed sample and the pressure gauge is kept at a temperature higher than the temperature of the sample and lower than the temperature of the gauge.

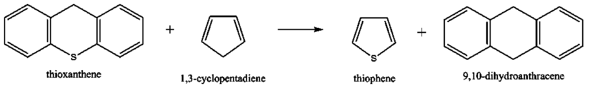
Computational Studies. The standard *ab initio* molecular calculations for thioxanthene were performed with the Gaussian 03 suite of programs.[19] The G3(MP2)//B3LYP approach[20] was employed throughout this work. In this approach, the molecular geometry is optimized with the hybrid B3LYP method[21,22] and the atomic electron density is described with the 6-31G(d) basis set. The B3LYP/6-31G(d) equilibrium structure is used to calculate the vibrational frequencies (and thermal corrections for $T = 298.15$ K). The zero-point energy, E(ZPE), was scaled by a factor of 0.96 to take into account known deficiencies at this level. Then, single point electronic energy calculations are performed using higher levels of electronic structure theory, quadratic configuration interaction [QCISD(T)] and the second-order Moller−Plesset (MP2) with the 6-31G(d) and GTMP2Large basis sets, respectively. The energies (including the ZPE) computed at $T = 0$ K were thermally corrected for $T = 298.15$ K by introducing the vibrational term computed at the B3LYP/6-31G(d) level and the translational, rotational, and pV terms. The enthalpy of formation in the gas phase for thioxanthene was estimated from the calculated enthalpies of several gas-phase working reactions, c.f. eqs 1−5, using the experimental standard molar gas-phase enthalpies of formation of the atoms and molecules included there, chosen on the basis of experimental thermochemical data availability. It should be pointed out that some of the reactions are not isodesmic and that some errors due to the consideration of different bonds in the reactants and in the products may not be compensated (c.f. bonds between atoms are not considered in the products of the reaction described by eq 1).



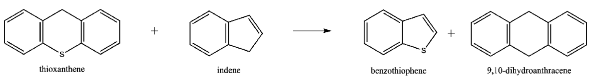
(1)



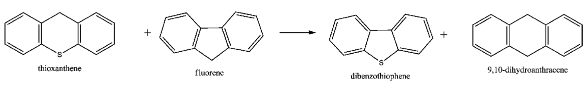
(2)



(3)

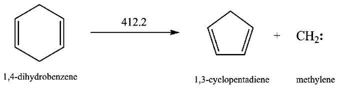


(4)

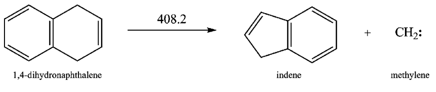


(5)

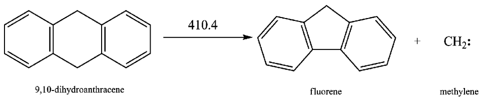
In addition to the computational work presented above, we also developed G3(MP2)//B3LYP calculations for some cyclic and polycyclic compounds, in order to predict the enthalpy required for the transformation of 6-member to 5-member cyclic compounds (by the expenses of the removal of a methylene group). For that purpose, three groups of compounds (homocyclic, O-heterocyclic, and S-heterocyclic species) and the enthalpies of the reactions, expressed in kJ·mol^{-1}, described by eqs 6−14 were considered.



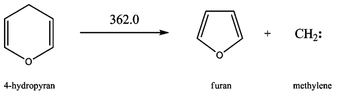
(6)



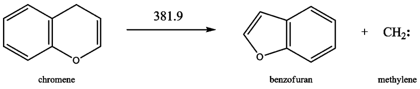
(7)



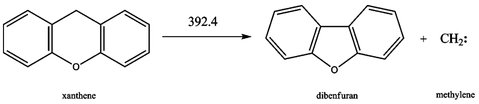
(8)



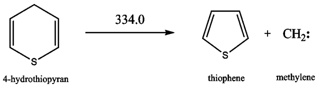
(9)



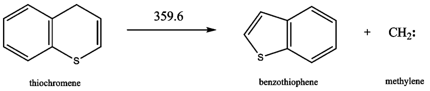
(10)



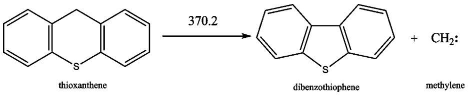
(11)



(12)



(13)



(14)

3. Results and Discussion

Calorimetric Data. In the combustion experiments with thioxanthene, the products of the process consist of a gaseous phase and an aqueous mixture of sulfuric acid for which the thermodynamics properties are known. Its combustion reaction is represented by the following equation:

$$C_{13}H_{10}S(cr) + 17O_2(g) + 111H_2O(l) \rightarrow 13CO_2(g) + H_2SO_4\cdot 115H_2O(l) \quad (15)$$

