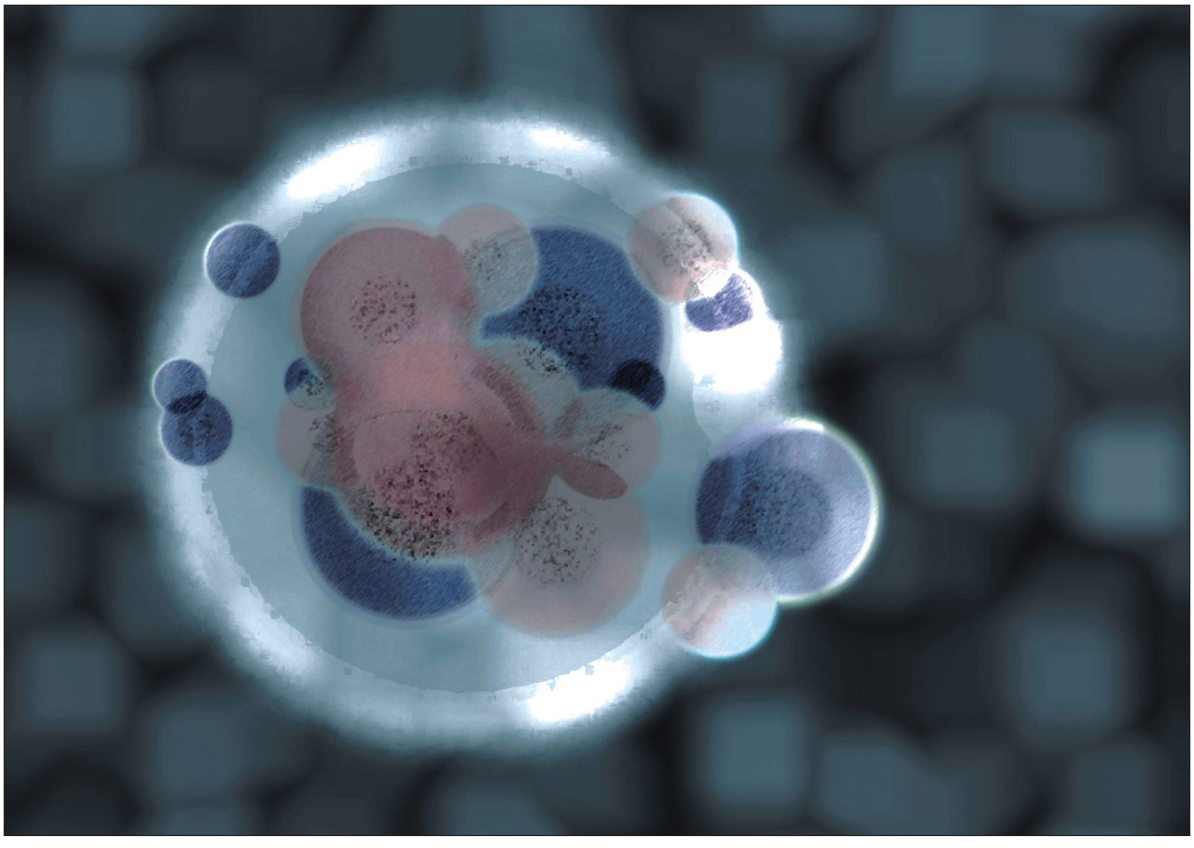

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Thermoanalytical Behaviour of 2-amino- and 2-oxo- Substituted Pyrimidines

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Abstract: Thermoanalytical behaviour of 2-amino- and 2-oxo- substituted pyrimidines studied in an inert atmosphere (N_2) has been described. The simultaneous TG-DTA profiles recorded over the temperature range of ambient-700°C, with a heating rate programmed at 10°C/ min, indicate fairly resolved mass loss stages and peaks. The thermal stability and degradation pattern of the substituted pyrimidines is discussed.

Key words: Substituted pyrimidines, thermoanalytical behaviour, TG-DTA

Introduction

Purine and pyrimidine derivatives and nucleoside analogues form a biologically and pharmaceutically important group of compounds (Youssef *et al.*, 1989; Gaye-Saye and Aaron, 1994). The nucleoside analogue, azidothymidine, 3′-azido-3′-deoxythymidine (AZT, BW A-509 U, Zidovudine, Retrovir®) is used in the treatment of acquired immune deficiency syndrome (AIDS) and AIDS-related complex (ARC) (Tomankova and Sabartova, 1990). Fluorinated pyrimidines and their nucleosides are well known to show a significant cytotoxic activity. Among them, 5-fluorouracil (5-FU), considered as one of the most active anticancer drugs, is widely used for the treatment of some solid tumors of breast, colon and rectum (Guerrieri *et al.*, 1994).

