Journal of Thermal Analysis and Calorimetry, Vol. 89 (2007) 3, 783–792

THERMAL STABILITY AND DECOMPOSITION OF PHARMACEUTICAL COMPOUNDS

Elena Lizarraga[*]*, C. Zabaleta and J. A. Palop*

Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Navarra, Irunlarrea 1, 31008 Pamplona, Spain

Thermal analysis of fusion and decomposition processes were carried out on recently synthetized pharmaceutical compounds in order to establish thermal stability criteria. This study was carried out using thermogravimetry, TG, and differential scanning calorimetry, DSC. Degradation and fusion temperatures have been produced as thermal data with the aim of to study the thermal stability of the compounds.

Relationship is found among stability and a series of effects of structure of the compounds. The compounds which present an amide functional group in the central molecule are more stable because they have a comparatively higher fusion and degradation temperature. In addition, the stability of this type of compounds depends on the position of the electrophilic substitution (in *ortho, meta or para*). Likewise, the groups linked to the aromatic ring with high electronic density give stability, and therefore are able to delocalize the charge in a greater spacial interval.

Therefore, criteria for the selection of substituents have established that improve the stability of compounds

Keywords: *calorimetry, degradation process, pharmaceuticals, structure, thermal analysis, thermal decomposition, thermal stability, thermogravimetric analysis*

Introduction

Thermal analysis during the complete development of a new drug has many applications [1, 2]. The information obtained regarding the compounds under study is useful for the initial chemical research phase [3]. This thermal study will contribute to a better knowledge and management of these compounds whose biological activity is pursued.

In the chemical research phase, thermal analysis plays an important role. The purity of the compound, the compound's ability to be able to exist in various crystalline forms as well as to characterize polymorphs and other forms of solid state should be investigated. Both calorimetry and thermogravimetry can also be used in the evaluation of compound stability [4–9]. Predicting stability or instability at a very early stage of product development, such as immediately after the initial synthesis process, provides valuable information.

Experimental

Materials

The compounds have been provided by the Organic and Pharmaceutical Synthesis Unit of the University of Navarra.

Given that a routine task carried out in Medicinal Chemistry when searching for products (based on their biological activity) that might be useful for therapeutic purposes is to synthetize products which possess relatable structures, we selected some of their compounds for our study.

The compounds selected were those with a symmetrical disubstitution. This group of symmetrical compounds shows great structural variety. This variety of structures is based on the number of aromatic rings present, the positional isometry in the substituent and the functional group which links the principal chain and the substituent (Tables 1–12).

Each product is accompanied by identification assays which include: elemental analysis, infrared spectroscopy, ^{1}H-RMN spectroscopy, HPLC, thermomicroscopy, mass spectrometry and possible additional observations related to the solubility of the product, alteration of the properties of light or heat, etc. The compounds achieve a high grade of purity because many of them were prepared for carrying out biological assays.

Methodology

The calorimetric studies are carried out with a Perkin-Elmer DSC-7, and thermogravimetric studies, with a Perkin-Elmer TGA-7.

* Author for correspondence: elizarraga@unav.es

1388–6150/$20.00

Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

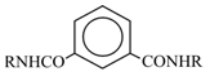
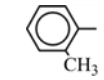
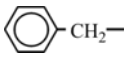
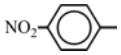
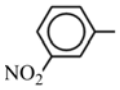
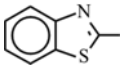
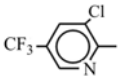
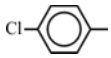
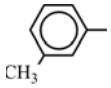
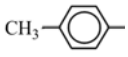
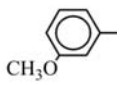
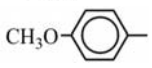
The calorimeter is calibrated with indium and zinc (provided by Perkin-Elmer and fabricated according to guideline ISO35) at 10°C min^{-1} and a nitrogen flow of 40 mL min^{-1}. The gases connected to the equipment are nitrogen and air with a purity of 99.999%.

The thermobalance is calibrated with alumel and nickel at 10°C min^{-1}. The calibration of the oven temperatures is carried out automatically. Mass calibration is carried out with a certified mass of 100 mg (ASTM E617).

First of all, the stability of each compound is determined in the range of fusion temperatures, studying possible desolvations, solid–solid transitions, fusion, purity, etc. The processes to be carried out are: determination of fusion stability, fusion with or without decomposition and evaluation of the existence of polymorphism. This facilitates the selection of those compounds which are stable, pure, and do not present polymorphism.