The energy associated with the isothermal bomb process, ΔU(IBP), was calculated through

$$\Delta U(\mathrm{IBP}) = -\{\varepsilon(\mathrm{calor}) + c_p(\mathrm{H_2O,l})\Delta m(\mathrm{H_2O})\}\Delta T_{\mathrm{ad}} + (T_{\mathrm{i}} - 298.15)\varepsilon_{\mathrm{i}} + (298.15 - T_{\mathrm{i}} - \Delta T_{\mathrm{ad}})\varepsilon_{\mathrm{f}} + \Delta U(\mathrm{ign}) \quad (16)$$

where ΔT_{ad} is the calorimeter temperature corrected for the heat exchange, work of stirring, and frictional work of bomb rotation, Δm(H$_2$O) represents the deviation of the mass of water added to the calorimeter from 5217.0 g, the water assigned to ε(calor), T_{i} is the initial temperature rise, ε_{i} and ε_{f} are the energy equivalents of the contents in the initial and final states, respectively, ΔU(ign) is the electric energy for the ignition, and c_p(H$_2$O,l) is the massic heat capacity at constant pressure for liquid water. The standard state corrections or Washburn corrections, ΔU_{Σ}, were calculated as recommended in the literature for organic sulfur compounds.[23,24] From the individual values of $\Delta_{\mathrm{c}}u°$ for each experiment, the mean standard ($p° = 0.1$ MPa) massic energy of combustion and the corresponding standard deviation of the mean have been calculated (the overall results are presented in Table S1 of the Supporting Information). Table 1 lists the mean value of the standard ($p° = 0.1$ MPa) massic energy of combustion and the derived molar energy and enthalpy of combustion, respectively, $\langle\Delta_{\mathrm{c}}u°\rangle$, $\Delta_{\mathrm{c}}U_{\mathrm{m}}^{\circ}$, and $\Delta_{\mathrm{c}}H_{\mathrm{m}}^{\circ}$, as well as the standard ($p° = 0.1$ MPa) molar enthalpy of formation, $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}$, of crystalline thioxanthene. In accordance with the normal thermochemical practice, the uncertainties assigned to the standard ($p° = 0.1$ MPa) molar enthalpies of combustion and formation are twice the overall standard deviation of the mean and include the uncertainty of the calibration. To derive $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}$ from $\Delta_{\mathrm{c}}H_{\mathrm{m}}^{\circ}$, standard ($p° = 0.1$ MPa) molar enthalpies of formation of H$_2$O(l), CO$_2$(g), and H$_2$SO$_4$ in 115H$_2$O(l), at $T =$

TABLE 1: Mean standard ($p^\circ = 0.1$ MPa) Massic Energy of Combustion, $\langle\Delta_c u^\circ\rangle$, Derived Molar Energy of Combustion, $\Delta_c U_m^\circ$, Molar Enthalpy of Combustion, $\Delta_c H_m^\circ$, and Molar Enthalpy of Formation, $\Delta_f H_m^\circ$, for Crystalline Thioxanthene at $T = 298.15$ K

$\langle\Delta_c u^\circ\rangle$/J·g^{-1}	$\Delta_c U_m^\circ$/kJ·mol^{-1}	$\Delta_c H_m^\circ$/kJ·mol^{-1}	$\Delta_f H_m^\circ$/kJ·mol^{-1}
−36585.2 ± 7.6	−7254.2 ± 3.2	−7264.2 ± 3.2	117.4 ± 4.1

TABLE 2: Standard ($p^\circ = 0.1$ MPa) Molar Enthalpy of Sublimation, $\Delta_{cr}^{g}H_m^\circ$, for Thioxanthene, at $T = 298.15$ K, Determined by Calvet Microcalorimetry

number of experiments	T/K	$\Delta_{cr,298.15\,K}^{g,T}H_m^\circ$ kJ·mol^{-1}	$\Delta_{298.15\,K}^{T}H_m^\circ(g)$ kJ·mol^{-1}	$\Delta_{cr}^{g}H_m^\circ$(298.15 K) kJ·mol^{-1}
6	376.0	118.8 ± 0.4	17.135 ± 0.003[a]	101.7 ± 1.6

[a] Uncertainties of the computational method and scaling factor are not included (see text).

298.15 K, of respectively, −(285.830 ± 0.042),[25] −(393.51 ± 0.13),[25] and −(887.81 ± 0.01) kJ·mol^{-1} [25] were used.

