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Thermal stability and decomposition of sulphur and selenium compounds

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Juan Antonio Palop · Carmen Sanmartín**

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Abstract Thermal analysis of fusion and decomposition processes was carried out on organosulphur and organoselenium compounds in order to establish thermal stability criteria. Degradation and fusion temperatures of 20 biological active compounds, synthesized by our research group were determined using thermogravimetry (TG) and differential scanning calorimetry (DSC). Analysis of the thermal data indicated that: (a) in general, sulphur compounds are more stable than selenium compounds; (b) the pyridine ring diminished stability of sulphur and selenium compounds much more than the carbocyclic aromatic rings did (6a > 9a; 2b > 3b); (c) selenomethyl derivatives are more stable than selenoethyl and selenoisopropyl compounds; (d) a chlorine atom on selenocompounds has surprising effects.

Keywords Thermal analysis · Decomposition · Thermogravimetry · Stability · Organoselenium · Cytotoxics

Introduction

Thermogravimetry (TG) is an analytical, quantitative and comparative method, capable of producing fast and reproducible results. Differential scanning calorimetry (DSC) is an analytical tool of great importance for the identification and purity testing of medicinal compounds, yielding results rapidly and efficiently. Thermal analysis has many applications in the development of new active compounds [1–6].

The essential trace mineral, selenium, is of fundamental importance to human health. Selenium deficiency can have adverse consequences for disease susceptibility and the maintenance of optimal health. Numerous studies suggest that deficiency of selenium affects immune function, viral infection, thyroid function and cardiovascular diseases. The chemopreventive and cytotoxic effects of organic selenocompounds in various types of cancer are currently being studied. Recently, our research group has demonstrated the cytotoxic effect of several compounds studied in this work in the prostate cancer cell line PC-3 and the importance of selenium atom in these compounds [7].

Ip [8] and El-Bayoumi [9] reported comparative studies between analogous sulphur and selenium compounds and demonstrated that selenium is much more active than sulphur in inhibiting cancer cell growth. We demonstrated the importance of selenium atom, in comparison with sulphur, in symmetrical imidoselenocarbamate derivatives [7]. As a result, in this paper, we proposed the study of thermal stability of some imidoselenocarbamate compounds and the differences in their thermal stability when selenium atom is substituted by sulphur atom. Also, we have evaluated the effect of different alkyl substitutions on selenium atom.

Experimental

Materials

The compounds were synthesized according to the general method described by our research group [7]. The compounds had a symmetrical disubstitution with great structural

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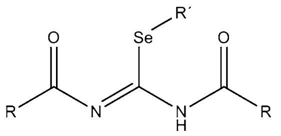
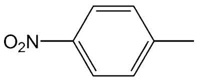
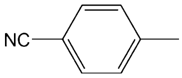
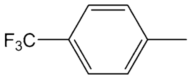
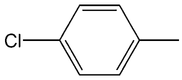
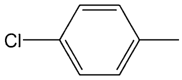
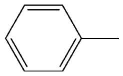
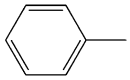
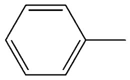
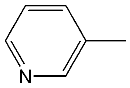
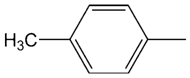
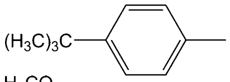
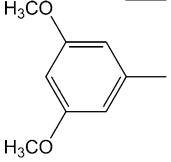
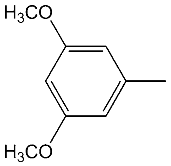
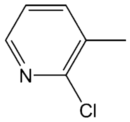
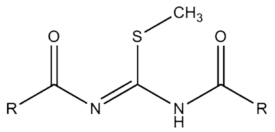
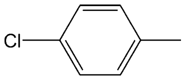
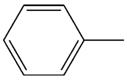
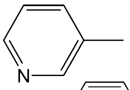
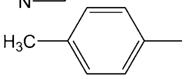
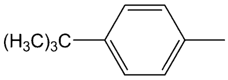
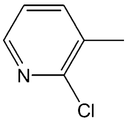
Table 1 Thermal data obtained for Series A compounds