Calorimetric analyses are performed in aluminium capsules for volatiles of 10 μL, at a heating rate of

Table 1 Fusion and degradation processes of serie A compounds

	SERIE A		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	246.6	163.3	352.3
	138.0	84.6	363.3
	>300		414.0
	278.6	78.6	401.8
	194.8	128.4	338.2
	136.4	222.1	387.2
	230.9	117.5	315.0
	225.9	114.0	373.4
	223.1	109.0	379.2
	256.6	137.3	348.0
	272.9	146.0	357.9
	–	–	370.5
	278.4	157.8	386.8
	216.6	132.9	361.9

– Product not disposable
* Fusion with decomposition

10°C min^{-1}, using a sample of approximately 3 mg, to find the T_{onset}, T_{max} and the enthalpy of fusion, ΔH_f.

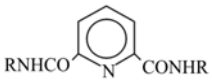
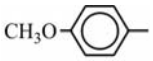
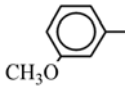
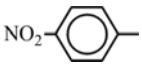
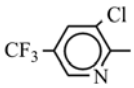
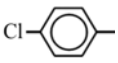
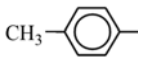
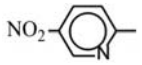
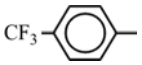
Five calorimetric analysis are carried out in the same day and during five different days. The mean, standard deviation, variation coefficient and mean confidence interval are calculated.

Thermogravimetric analyses are carried out under air 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, are calculated.

Five thermogravimetric analysis are carried out in the same day and during five different days to calculate the mean, standard deviation, variation coefficient and mean confidence interval.

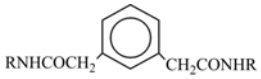
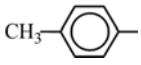
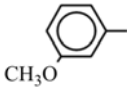
In order to avoid variability of the data with factors such as sample size, heating rate, volume of the capsules, particle size, etc. and, given that the studies are

Table 2 Fusion and degradation processes of serie B compounds

	SERIE B		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	271.8	149.9	339.3
	279.9	163.7	378.6
	205.4	145.9	364.3
	–	–	409.0
	212.4	79.9	315.2
	243.0	95.6	367.2
	219.6	103.8	337.3
	–	–	390.9
	>300		324.3

– Product not disposable

Table 3 Fusion and degradation processes of serie C compounds

	SERIE C		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	200.1	129.7	329.8
	220.7	132.1	332.3
	196.6	158.5	343.9

going to be of compared thermal stability, the mass of all of the compounds is established at approximately 3 mg, the heating rate is set at 10°C min^{-1} and the volume of the capsules used in calorimetry is 10 μL.

Results and discussion

Thermal stability in the fusion

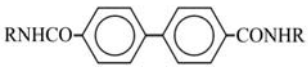
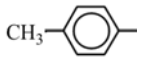
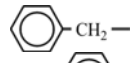
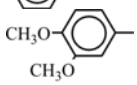
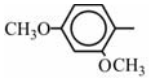
Series which present an amide group as a link between the principal chain and the substituent

Series A (Table 1): dependence with regard to the *ortho*, *meta* or *para* substitution can be studied. It has been determined that for any group substituted in the benzene, the position *para* gives more stability than the *metha* or *ortho* positions.

Therefore, substituents which possess identical positional isometry are compared. For the *para*, *metha* and *ortho* substitution, it is observed that the thermal stability decreases in relation to the group that is substituted in the benzene as follows: NO_2>CH_3O>CH_3>Cl.

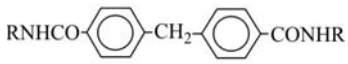
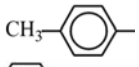
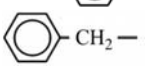
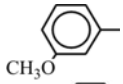
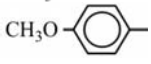
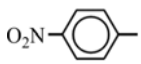
The fusion temperature values presented by the compounds are relatively high and therefore, in general, these series of compounds have great thermal stability in the fusion. Similar behavior has been found for series B, C, D and E (Tables 2–5).