Results of Calvet microcalorimetry measurements of the enthalpy of sublimation for thioxanthene are given in Table 2. The observed enthalpy of sublimation, at the experimental temperature T, $\Delta_{cr,298.15\,K}^{g,T}H_m^\circ$, correspondent to the mean of six experiments with uncertainties given by their standard deviations, was corrected to $T = 298.15$ K by eq 17 using the molar heat capacity in the gaseous phase for thioxanthene given by eq 18, which was derived from statistical thermodynamics using the vibrational frequencies calculated at the B3LYP/6-31G(d) level.[26] The calculated molar heat capacities in the gaseous phase for thioxanthene between 150 and 550 K are given in Table S2 of the Supporting Information.

$$\Delta_{298.15\,K}^{T}H_m^\circ(g) = \int_{298.15\,K}^{T} C_{p,m}^\circ(g)\,dT \qquad (17)$$

$$C_{p,m}^\circ(g)/(J\cdot K^{-1}\cdot mol^{-1}) = -1.06004 \times 10^{-6}(T/K)^3 + 7.73782 \times 10^{-4}(T/K)^2 + 4.785420 \times 10^{-1}(T/K) - 11.83800 \qquad (R^2 = 0.9999) \quad (18)$$

The uncertainty associated with the standard ($p^\circ = 0.1$ MPa) enthalpy of sublimation, at $T = 298.15$ K, $\Delta_{cr}^{g}H_m^\circ$(298.15 K), is twice the standard deviation of the mean and includes the estimated uncertainties associated with the calibration procedure and the molar heat capacity for thioxanthene in the gaseous state.

Vapor Pressures and Enthalpies of Phase Transitions. Table 3 presents the results of measured vapor pressures over the crystalline phase, between 337.87 and 402.30 K with pressure gauge 1, and over the liquid phase, between 382.45 and 446.75 K with pressure gauge 2. Liquid vapor pressures at temperatures lower than 402.7 K correspond to undercooled liquid. After crystallization of the undercooled liquid, some sublimation pressures previously measured using gauge 1 were repeated at the same temperatures using gauge 2 in order to evaluate the accuracy of this gauge in the low vapor pressure region. Data obtained through gauges 1 and 2 were in excellent agreement.

The experimental results of the solid and liquid vapor pressures were fitted (independently) by the Clarke and Glew eq 19[27]

$$R\ln\left(\frac{p}{p^\circ}\right) = -\frac{\Delta_{cd}^{g}G_m^\circ(\theta)}{\theta} + \Delta_{cd}^{g}H_m^\circ(\theta)\left(\frac{1}{\theta} - \frac{1}{T}\right) + \Delta_{cd}^{g}C_{p,m}^\circ(\theta)\left[\left(\frac{\theta}{T}\right) - 1 + \ln\left(\frac{T}{\theta}\right)\right] \quad (19)$$

where p is the vapor pressure, p° is a selected reference pressure (in this work, $p^\circ = 10^5$ Pa), θ is a selected reference temperature (in this work, $\theta = 298.15$ K), R is the molar gas constant ($R = 8.31447$ J·K^{-1}·mol^{-1}), $\Delta_{cd}^{g}G_m^\circ$ is the difference in molar Gibbs energy between the gaseous and the crystalline or liquid phases (condensed phase) at the selected reference pressure.[28] The term $\Delta_{cd}^{g}H_m^\circ$ is the difference in molar enthalpy between the gaseous and condensed phases and $\Delta_{cd}^{g}C_{p,m}^\circ$ is the difference between the heat capacities of the perfect gas and of the condensed phase. The fitting of the experimental (p,T) data to eq 19 was performed using an estimated value for $\Delta_{cd}^{g}C_{p,m}^\circ$ derived using eq 20. This equation is a rearrangement of eq 21 proposed by Chickos et al.[29] for estimation of $\{C_{p,m}^\circ(g) - C_{p,m}^\circ(cr)\}$, at the temperature 298.15 K, from a known value of $C_{p,m}^\circ$(cr). Thus, the value $C_{p,m}^\circ$(g, 298.15 K) = 195.17 J·K^{-1}·mol^{-1}, derived from eq 18, was inserted in eq 20, yielding $\Delta_{cr}^{g}C_{p,m}^\circ = -35.2$ J·K^{-1}·mol^{-1}.

$$\Delta_{cr}^{g}C_{p,m}^\circ(\theta)/(J\cdot K^{-1}\cdot mol^{-1}) = -\{0.9 + 0.176C_{p,m}^\circ(g)\} \quad (20)$$

$$\Delta_{cr}^{g}C_{p,m}^\circ(\theta)/(J\cdot K^{-1}\cdot mol^{-1}) = -\{0.75 + 0.15C_{p,m}^\circ(cr)\} \quad (21)$$

The result $\Delta_{l}^{g}C_{p,m}^\circ = -(72 \pm 23)$ J·K^{-1}·mol^{-1} was derived directly from the regression of the fitting of eq 19 to the liquid vapor pressure−temperature data. The enthalpy of fusion at the derived triple point (T_{tp} = 402.71 K; p_{tp} = 144.7 Pa) was calculated as $\Delta_{cr}^{l}H_m^\circ$(402.71 K) = (26.8 ± 0.4) kJ·mol^{-1}, from the results of the molar enthalpies of sublimation and of vaporization, at this temperature, presented in Table 4. This table also presents the results of the molar standard ($p^\circ = 0.1$ MPa) enthalpies and Gibbs energies of sublimation and of vaporization at 298.15 K and at the mean temperatures of the pressure measurements for both crystalline and liquid phases. Figure 1 represents the phase diagram (ln p versus 1000/T) of thioxanthene at low pressures.