			Series A		
			Fusion process (DSC)**		Degradation process (TG)
R	*R′*	Ref.	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	–CH$_3$	1a	*	*	251.3 ± 1.0
	–CH$_3$	2a	219.5 ± 2.8	44.4 ± 14.3	224.7 ± 1.0
	–CH$_3$	3a	172.9 ± 0.3	30.7 ± 0.8	214.1 ± 0.4
	–CH$_3$	4a	194.4 ± 0.9	39.2 ± 3.0	229.2 ± 0.4
	–CH–(CH$_3$)$_2$	5a	164.6 ± 0.3	31.6 ± 1.2	216.9 ± 1.3
	–CH$_3$	6a	139.5 ± 0.2	30.6 ± 0.6	216.0 ± 2.2
	–CH$_2$–CH$_3$	7a	105.9 ± 0.1	28.9 ± 1.6	202.8 ± 2.2
	–CH–(CH$_3$)$_2$	8a	107.0 ± 0.4	21.54 ± 1.5	201.0 ± 1.6
	–CH$_3$	9a	158.3 ± 0.0	37.0 ± 0.0	180.8 ± 0.5
	–CH$_3$	10a	148.5 ± 0.3	32.7 ± 4.9	215.5 ± 1.0
	–CH$_3$	11a	164.3 ± 0.3	28.5 ± 1.1	219.2 ± 3.1
	–CH$_3$	12a	163.6 ± 0.3	39.6 ± 0.3	219.2 ± 2.1
	–CH–(CH$_3$)$_2$	13a	153.7 ± 0.2	39.2 ± 1.0	214.4 ± 1.8
	–CH$_3$	14a	186.8 ± 0.2	42.4 ± 1.3	198.2 ± 0.5

* Fusion with degradation

** More stable polymorph

Table 2 Thermal data obtained for Series B compounds

		Series B		
		Fusion process (DSC)**		Degradation process (TG)
R	Ref.	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	1b	182.1 ± 0.4	38.5 ± 0.6	229.9 ± 1.2
	2b	149.0 ± 0.1	33.5 ± 0.6	224.8 ± 2.8
	3b	164.0 ± 0.5	37.4 ± 0.1	199.4 ± 0.6
	4b	160.2 ± 0.1	33.9 ± 0.4	230.5 ± 0.3
	5b	167.2 ± 0.4	35.7 ± 0.8	238.4 ± 4.9
	6b	142.2 ± 0.4	27.7 ± 1.6	159.8 ± 0.3

** More stable polymorph

variety. In addition, compounds showed the presence of a sulphur or selenium atom with an alkyl substituent (Tables 1 and 2). All compounds were synthesized with a high grade of purity as they had been previously evaluated as cytotoxic agents in biological assays. Each product was identified by elemental analysis, infrared spectroscopy, ^{1}H-NMR spectroscopy and mass spectrometry.

Methodology

The *thermogravimetric studies* were carried out with a Perkin-Elmer TGA-7 and the calorimetric studies were carried out with a Perkin-Elmer DSC Diamond. The thermobalance was calibrated with alumel and nickel at 10 °C min^{-1}. The calibration of the oven temperatures was carried out automatically. Mass calibration was carried out with a certified mass of 10 mg (ASTM E617).

The calorimeter was calibrated with indium and zinc (provided by Perkin-Elmer and fabricated according to guideline ISO35) at 10 °C min^{-1} and a nitrogen flow of 20 mL min^{-1}. The gases connected to the equipment were nitrogen and air with a purity of 99.999%.

Thermogravimetric analyses were carried out under nitrogen atmosphere with a gas flow of 40 mL min^{-1} at 10 °C min^{-1}, using a sample of approximately 3 mg. The $T_{initial}$, T_{onset} and T_{max}, as well as any associated mass loss were calculated. All of the experiments were performed at least three times and the values were expressed as mean ± standard deviation.