Table 4 Fusion and degradation processes of serie D compounds

	SERIE D		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	–	–	409.9
	283.5	132.3	390.9
	–	–	418.8
	256.3	94.9	404.7
	219.8	81.6	230.2

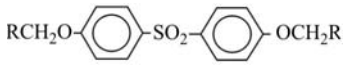
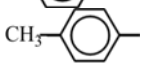
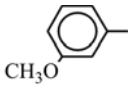
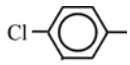
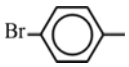
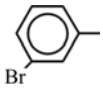
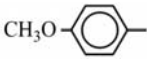
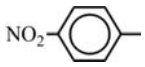
– Product not disposable

Table 5 Fusion and degradation processes of serie E compounds

	SERIE E		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	252.4	135.2	403.4
	276.8	135.9	400.7
	204.8	127.6	388.3
	170.4	73.9	398.9
	281.1	151.5	412.8
	–	–	432.3

– Product not disposable

Table 6 Fusion and degradation processes of serie F compounds

	SERIE F		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	186.6	68.44	338.3
	*	*	332.2
	145.9	101.0	366.2
	162.5	79.5	–
	180.4	85.9	365.7
	176.0	83.6	363.7
	180.8	72.1	302.0
	–	–	337.2
	197.6	84.9	345.2

– Product not disposable
* Fusion with decomposition

Series that present another type of group, such as the ether or ketone group, as a link between the principal chain and the substituent

Series F (Table 6): presents an ether group between the principal chain and the substituent. The compounds show fusion temperatures and enthalpy of fusion values that are comparatively less than those found for the series mentioned previously in this report; the functional group present in the substituent as well as the position of the substituent are not determining factors as no significant differences are observed among the compounds. This same behavior was found for series G, H, I, J, K and L (Tables 7–12).

The fusion of the compound F-002 occurs with decomposition and the compound H-001 presents polymorphism (Figs 1 and 2). For this reason, these aforementioned compounds are not appropriate for the study.

Conclusions regarding the stability in the fusion

With regard to the functional groups that are present, the presence of functional groups in the molecule that can establish hydrogen bonds is a determining factor. Series are found that have an amide group between the substituent and the principal chain whose thermal characteristic is that of presenting fusion temperatures which are clearly superior. This is due to the type of especially reinforcible intermolecular attraction that the hydrogen bond provides (Fig. 3).

Nevertheless, the special character of the nitrated molecules due to their highly electro-withdrawing potency should be pointed out.

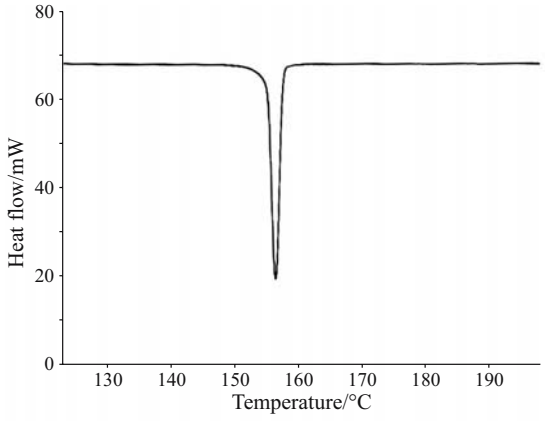


Fig. 1 DSC curve of compound F-002 at 10°C min^{-1}

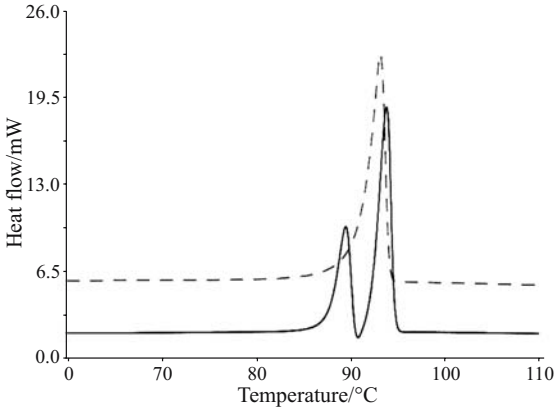


Fig. 2 DSC curve of compound H-001 at 10°C min^{-1}, second DSC curve at 10°C min^{-1}

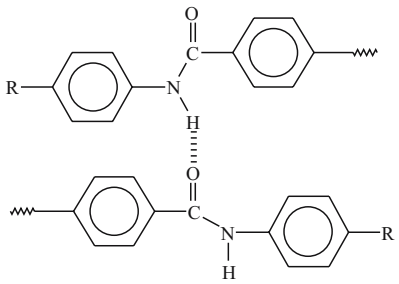


Fig. 3 Hydrogen bonds between amide groups

With regard to the functional groups present in the substituent and their positional isometry, it can be concluded that, in general, the stability is always in the following descending order: NO_2>CH_3O>CH_3>Cl and *para*>*meta*>*ortho* (the isomer *para* fits better in the crystalline reticle because the structure is more symmetric; it is more packageable).