In the DSC analysis performed for the study of possible phase transitions, the temperature of fusion $T = 403.25$ K and the enthalpy of fusion at this temperature, $\Delta_{cr}^{l}H_m^\circ$ = (27.33 ± 0.40) kJ·mol^{-1} were also determined, which are in excellent agreement with the triple point and the enthalpy of fusion derived from the vapor pressure measurements.

The vapor pressures of crystalline and liquid xanthene (a compound identical to thioxanthene where the S heteroatom is replaced by an O atom) were recently published.[30] Thioxanthene is less volatile than xanthene by an order of magnitude in the sublimation vapor pressures at 298.15 K ($p = 4.2 \times 10^{-3}$ Pa for thioxanthene and $p = 4.5 \times 10^{-2}$ Pa for xanthene) calculated from eq 22.

$$\ln(p/10^5\ \text{Pa}) = -\Delta_{cr}^{g}G_m^\circ(298.15\ \text{K})/298.15R \quad (22)$$

Enthalpy of Formation in the Gaseous Phase. The results of the standard ($p^\circ = 0.1$ MPa) molar enthalpy of sublimation, at the temperature 298.15 K, derived from Calvet microcalorimetry, $\Delta_{cr}^{g}H_m^\circ$ = (101.7 ± 1.6) kJ·mol^{-1}, and from vapor pressure measurements, $\Delta_{cr}^{g}H_m^\circ$ = (100.9 ± 0.4) kJ·mol^{-1}, are in excellent agreement. Thus, in order to calculate the enthalpy of formation in the gaseous phase, we used the mean of these

TABLE 3: Experimental Data on Vapor Pressure of Thioxanthene[a]

crystalline phase (gauge 1)			liquid phase (gauge 2)		
T/K	p/Pa	100Δp/Pa	T/K	p/Pa	100Δp/Pa
337.87	0.49	2.1	382.45	45.00	1.4
342.83	0.82	1.9	387.40	59.30	0.20
347.79	1.30	−1.9	392.26	77.30	−0.70
352.76	2.10	−2.2	397.30	101.4	−1.2
357.72	3.43	−0.15	402.30	132.6	−0.88
362.67	5.38	−0.35	404.76	150.7	−0.85
367.63	8.30	−1.1	407.24	171.8	−0.44
372.60	12.83	−0.52	412.15	221.5	0.39
377.55	19.50	−0.24	417.13	281.9	0.28
382.50	29.50	0.73	422.00	359.7	1.6
387.45	43.49	0.23	427.03	451.4	1.3
392.40	64.15	0.84	431.95	552.0	−0.58
397.35	93.15	0.89	436.89	689.3	0.20
399.85	111.3	0.25	441.85	856.3	0.96
402.30	131.9	−0.58	446.75	1019	−1.8

[a] $\Delta p = p - p_{\mathrm{calc}}$, where p_{calc} is calculated from the equation of Clarke and Glew (eq 19) with parameters given in Table 4.

TABLE 4: Parameters of Clarke and Glew (eq 19) Derived from Static Vapor Pressure Results for Crystalline and Liquid Thioxanthene at the Standard Pressure $p^\circ = 10^5$ Pa

phase	ΔT/K	θ/K	$\Delta_{\mathrm{cr,l}}^{\mathrm{g}}G_{\mathrm{m}}^{\circ}(\theta)$/ kJ·mol^{-1}	$\Delta_{\mathrm{cr,l}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ}(\theta)$/ kJ·mol^{-1}	R^2	$\Delta_{\mathrm{cr}}^{\mathrm{g}}C_{p,\mathrm{m}}^{\circ}$/ J·K^{-1}·mol^{-1}	s[f]
crystalline	337.9−402.3	298.15	42.12 ± 0.04	100.9 ± 0.2	0.99999	−35.2[d]	0.013
		370.1[b]	28.22 ± 0.01	98.4 ± 0.2			
		402.71[c]	22.10 ± 0.02	97.2 ± 0.2			
liquid[a]	382.4−446.8	298.15	35.68 ± 0.40	77.8 ± 2.6	0.99999	−(72 ± 23)[e]	0.011
		414.6[b]	20.67 ± 0.01	69.5 ± 0.2			
		402.71[c]	22.08 ± 0.01	70.4 ± 0.3			

[a] Including undercooled liquid. [b] Mean temperature. [c] Calculated temperature of triple point. [d] Estimated value. [e] Adjustable parameter. [f] s is the standard deviation of the fit defined as $s = [(\sum_{i=1}^{n} (\ln p - \ln p_{\mathrm{calc}})_i^2)/(n - m)]^{1/2}$, where n is the number of experimental points used in the fit and m is the number of adjustable parameters in the Clarke and Glew equation.