Calorimetric analyses were carried out in aluminium capsules for volatiles of 10 μL, at a heating rate of 10 °C min^{-1}, using a sample of approximately 3 mg, in order to establish the T_{onset}, T_{max} and the enthalpy of fusion ΔH_f. All of the experiments were performed at least three times and the values were expressed as mean ± standard deviation.

Nuclear magnetic resonance: the ^{1}H-NMR spectra have been obtained using a Bruker Advance 400 apparatus with DMSO-d$_6$ and CDCl$_3$ as solvents.

Molecular modelling methodology

The calculations were performed on a *Silicon Graphics* Octane2 workstation provided with the software package InsightII 2000 [10], and on a Dell Latitude D250 (Windows XP, PC) provided by the software package HyperChem Professional [11].

The three-dimensional models of the studied compounds were constructed using atoms and structural fragments from the *Builder* module (InsightII). The protocol can be summed up as follows: (a) Initial construction of the model. (b) Hierarchized systematic conformational analysis: Determination of the rotation-sensitive bonds; election of a 30° window to check each selected dihedron. First filtration: elimination of the conformations that are non-distinguishable by symmetry. Second filtration: elimination of conformations that present steric impediments. Third filtration: calculation of the energy of conformations and elimination of those conformations whose relative energy is greater than 41.8 KJ mol^{-1} at a global minimum. Fourth filtration: optimization of the geometry of the conformations and elimination of those whose relative energy is greater than 41.8 KJ mol^{-1} at a global minimum. All of the molecular mechanics calculations were carried out using the consistent valence force field ESFF [12] (*Search and Compare* module, InsightII). (c) Analysis of conformational trajectory (*Analysis* module InsightII) and selection of representative lowest energy conformation. Root mean square (rms) deviations of the structures were monitored. (d) Mechano-quantics optimization of the conformations obtained in the previous step, with the molecular orbital calculations package *Mopac* (AM1 [13] and PM3 [14] semi-empirical approaches, *AMPAC/MOPAC* InsightII module).

The bond order calculation was performed on a Dell Latitude D250 (Windows XP, PC) provided by the software package HyperChem Professional. The lowest energy conformations of selected compounds, obtained after the conformational analyses were carried out, were submitted to a new minimization (Eigenvector following algorithm, with a criterion convergence $<4.2 \times 10^{-3}$ kJ Å^{-1} mol^{-1}), under the PM3 semiempirical method calculation. The bond order was directly computed for the selected compounds and evaluated as an approximate quantitative descriptor for the bond strength.

Results and discussion

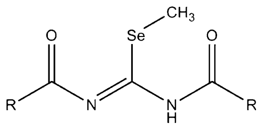
Thermal stability in the decomposition

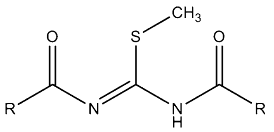
Tables 1 and 2 show the degradation temperatures (as T_{onset}) for compounds belonging to series A and B.

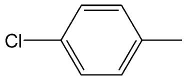
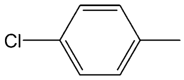
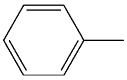
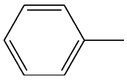
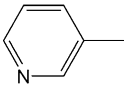
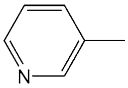
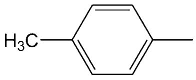
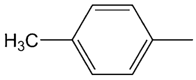
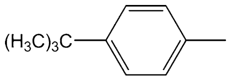
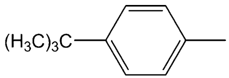
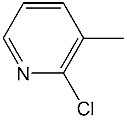
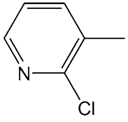
As can be observed in Table 3, the degradation temperature values presented by the sulphur compounds are relatively high and therefore, these sulphur compounds have greater thermal stability than selenium compounds (2b > 6a; 3b > 9a; 4b > 10a; 5b > 11a).

However, when a structure contained a chlorine atom substituted in aromatic or pyridine ring, sulphur and selenium compounds were on the same level of stability (1b and 4a in Table 3) or they inverted their stability (6b and 14a in Table 3). The data collected regarding the thermal behaviour for compounds 6b and 14a led us to determine the bond orders of certain compounds (3b, 6b, 9a and 14a).