Considering the series with amide group as a link between the principal chain and the substituent, the following considerations should be made: with regard to the nitro group, it should be pointed out that when this group is *para*-substituted, it infers great stability to the solid because it increases the possibilities of implanting highly stable intermolecular hydrogen bonds (Fig. 4):

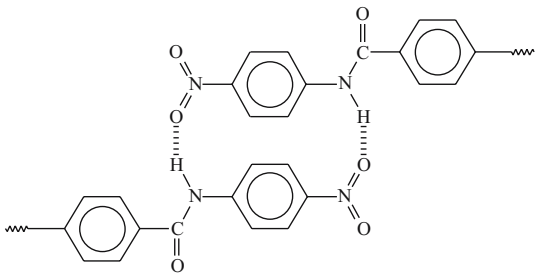


Fig. 4 Intermolecular hydrogen bonds between amide and nitro groups

However, when the nitro group is substituted in position *ortho*, due to the proximity of this group to the amide group, the formation of intramolecular hydrogen bonds is favored (Fig. 5), which, in turn, decreases the formation of the intermolecular links and this results in a decrease of the fusion parameters.

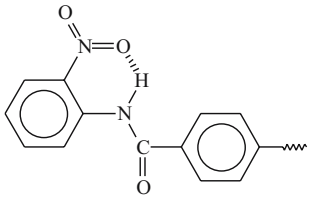


Fig. 5 Intramolecular hydrogen bonds between amide and nitro groups

The methoxy group, due to its angular geometry, possesses a dipolar moment ($\mu \neq 0$). Like the ether group, the methoxy group will form hydrogen bonds while having less possibilities than the nitro group. The intermolecular forces that consolidate the crystalline structure will be dipole–dipole interactions and, if we are dealing with a compound with an amide group, the intermolecular forces will be intermolecular hydrogen bonds, but of less consistency and force than in the case of the substituent being a nitro group.

It should be pointed out that for this type of methoxylated compounds there is a difference in thermal stability in terms of positional isometry. The *para* isomer fits in the crystalline reticle better due to the fact that the structure is more symmetric. By this, we mean they are more 'packageable'.

Based on the fact that the hydrogen bond is a particularly strong attraction and much stronger than the other dipole-dipole attractions, the groups that have the possibility to form said hydrogen bonds will present crystalline structures that are very compact and rigid, and therefore, their fusion temperature will be higher.

With regard to aromatic substitution, the *para* isomer melts at a temperature which is considerably higher than the other two positional isomers. The more symmetric a compound is, the higher its fusion temperature will be and the lower the solubility will be; the relationship is found among thermal stability at the point of fusion, symmetry, packaging and solubility.

For the compounds that do not have the possibility of forming hydrogen bonds, the differences in terms of positional isomers are not very marked, possibly due to the fact that the order is not as rigid, and the symmetry and packaging present other possibilities.

Table 7 Fusion and degradation processes of serie G compounds

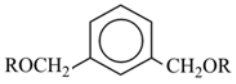
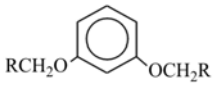
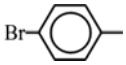
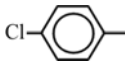
	SERIE G		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	75.6	122.6	251.1

Table 8 Fusion and degradation processes of serie H compounds

	SERIE H		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	92.6*	45.4*	297.4
	73.1	81.3	287.9

* More stable polymorph

Table 9 Fusion and degradation processes of serie I compounds

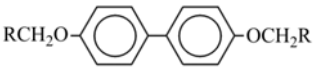
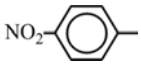
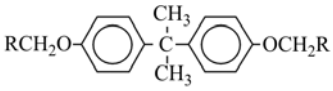
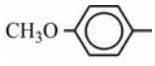
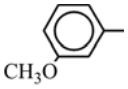
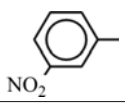
	SERIE I		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	120.6	63.5	299.5

Table 10 Fusion and degradation processes of serie J compounds

	SERIE J		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	134.7	125.0	297.7
	66.0	75.1	323.8
	–	–	297.7