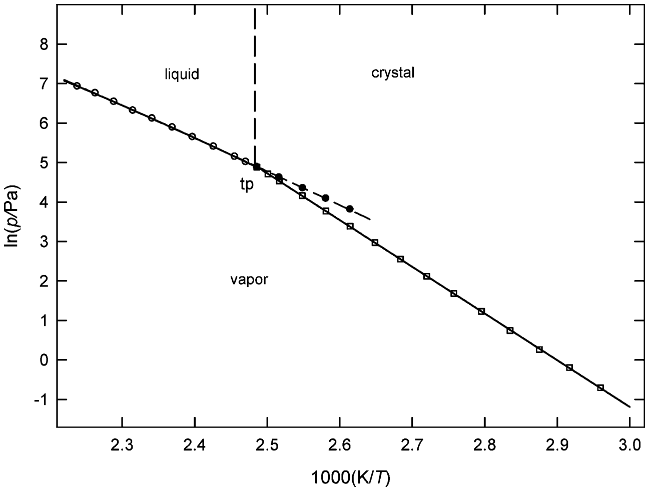


Figure 1. Phase diagram of thioxanthene at low pressures. ○, stable liquid vapor pressures; ●, metastable liquid vapor pressures (undercooled liquid); □, sublimation vapor pressures. Triple point (tp) coordinates: $T = 402.71$ K, $p = 144.7$ Pa.

two values, $\Delta_{\mathrm{cr}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ} = (101.3 \pm 0.8)$ kJ·mol^{-1}, which combined with the result derived for the enthalpy of formation in the crystalline phase, $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}(\mathrm{cr}) = (117.4 \pm 4.1)$ kJ·mol^{-1}, yield the result $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}(\mathrm{g}) = (218.7 \pm 4.2)$ kJ·mol^{-1}.

Computational Results. In Figure 2 are shown three different views of gaseous thioxanthene optimized at the B3LYP/6-31G(d) level of theory. Selected bond lengths and bond angles are also included in that figure. Thioxanthene presents a butterfly-like structure with an angle between the two terminal rings of 126.4°. This heteropolycyclic compound has a plane of symmetry, bisecting the molecule through the methylene group and the sulfur atom, and it belongs to the C_s group of symmetry. Additional structural details are given in Table S3 of the Supporting Information, containing bond lengths, bond angles, and dihedral angles for thioxanthene.

The estimated enthalpies of formation in the gaseous phase, at $T = 298.15$ K, for thioxanthene are presented in Table 5. The values have been calculated with the G3(MP2)//B3LYP absolute enthalpies at $T = 298.15$ K for thioxanthene and for the auxiliary species in the gas-phase working reactions described by eqs 1−5 (values appear in Table S4 of the Supporting Information), as well as the experimental gas-phase enthalpies of formation at $T = 298.15$ K for the auxiliary compounds. As can be seen in Table 5, the estimated enthalpy of thioxanthene when the reaction of atomization is used (eq 1) is smaller than the experimental result (and also than the values calculated with the reactions described by eqs 2−5). This difference is attributed to a deficient compensation of the different types of bonds in reactants and products of reaction (absence of bonds in the products), as already noted in the section with the computational details. This deficiency may be minimized if an empirical correction procedure such as that developed by Anantharaman and Melius,[31] i.e., the bond additivity correction (BAC) scheme where atomic, molecular, and bondwise corrections are added to theoretical enthalpies of formation of molecules. In fact, if BAC corrections are considered, the enthalpy of formation is in better agreement with the experimental result (the absolute difference between experimental and computational values is reduced from 11.5 to 7.2 kJ·mol^{-1}).