Several analytical procedures have been developed for the analysis and physicochemical investigations (Abdullah, 1996; Stevens *et al.*, 1984) of this group of compounds in pharmaceutical, biological, physiological and other samples. These procedures and techniques include: infrared, UV, SRTP (synchronous room-temperature phosphorescence) spectroscopy (Belikov *et al.*, 1989; Amici *et al.*, 1989; Gaye-Seye and Aaron, 1994), gas, thin layer and liquid chromatography (Simek *et al.*, 1994; Simanov, 1994; Guerrieri *et al.*, 1994; Ashihara *et al.*, 1990; Tomankova and Sabartova, 1990). Their luminescence properties have been investigated extensively, because of the fundamental interest in biochemistry and essential role in photochemical and photophysical processes of nucleic acids (Daniels, 1983).

Thermal analyses techniques (TG, DTA, DSC, TMA, EGA, EGD, etc.) find numerous applications in analytical chemistry (Brown, 1988; Haines, 1995; Shah *et al*., 1998; Khuhawar *et al*., 1998; Abbasi *et al*., 1998). Thermal studies have been seldom reported for this class of compounds. Belikov *et al*. (1989), have reported the study of interaction between β-cyclodextrin and pyrimidinedione derivatives by thermogravimetry and infrared spectroscopy. Surga *et al.* (1995), have studied some coordination compounds of 2-merceptopyrimidines.

In the present paper, we report thermoanalytical behaviour of some 2-amino- and 2-oxo-pyrimidines in a dynamic N_2 atmosphere, over the temperature range of 25-700°C. The thermal stability and degradation pattern of the pyrimidines: P1 2-amino-4 (p-methoxyphenyl) 6-hydroxyphenyl-3,6-dihydropyrimidine; P2 2-amino-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine; P3 2-oxo-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine and P4 2-oxo-4 (p-chloro) 6-diphenyl-3,6-dihydropyrimidine is discussed.

Materials and Methods

The studies were conducted in the thermal analyses laboratories of the Center of Excellence in Analytical Chemistry, University of Sindh, Jamshoro. The details are summarized as under:

Chemicals and Glassware: The spectroscopic and AnalaR grade chemicals were obtained from Merck/Fluka (Germany) and glassware from Quick-fit (England) or Brand (Germany).

Synthesis of 2-amino-pyrimidines: Guanidine hydrochloride and the substituted 1,3-diphenyl-2-propen-1-ones (2: 1 molar ratio) were mixed in dry ethanol. The mixture was made alkaline using KOH pallets, and then heated under reflux on a steam bath for 4-6 hours. The alcohol was removed by distillation and the residues were taken up in inert solvent (diethyl ether/benzene), acidified and washed with water, and dried with sodium sulfate. The solvent was evaporated to a thick residual mass, which was crystallized with ethanol. The crystallized material was chromatographed on silica-gel column. The distillation of the eluent gave various yields of crystallized 2-amino-4,6-dimethyl-3,6-dihydropyrimidines (Rahman *et al*., 1994).

Synthesis of 2-oxo-pyrimidines: The α,β-unsaturated compound (0.01 mole) was treated with carbamide (0.03 mole) and stirred thoroughly in dry ethanol (50 ml) for 1-2 hour, later added dilute sulfuric acid (5 ml, 6 N). The mixture was refluxed for 4-6 hour on a steam bath. It was basified and taken into dichloromethane (25 ml), washed with water, dried and evaporated to crystalline 2-oxo-4,6-diphenyl-3,6-dihydropyrimidines (Rahman *et al*., 1994).

Apparatus: A Shimadzu (Japan) Model DT-30 B thermal

analyzer with a highly sensitive thermobalance (DGC-30), high temperature type thermocouple (HTT, Pt-Rh 13%, range ambient-1500°C) and multichannel recorder (R-123T) were employed. The instrument was calibrated with the ICTA (International Confederation for Thermal Analysis) certified calibrants. The simultaneous TG-DTA curves were recorded in a dynamic nitrogen atmosphere (flow rate 30-40 ml/ min) over the temperature range of 25-700°C and a heating rate of 10°C/ min. The α-Al_2O_3 powder was used as a reference material for DTA. The samples were accurately weighed (10±0.01 mg) in platinum cells using Mettler M-5 microbalance.