Table 3 Degradation temperature values as T_{onset} obtained for some sulphur and selenium compounds





R	Ref.	T_{onset}/°C	*R*	Ref.	T_{onset}/°C
	4a	229.2 ± 0.4		1b	229.9 ± 1.2
	6a	216.0 ± 2.2		2b	224.8 ± 2.8
	9a	180.8 ± 0.5		3b	199.4 ± 0.6
	10a	215.5 ± 1.0		4b	230.5 ± 0.3
	11a	219.2 ± 3.1		5b	238.4 ± 4.9
	14a	198.2 ± 0.5		6b	159.8 ± 0.3

According to the Molecular Orbital Theory, the bond order (*bo*) is equivalent to the number of electrons in the antibonding molecular orbital minus the number of electrons in the bonding molecular orbital divided by two. This parameter can be used as a quantitative descriptor for the bond strength and it can be related to the aforementioned behaviour.

Therefore, we carried out molecular modelling studies on sulphur and selenium compounds with and without a chlorine atom substituted in pyridine ring. (Figs. 1 and 2).

Sulphur compounds (3b, 6b)

Based on the results, we obtained from these molecular modelling studies, we observed (Table 4) that the **S–CH$_3$** bond order diminished in those compounds in which a chlorine atom in the pyridine ring is present in the structure (diminished in 6b compared with 3b). This bond is the weakest one of the molecule.

The curve obtained for compound 6b (Fig. 3) shows a multi-step degradation process. The first step of degradation was related to the loss of the methyl group bonded to the sulphur atom. In order to prove this fact, we heated compound 6b in thermobalance until it had 94% of mass. At this point, we carried out a proton nuclear magnetic resonance experiment (Fig. 4) and we observed that the methyl peak ($\delta = 2.6$ ppm) was diminished with respect to

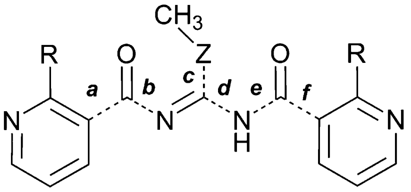


Fig. 1 General structure for the analyzed compounds showing the bonds (*dotted line*, *a–f*) selected for the conformational analysis

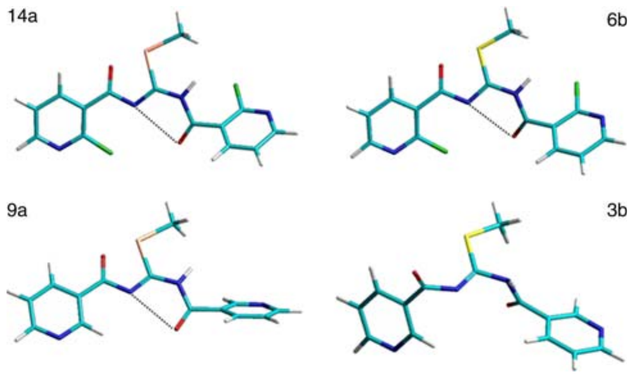
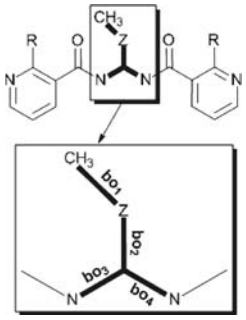


Fig. 2 Lowest energy conformation for representative compounds (selenium in *orange*, sulphur in *yellow*, chlorine in *green*; bond imine nitrogen/carbonylic oxygen in *dotted line*)

Table 4 Bond order (average value for representative low energy conformations) for selected bonds (bold lines, **bo$_{1-4}$**)



Ref.	Z	R	bo$_1$	bo$_2$	bo$_3$	bo$_4$
3b	S	H	0.9998	0.9856	1.8780	0.9600
6b	S	Cl	0.8885	1.0209	1.6520	1.0983
9a	Se	H	0.8249	0.9366	1.6375	1.1626
14a	Se	Cl	0.8277	0.9396	1.6484	1.1787