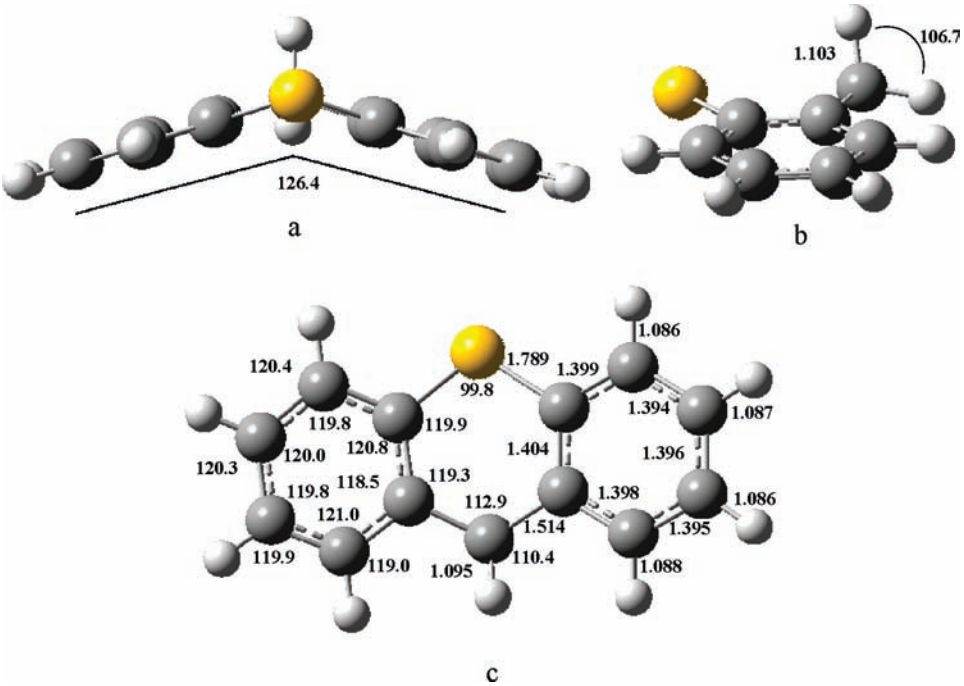


Figure 2. Structure optimized at the B3LYP/6-31G(d) level of theory for the gaseous molecule of thioxanthene. Selected bond lengths (Å) and bond angles (deg) are included.

TABLE 5: Calculated Enthalpies of Formation in the Gas Phase, at $T = 298.15$ K, for Thioxanthene[a]

reaction	$\Delta_f H^\circ_m(g)$/kJ·mol^{-1}
1	207.2[b]
	225.9[c]
2	220.8
3	222.1
4	218.7
5	236.3[d]
	244.4[e]
	219.4[f]

[a] The experimental value determined in this work is 218.7 ± 4.2 kJ·mol^{-1}. [b] Without bond additivity corrections. [c] With bond additivity corrections. [d] Value estimated using $\Delta_f H^\circ_m(g)$ for fluorene from ref 32. [e] Value estimated using $\Delta_f H^\circ_m(g)$ for fluorene from ref 33. [f] Value estimated using $\Delta_f H^\circ_m(g)$ for fluorene from ref 34.

The values calculated with the aid of the reactions described by eqs 2−4 are in excellent agreement with the experimental result. In fact, the enthalpy of formation estimated with eq 4 matches the experimental result, $\Delta_f H^\circ_m(g) = 218.7 \pm 4.2$ kJ·mol^{-1}, while the two other results are included in the uncertainty interval associated with the experimental value.

In case of working reaction 5, and when the two available experimental results for the enthalpy of formation in the gaseous phase for fluorene from the literature are considered, i.e., that of Sabbah, $\Delta_f H^\circ_m(g) = 166.9 \pm 4.1$ kJ·mol^{-1},[32] or that of Rakus et al., $\Delta_f H^\circ_m(g) = 175.0 \pm 1.5$ kJ·mol^{-1},[33] the calculated enthalpies of formation for thioxanthene differ by ∼26 and 18 kJ·mol^{-1} from our experimental result, respectively. The very good agreement between theory and experiment found above when different working reactions are considered suggests that one (or both) of the experimental $\Delta_f H^\circ_m(g)$ values for fluorene is probably in error. In fact, in a preceding work,[34] we estimated a value for the enthalpy of formation in the gaseous phase for fluorene, $\Delta_f H^\circ_m(g) = 191.9$ kJ·mol^{-1}, that differs by ∼25 and ∼17 kJ·mol^{-1} from the experimental results of Sabbah[32] and Rakus et al.,[33] respectively. Using that estimated value for fluorene and the reaction described by eq 5, the value of the enthalpy of formation in the gas phase of thioxanthene, $\Delta_f H^\circ_m(g) = 219.4$ kJ·mol^{-1}, is now in perfect agreement with our experimental value and also with those calculated from the enthalpies of reactions described by eqs 2−4. Therefore, since the computational approach used in this work provides very good estimates for the gaseous enthalpy of formation at $T = 298.15$ K for thioxanthene and that in a preceding work similar conclusions were obtained for dibenzothiophene,[34] it seems that the most accurate $\Delta_f H^\circ_m(g)$ value for fluorene is the computed value, i.e., 191.9 kJ·mol^{-1}.[34]