Results and Discussion

Thermoanalytical Behaviour: The simultaneous TG-DTA curves for 2-amino- and 2-oxo- substituted pyrimidines studied here are shown in Fig. 1-4 and the data is listed in Table 1. The detailed interpretation of the curves is as under:

2-amino-4 (p-methoxyphenyl) 6-hydroxyphenyl-3,6-dihydropyrimidine: The TG curve of P1 shows (Fig. 1) 100% mass loss in three steps. First loss of about 49.5% appears from 160°C and is completed up to 388°C. Second loss (11%) occurs between 388-540°C, followed by another 39.5% mass loss up to 660°C. While on DTA curve, two endothermic peaks appear at 362°C and 650°C. The peak at 650°C is large in intensity, as compared to the other.

2-amino-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine:The TG trace of P2 records (Fig. 2) 97% mass loss in three steps. First major loss of 76% is detectable at 142°C and ends at 380°C. Second loss (3.5%) is rather slow, which occurs between 380-548°C, followed by third 17.5% loss up to 628°C, leaving behind 3% carbonaceous residue. While the DTA trace shows an exothermic peak at 128°C and two endothermic peaks at 388°C and 588°C.

Table 1: Thermal curves (TG-DTA) data for 2-amino- and 2-oxo-pyrimidines

Pyrimidine	Mass Loss (%)	T °C (T_i-T_f)	DTA Peak	T °C (T_m)
P1	49.5	160-388	-	362
	11	388-540	-	650
	39.5	540-660		
P2	76	142-380	+	128
	35	380-548	-	388
	17.5	548-628	-	588
P3	95	190-338	+	82
	1	338-454	+	104
	4	454-505	+	330
			-	490
P4	71	170-350	+	108
	6	350-528	-	360
	22	528-670	-	410
			-	625

Key: +, - denote Exothermic and Endothermic Peaks; P1 2-amino-4 (p-methoxyphenyl) 6-hydroxyphenyl-3,6-dihydropyrimidine; P2 2-amino-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine; P3 2-oxo-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine; P4 2-oxo-4 (p-chloro) 6-diphenyl-3,6-dihydropyrimidine

2-oxo-4 (p-methoxy) 6-diphenyl-3,6-dihydropyrimidine: The

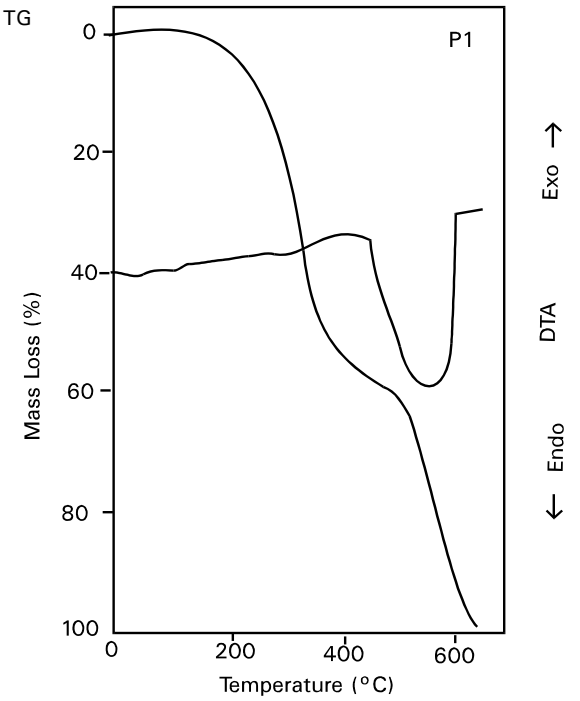

Fig. 1: TG-DTA curves of 2-amino-4 (p-methoxyphenyl) 6-hydroxyphenyl-3, 6-dihydropyrimidine in N_2

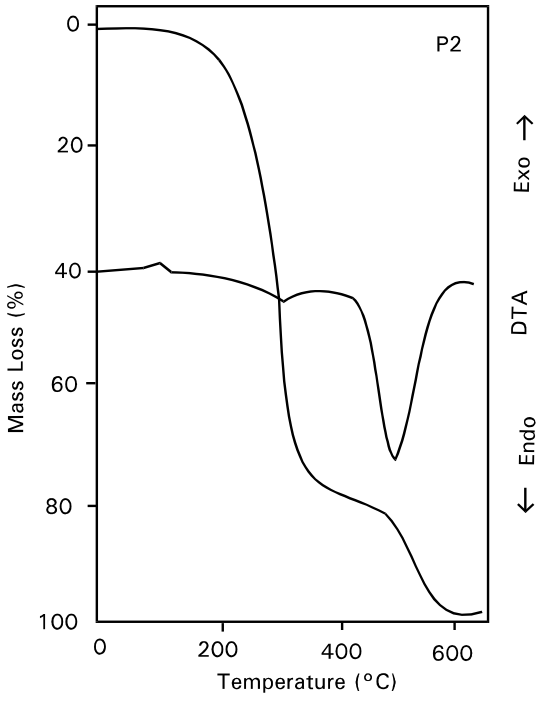

Fig. 2: TF-DTA curves of 2-amino-4 (p-methoxy) 6-diphenyl-3, 6-dihydropyrimidine in N_2