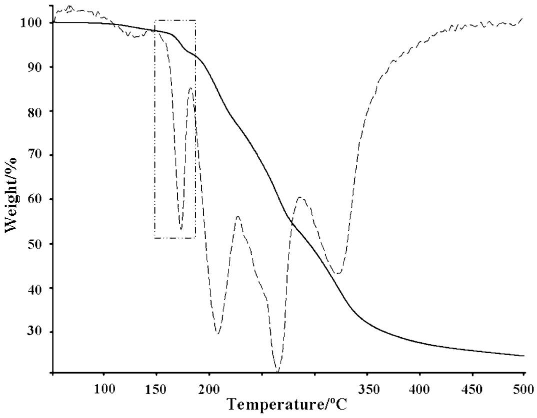


Fig. 3 Curve of the decomposition process obtained for compound 6b

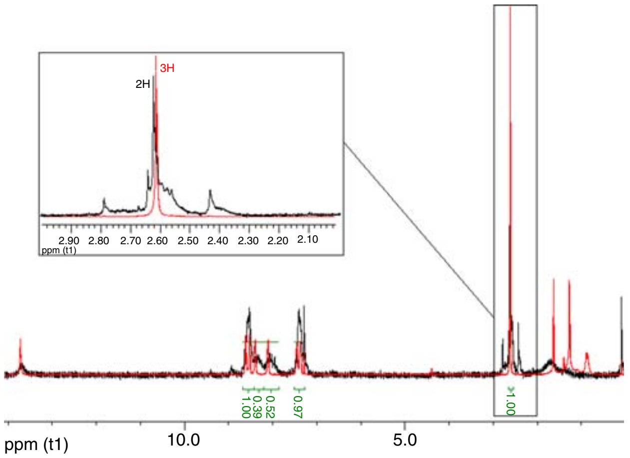


Fig. 4 ^{1}H-NMR spectra obtained for compound 6b before heat treatment (*red line*) and after heat treatment (*black line*)

aromatic ones ($\delta = 8.6$, 8.4, 8.1 and 7.4 ppm) and that another part of the compound was degradated.

Selenium compounds (6a, 14a)

The **Se–CH$_3$** bond order obtained (Table 4) in compound 14a (compound with an atom of chloro in pyridine ring) was equal to this same bond order in 9a (with no chloro) and it was similar to said bond order in compound 6b (sulphur compound with chloro atom). However, the curves obtained for compounds with selenium (9a, 14a) show a one-step degradation process (Fig. 5).

This can be explained by the presence of intermolecular bonds between nitrogen atom of pyridine and oxygen atom (9a; Fig. 6) or between chlorine and oxygen atoms with selenium (14a; Fig. 7), which have an empty *d* orbital. Therefore, the methyl group was trapped between intermolecular bonds (Fig. 7) and consequently, the loss of this methyl group was not possible. These intermolecular bonds could not exist in compound 6b, since sulphur atoms have no empty *d* orbitals. Therefore, the first step of degradation in compound 6b (Fig. 3) is not present in curve of compound 14a (Fig. 8).