Interestingly, the G3MP2B3 calculated enthalpies of the reactions of abstraction of a methylene group in homocyclic compounds with increasing number of rings (eqs 6−8) are very similar. The values are included in the interval 408.2−412.2 kJ·mol^{-1}. Identical methylene abstraction reactions were taken into consideration for two groups of heterocyclic compounds, containing oxygen (eqs 9−11) or sulfur (eqs 12−14) as a heteroatom. For the O-heterocyclic compounds, the values range from 362.0 to 392.4 kJ·mol^{-1}, and for S-heterocyclic compounds, they vary between 334.0 and 370.2 kJ·mol^{-1}. It is possible to observe in the reactions involving heterocycles that the enthalpic increment increases with the number of rings in the compounds. This increase is most probably due to loss of aromaticity (products of reaction are planar, and aromaticity plays an important role in their stabilization) on going from monocyclic to bicyclic and from bicyclic to tricyclic compounds.[35] Comparing the increments of the two heterocyclic groups, it is evident that the S-heterocyclic compounds have smaller enthalpic increments than those with oxygen, leading us to presume that, when compared with the O-heteroatom, the S-heteroatom augments the aromaticity of the compounds.

4. Final Remarks

An excellent agreement is found between experimental (218.7 ± 4.2 kJ·mol^{-1}) and computational (220.2 ± 2.3 kJ·mol^{-1})[36] standard molar enthalpies of formation, at $T = 298.15$ K, of thioxanthene in the gas phase, which supports previous evidence that the computational approach considered in this work is an excellent choice when dealing with sulfur-containing compounds.[37] Furthermore, the consistency of the values for the enthalpy of sublimation experimentally determined from Calvet microcalorimetry and from the use of a static method (difference between experimental values of only 0.8 ± 0.8 $\mathrm{kJ \cdot mol^{-1}}$) shows that the consideration of gaseous heat capacities, derived from theoretical calculations, is extremely important to achieve accurate enthalpies of sublimation, at $T = 298.15$ K, when using the Calvet microcalorimetry technique.

The enthalpies of formation in the crystalline state and of sublimation for thioxanthene at $T = 298.15$ K were also obtained experimentally, and their values are 117.4 ± 4.1 and 101.3 ± 0.8 $\mathrm{kJ \cdot mol^{-1}}$, respectively.

Acknowledgment. Thanks are due to Fundação para a Ciência e Tecnologia (FCT), Lisbon, Portugal, for financial support to Centro de Investigação em Química - UP and CICECO. V.L.S.F. thanks FCT and European Social Fund for the award of a Ph.D. Research Grant SFRH/BD/41672/2007.

Supporting Information Available: Tables showing typical combustion results, at $T = 298.15$ K ($p° = 0.1$ MPa), for thioxanthene; standard ($p° = 0.1$ MPa) molar heat capacities in the gaseous phase for thioxanthene; calculated structural parameters, bond lengths, bond angles, and dihedral angles for thioxanthene in the gaseous phase using the G3(MP2)//B3LYP method; and G3(MP2)//B3LYP enthalpies at $T = 298.15$ K for thioxanthene and for the auxiliary species and the experimental gas-phase enthalpy of formation at $T = 298.15$ K. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Julien, R. M. *A Primer of Drug Action*, 5th ed.; W. H. Freeman and Company: Portland, OR, 1988.

(2) Liska, K. *Drug and the Human Body*, 6th ed.; Prentice Hall: San Diego, CA, 1999.

(3) Belal, F.; Hefnawy, M. M.; Aly, F. A. *J. Pharm. Biomed. Anal.* **1997**, *16*, 369–376.

(4) Gillean, J. A., III; Phelps, D. W; Cordes, A. W. *Acta Crystallogr.* **1973**, *B29*, 2296–2298.

(5) Wieser, M. E. *Pure Appl. Chem.* **2006**, *78*, 2051–2066.

(6) Sunner, S. In *Experimental Chemical Thermodynamics*; Sunner, S., Månsson, M., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol. 1, Chapter 2.

(7) Ribeiro da Silva, M. A. V.; Ferrão, M. L. C. C. H.; Jiye, F. *J. Chem. Thermodyn.* **1994**, *26*, 839–846.

(8) Santos, L. M. N. F. Ph.D. Thesis, University of Porto, 1995.

(9) Santos, L. M. N. B. F.; Silva, M. T; Schröder, B.; Gomes, L. *J. Therm. Anal. Calorim.* **2007**, *89*, 175–180.

(10) Waddington, G.; Sunner, S.; Hubbard W. N. In *Experimental Thermochemistry*; Rossini, F. D., Ed.; Interscience: New York, 1956; Vol. 1, Chapter 7.

(11) Vogel, A. I. *Quantitative Inorganic Analysis*; Longman: London, 1978.