– Product not disposable

Table 11 Fusion and degradation processes of serie K compounds

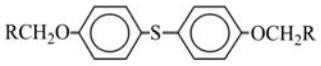
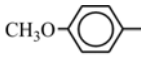
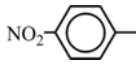
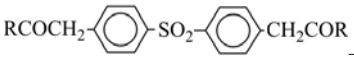
	SERIE K		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	149.0	133.0	282.7
	119.8	63.8	296.1

Table 12 Fusion and degradation processes of serie L compounds

	SERIE L		
	Fusion process (DSC)		Degradation process (TG)
R	T_{onset}/°C	ΔH_f/J g^{-1}	T_{onset}/°C
	132.8	77.0	340.3

Thermal stability in the decomposition

Series that present an amide group as a link between the principal chain and the substituent

Series A (Table 1): for any functional group present in the substituent, it is found that the farther apart the molecules' groups are, the more the degradation values of the compounds increase. By this, the *para* isomer is more stable than the *meta* isomer and this last is more stable than the *ortho* isomer (*para*> *metha*>*ortho*).

For identical positional isomers, in terms of the functional groups linked to the ring, an effect is observed in the degradation temperature and therefore, it is also observed in the thermal stability: the nitrated compound possesses greater stability than the rest of the series (NO_2>CH_3O>Cl>CH_3). These high values observed for the nitrated compounds are due to the potent electronic delocalization between the aromatic ring and the substituted nitro group. The compounds that possess the methoxyl group are stabilized by the potent electron-releasing ability of said substituent due to the effect of resonance. Similar behavior has been found for the series B, C, D and E (Tables 2–5). A curve type of compounds of these series is shown in Fig. 6.

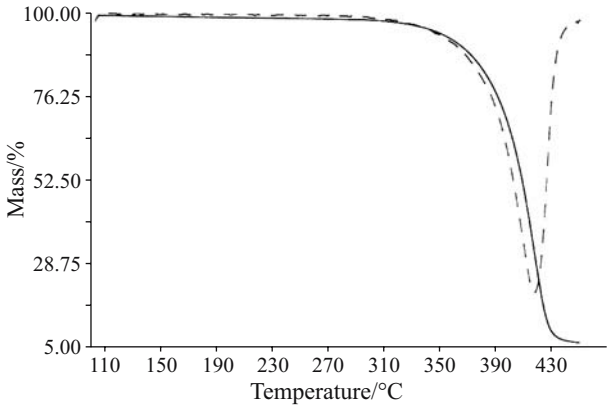


Fig. 6 — – TG and - - - – DTG curves of compounds of series A–E

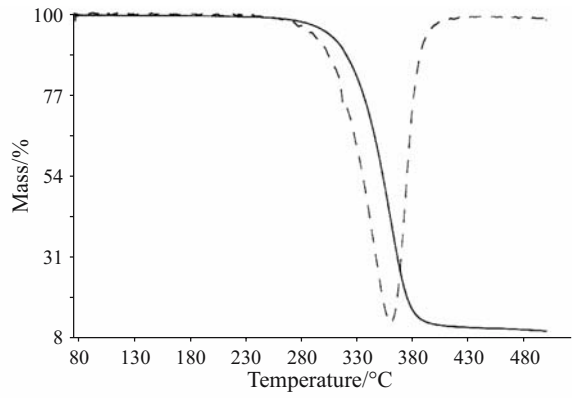


Fig. 7 — – TG and - - - – DTG typical curves of compounds of series F–L

Fig. 8 Tautomerism keto-iminic

Series that present a different type of group, such as the ether or ketone group, as a link between the principal chain and the substituent

Series F (Table 6): After comparing this series with the previous ones (series A, B, C, D and E) it is observed that the mean value of the degradation temperatures is lower. With regard to the values corresponding to this parameter that were found for each of the structures within this series, the differences among them was minimal, much less than when contemplating the previous series. The substitutions *para*, *meta*, and *ortho* have lesser significance and in fact, when comparing the conclusions made regarding the previous series, one can even find an inversion. The same type of behavior has been observed in the G, H, I, J, K and L series (Tables 7–12). A thermogram type is shown in Fig. 7.

Conclusions regarding the thermal stability in the decomposition

It has been found that the thermal stability of the compounds can be conditioned by a series of effects, such as the functional groups that are present in the central molecule, the functional groups present in the substituent under consideration, effects in the orientation of the substituent, etc.