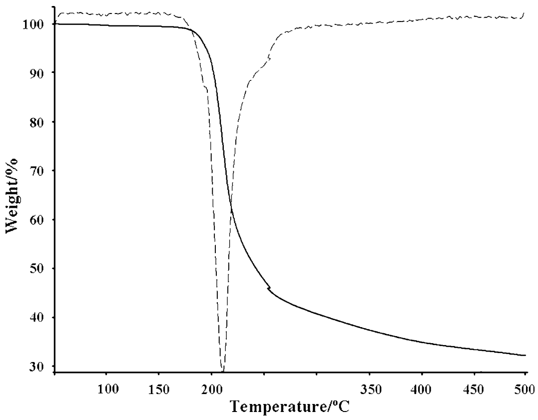


Fig. 5 Curve of the decomposition process obtained for compound 14a

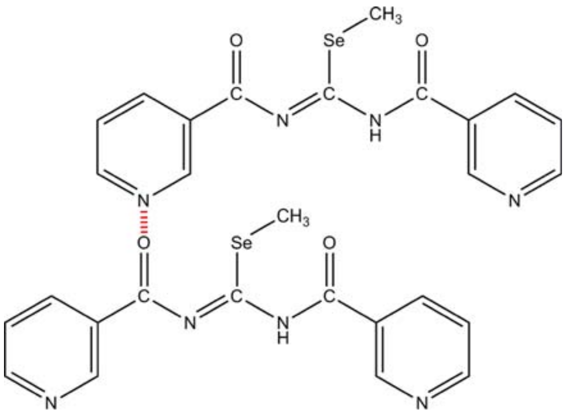


Fig. 6 Intermolecular bonds (||||) between nitrogen atom of pyridine and oxygen atom in compound 9a

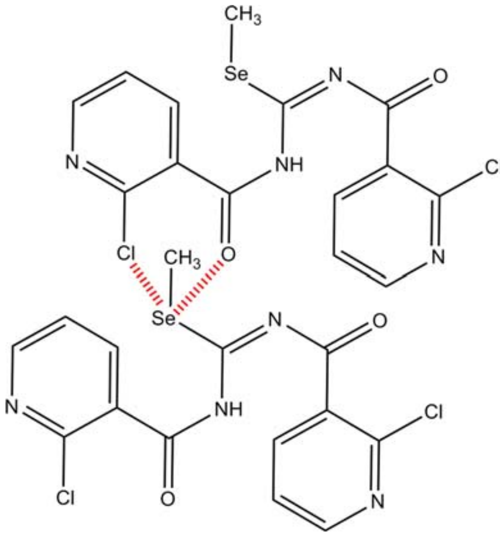


Fig. 7 Intermolecular bonds (||||) between chlorine and oxygen atoms with selenium in compound 14a

The values of T_{onset} for fusion process seem to support the presence of intermolecular bonds in compounds 9a and 14a. We observed that T_{onset} of compound 9a is higher than that of 6a ($\Delta T_{\text{onset}} = 18.8$ °C). However, compound 6a is much more stable for degradation process ($\Delta T_{\text{onset}} = 35.2$ °C). When we compared T_{onset} values for fusion process of 14a with those of 9a, we observed that the T_{onset} values for compound 14a are higher ($\Delta T_{\text{onset}} = 28.5$ °C). This fact is based on the presence of two intermolecular bonds in compound 14a (Fig. 7).

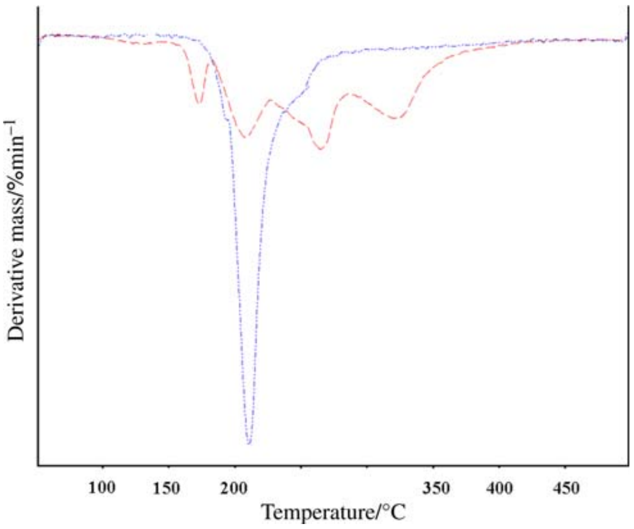


Fig. 8 Derivative curve of the decomposition process obtained for compounds 6b (*red line*) and 14a (*blue line*)