(12) Wagman, D. D.; Evans, W. H.; Parker, V. B.; Schumm, R. H.; Halow, I.; Bailey, S. M.; Churney, K. L.; Nuttal, R. L. The NBS Tables of Chemical Thermodynamic Properties. *J. Phys. Chem. Ref. Data* **1982**, *11*, 1.

(13) Coops, J.; Jessup, R. S.; van Nes, K. In *Experimental Thermochemistry*; Rossini, F. D., Ed.; Interscience: New York, 1956; Vol. 1, Chapter 3.

(14) Washburn, E. N. *J. Res. Natl. Bur. Stand. (U.S.)* **1933**, *10*, 525–558.

(15) Adedeji, F. A.; Brown, D. L. S.; Connor, J. A.; Leung, W. L.; Paz-Andrade, I. M.; Skinner, H. A. *J. Organomet. Chem.* **1975**, *97*, 221–228.

(16) Santos, L. M. N. B. F.; Schröder, B.; Fernandes, O. O. P.; Ribeiro da Silva, M. A. V. *Thermochim. Acta* **2004**, *415*, 15–20.

(17) Sabbah, R.; Xu-wu, A.; Chickos, J. S.; Planas Leitão, M. L.; Roux, M. V.; Torres, L. A. *Thermochim. Acta* **1999**, *331*, 93–208.

(18) Monte, M. J. S.; Santos, L. M. N. B. F.; Fulem, M.; Fonseca, J. M. S.; Sousa, C. A. D. *J. Chem. Eng. Data* **2006**, *51*, 757–766.

(19) Frisch, M. J; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li; X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.01; Gaussian, Inc.: Wallingford, CT, 2004.

(20) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *11*, 7650–7657.

(21) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.

(22) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(23) Hubbard, W. N.; Scott, D. W.; Waddington, G. In *Experimental Thermochemistry*; Rossini, F. D., Ed.; Interscience: New York, 1956; Vol. 1, Chapter 5.

(24) Good, W. D.; Scott, D. W. In *Experimental Thermochemistry*; Skinner, H. A., Ed.; Interscience: New York, 1962; Vol. 2, Chapter 2.

(25) Cox, J. D.; Wagman, D. D.; Medvedev, V. A., Eds.; *CODATA Key Values for Thermodynamics*; Hemisphere: New York, 1989.

(26) Irikura, K. K. THERMO.PL, National Institute of Standards and Technology, 2002 (http://www.cstl.nist.gov/div838/group_06/irikura/prog/thermo.html).

(27) Clarke, E. C. W.; Glew, D. N. *Trans. Faraday Soc.* **1966**, *62*, 539–547.

(28) Please note that the gaseous phase is supposed to have characteristics of ideal gas at the pressure $p°$.

(29) Chickos, J. S.; Hosseini, S.; Hesse, D. G.; Liebman, J. F. *Struct. Chem.* **1993**, *4*, 271–278.

(30) Monte, M. J. S.; Santos, L. M. N. B. F.; Sousa, C. A. D.; Fulem, M. *J. Chem. Eng. Data* **2008**, *53*, 1922–1926.

(31) Anantharaman, B.; Melius, C. F. *J. Phys. Chem. A* **2005**, *109*, 1734–1747.

(32) Sabbah, R. *Bull. Soc. Chim. Fr.* **1991**, *128*, 350.

(33) Rakus, R.; Verevkin, S. P.; Schatzer, J.; Beckhaus, H. D.; Ruchardt, C. *Chem. Ber.* **1994**, *127*, 1095–1103.

(34) Freitas, V. L. S.; Gomes, J. R. B.; Ribeiro da Silva, M. D. M. C. *J. Chem. Thermodyn.* **2009**, *41*, 1199–1205.

(35) García-Cruza, I.; Valencia, D.; Klimova, T.; Oviedo-Roa, R.; Martínez-Magadán, J. M.; Gómez-Balderas, R.; Illas, F. *J. Mol. Catal. A: Chem.* **2008**, *281*, 79–84.

(36) This value is the mean result of the enthalpies of formation calculated with homodesmotic reactions described by eqs 2−5; the associated uncertainty (asun) was calculated as $\mathrm{asun} = \sqrt{((\sum \Delta^2)/(n-1))}$, where Δ are the differences between the experimental and calculated enthalpies of formation for thioxanthene (the value selected for reaction 5 is 219.4 $\mathrm{kJ \cdot mol^{-1}}$) listed in Table 5 and n is the number of occurrences, i.e., 4 values of Δ. If the BAC corrected value calculated with the atomization reaction (eq 1) is included, $\Delta_f H_m^{\circ}(g)$ for thioxanthene is 221.4 ± 4.1 $\mathrm{kJ \cdot mol^{-1}}$.

(37) Gomes, J. R. B.; Ribeiro da Silva, M. A. V. *J. Phys. Chem. A* **2004**, *108*, 11684–11690.

JP906413Y