With regard to the functional groups that are present in the central molecule, it has been observed that there is a clear dependence of the thermal stability with the existence of groups in the molecule that can originate tautomeric balances, such as the presence of an amide group between the substituent and the central part of the molecule.

As a matter of fact, the molecules with the aforementioned group can present a keto-iminic tautomerism in such a way that a balance exists between the structures I and II (Fig. 8).

Based on the methodology followed and the solvent used in the recrystallization process for the purification of the compounds, crystals of the more stable tautomer form (delocalizate form) are obtained almost exclusively (this tautomer is more insoluble).

This tautomerism reinforces the electronic delocalization of the structure of the molecule, with the resulting stabilization in the degradation process.

By this stabilization, the values corresponding to degradation temperature are comparatively higher in the series in which this functional group is present.

With regard to groups present in the substituent, thermal stabilization is induced by the presence of a nitro group, possibly due to the potent electronic delocalization which permits coplanarity of the aromatic ring and the substituted nitro group. The reaction rates associated to the degradation processes of these molecules are slow and therefore, at a certain temperature, they will take longer to degrade than the rest of the compounds.

The electronic effects are also found, depending on the other substituents present in the ring. The methoxyl group, with great electron-releasing potency, stabilizes due to the resonance effect. The possibility of 'fanning' of the orbital full of oxygen with the aromatic π system permits an electronic delocalization of high stabilizing potency, although not as intense as that which occurs with the nitro group.

The halogenated compounds present degradation temperatures that are a bit less than the previous ones. With regard to the electronic effects, the halogens show a double possibility of conflicting results: an important electron-withdrawing inducing effect and a moderate electron cession effect by resonance which, depending upon the halogen itself and upon the structural situation, can have a resultant variable. In the case studied, it appears that it transmits a very weak stabilization to the aromatic ring by means of electronic delocalization of a pair of halogen electrons in the π aromatic system.

Introducing a methyl group in the aromatic ring is the least stable situation among the examples available. The absence of fanning observed between the methyl sp^3 hybridization carbon and the π aromatic ring impedes the stabilizing electronic delocalization.

The effect of the orientation of the substituent follows the same model used up to now. It is observed that the value corresponding to the degradation increase in the *ortho*<*meta*<*para* orientation which appears to suggest that the controlling factor is of esteric type and of repelling type among groups due to the physical proximity, especially because the differences of temperature are more marked with the voluminous substituents.

Conclusions

Relationship is found among thermal stability and a series of effects of structure of a series of compounds such as the functional groups that are present in the central molecule, the functional groups present in the substituent and effects in the orientation of the substituent.

The compounds which present an amide functional group in the central molecule have fusion and degradation temperatures which are clearly superior. The presence of functional groups in the molecule than can establish hydrogen bonds and tautomeric balances is a determining factor.

With regard some groups present in the substituent and their positional isometry it can be conclued that additionally groups that reinforce the electronic delocalization and an adequate orientation in the aromatic substitution (steric factors) increase the stability that it is always in the following descending order: NO_2>CH_3O>CH_3 or Cl and *para>meta>ortho*.

Therefore, criteria for the selection of substituents have established, within the studied series, that always improve the stability of compounds.

References

1 D. Giron. J. Pharm. Biomed. Anal., 4 (1986) 755.
2 D. Giron, Acta Pharm. Yugos., 40 (1990) 95.
3 M. J. Hardy, in: E. L. Charsley and S. B. Warrington, Eds, Thermal analysis-techniques and applications, The Royal Society of Chemistry, Cambridge 1992, pp. 180–197.
4 L. J. Ford and P. Timmins, Pharmaceutical Thermal Analysis. Techniques and applications. Ellis Horwood, Chichester 1989.
5 M. Wesolowski and T. Konarski, J. Thermal Anal., 43 (1995) 279.
6 A. Vora, A. Riga, D. Dollimore and K. S. Alexander, Thermochim. Acta, 392–393 (2002) 209.
7 Y. Cheng *et al.*, Thermochim. Acta, 367–368 (2001) 23.
8 K. C. Thompson, Thermochim. Acta, 355 (2000) 83.
9 E. Lizarraga *et al.*, Thermochim. Acta, 427 (2005) 171.

Received: June 21, 2006
Accepted: October 10, 2006
OnlineFirst: February 26, 2007

DOI: 10.1007/s10973-006-7746-4