Thermal stability considerations

Compounds 6b and 14a (sulphur and selenium compounds, respectively) showed very different thermal behaviour. The curve of compound 6b (Fig. 3) showed a multi-step degradation process. However, the curve of compound 14a (Fig. 5) showed a one-step degradation process. Therefore, the peak of degradation for compound 14a occurred at a similar temperature to second-step of degradation process for compound 6b (Fig. 8). Consequently, if compound 6b did not lose the methyl group, both compounds would have had similar thermal stability. The difference in thermal stability between 6b and 14a could be explained by two factors: (a) the depletion of **S–CH₃** bond strength (using bond order as an approximate quantitative descriptor), makes the methyl group turn as if it were a labile group; (b) the presence of intermolecular bonds between chlorine and oxygen atoms with selenium (Fig. 7), trapping the methyl group and preventing its loss. These intermolecular bonds coincide with T_{onset} values for fusion process of compounds 14a and 9a ($\Delta T_{\mathrm{onset}} = 28.5$ °C).

Effect of the ramification and length of chain

With regard to the ramification and length of the chain bonded to selenium atom, we have observed that ethyl and isopropyl groups diminished thermal stability of selenium compounds (4a > 5a; 6a > 7a > 8a; 12a > 13a). The explanation to this could be that when we substituted more voluminous aliphatic groups on selenium atom, a steric repulsion between lateral chains R was provoked. These steric hindrances diminished thermal stability for compounds in series A.

Effect of the substituents

With respect to substituents on the aromatic ring, we cannot establish relationships between electron-withdrawing or electron-donating groups and thermal stability of compounds. However, we observed dependence between types of aromatic rings and stability. The pyridine ring diminished stability of sulphur and selenium compounds much more than the carbocyclic aromatic rings did (6a > 9a; 2b > 3b).

Thermal behaviour of fusion process

The T_{onset} and ΔH_{f} values for compounds of series A and B are shown in Tables 1 and 2. In Fig. 9, we can observe a typical fusion process for most of the compounds in these series.

In general, sulphur compounds have higher values of T_{onset} (2b > 6a; 3b > 9a; 4b > 10a; 5b > 11a). This fact was expected as the sulphur atom is smaller than the selenium atom. Therefore, the intermolecular interactions in the crystal will be stronger due to the fact that the molecules could be closer together within the crystal.

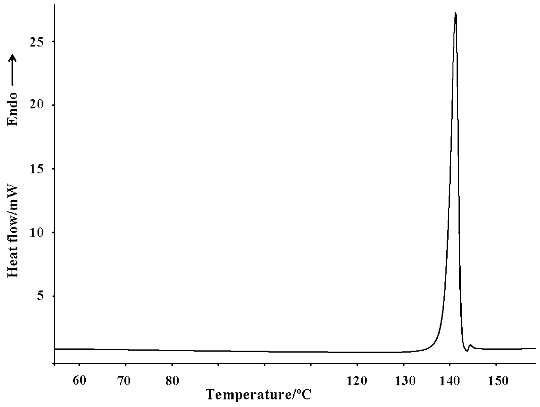


Fig. 9 DSC obtained for compound 6a

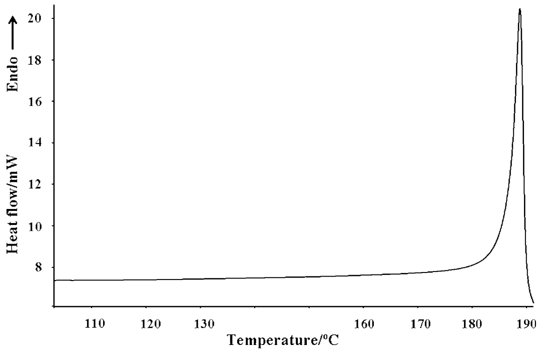


Fig. 10 DSC obtained for compound 14a

The selenocompound 14a has higher values of T_{onset} than its analogous sulphur (6b). This is due to the presence of intermolecular interactions between chlorine and oxygen atoms with selenium (Fig. 7). These interactions cause 14a to start degradation process just after fusion (Fig. 10). Compounds with groups that could act as donors in hydrogen bonding (Cl, CN and NO_2) substituted in aromatic ring have the highest T_{onset} values. These groups form hydrogen bonds with N–H group in compounds from series A (1a, 2a and 4a) and B (1b). In compound 1a, the hydrogen bond was so strong that the compound decomposed without previous fusion.

When we substituted an ethyl or isopropyl group in selenium atom, the T_{onset} diminished ($\Delta T_{\mathrm{onset}} = 12$–$15$ °C) (5a, 7a and 8a) with respect to a methyl group substitution (4a and 6a). The reason for this is that the presence of more voluminous groups in the selenium atom provokes molecules to be farther apart from each other within the crystal, making intermolecular interaction weaker. In the case of compounds 12a and 13a, the difference between methyl (12a) and isopropyl (13a) groups is lower ($\Delta T_{\mathrm{onset}} = 4.8$ °C), due to the voluminous aromatic part, which has two methoxy groups. This fact rests importance regarding the volume of alkyl group in selenium atom in crystal structure.

Conclusions

Analysis of the thermal data indicated that, in general, sulphur compounds are more stable than selenium compounds. However, a chlorine atom in selenocompounds has surprising effects. Sulphur and selenium compounds with a chlorine atom in aromating ring were on same level of stability or inverted the stability when the ring is pyridine. This difference in thermal stability could be explained by the presence of intermolecular bonds between chlorine atom with selenium.

With regard some substituents present on aromating ring and the ramification and length of chain, it can be concluded that the presence of electron-withdrawing groups in selenocompound structures improves their stability. Besides, selenomethyl derivatives are more stable than selenoethyl and selenoisopropyl compounds.

References

1. Giron D. Applications of thermal analysis in the pharmaceutical industry. J Pharm Biomed Anal. 1986;4:755–70.
2. Giron D. Thermal analysis in pharmaceutical routine analysis. Acta Pharm Yugos. 1990;40:95–157.
3. Lizarraga E, Zabaleta C, Palop JA. Thermal stability and decomposition of pharmaceutical compounds. J Therm Anal Cal. 2007;89:783–92.
4. Olar R, Badea M, Carp O, Marinescu D, Lazar V, Balotescu C, et al. Synthesis, characterisation and thermal behaviour of some thiosulfato- and sulfato copper(II) complexes. Antibacterial activity. J Therm Anal Cal. 2008;92:245–57.
5. Jingyan S, Jie L, Yun D, Ling H, Xi Y, Zhiyong W, et al. Investigation of thermal behavior of nicotinic acid. J Therm Anal Cal. 2008;93:403–9.
6. Bakalova A, Varbanov H, Buyukliev R, Momekov G, Ivanov D. Palladium(II) complexes with 5-methyl-5-(4-pyridyl)-2,4-imidazolidenedione. Synthesis, thermogravimetric and cytotoxic investigation. J Therm Anal Cal. 2008;95:241–6.
7. Plano D, Sanmartín C, Moreno E, Prior C, Calvo A, Palop JA. Novel potent organoselenium compounds as cytotoxic agents in prostate cancer cells. Bioorg Med Chem Lett. 2007;17:6853–9.
8. Ip C, Ganther HE. Comparison of selenium and sulfur analogs in cancer prevention. Carcinogenesis. 1992;13:1167–70.
9. El-Bayoumi K, Sinha R, Pinto JT, Rivlin RS. Cancer chemoprevention by garlic and garlic-containing sulfur and selenium compounds. J Nutr. 2006;136:864S–9S.
10. InsightII. Accelrys Software Inc. San Diego: Accelrys Software Inc.;2000.
11. Hypercube, Inc., Hyperchem Professional. Hypercube Inc 1115 NW 4th Street, Gainesville, FL 32601, USA.
12. Shi S, Yan L, Yang Y, Fisher-Shaulsky J, Thacher T. An extensible and systematic force field, ESFF, for molecular modeling of organic, inorganic, and organometallic systems. J Comp Chem. 2003;24:1059–76.
13. Dewar MJS, Zoebisch EG, Healy EF, Stewart JJP. AM1: a new general purpose quantum mechanical molecular model. J Am Chem Soc. 1985;107:3902–9.
14. Stewart JJP. Optimization of parameters for semi-empirical methods I-method. J Comp Chem. 1989;10:209–20.