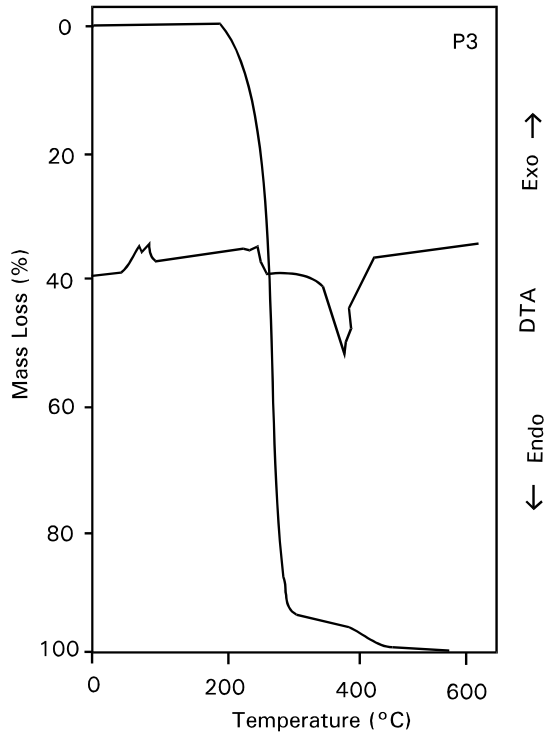

Fig. 3: TG-DTA curves of 2-oxo-4 (p-methoxy) 6-diphenyl-3, 6-dihydropyrimidine in N_2

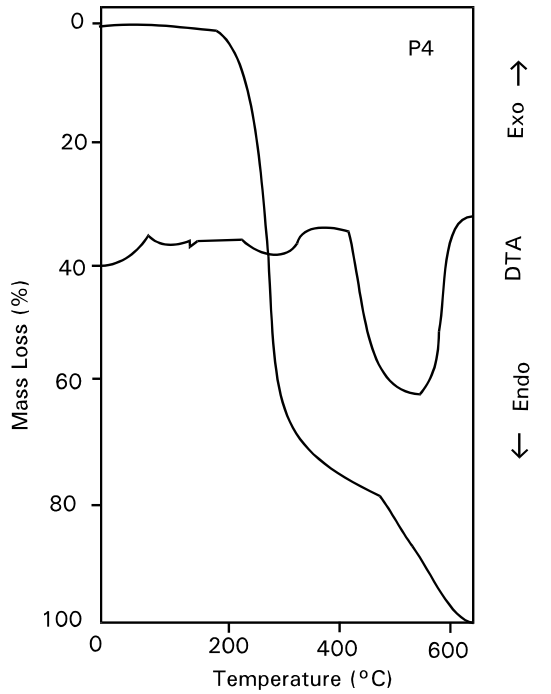

Fig. 4: TG-DTA curves of 2-oxo-4 (p-chloro) 6-diphenyl-3, 6-dihydropyrimidine in N_2

trace of P3 displays (Fig. 3) 100% mass loss in three steps. First major loss is observed between 190-338°C (95%), followed by another, quite a slow loss (1%) up to 454°C. Third mass loss is also a slow loss which occurs over the range 454-505°C. DTA curve shows a series of exothermic peaks at 82°C, 104°C and 330°C, and a large endothermic peak at 490°C.

2-oxo-4 (p-chloro) 6-diphenyl-3,6-dihydropyrimidine: The TG curve of P4 shows (Fig. 4) 99% mass loss in three steps. A major loss of 71% occurs in the first step over the temperature range 170-350°C, followed by second loss (6%), rather a slow loss up to 528°C. Third step shows 22% loss over the range 528-670°C. DTA curve records an exothermic peak at 108°C and three endothermic peaks at 360°C, 410°C (shoulder) and a large at 625°C.

From the thermal curves data, it is observed that the first mass loss is detectable between 142-190°C, for all the pyrimidines studied. The shape of the thermal curves is smooth and the curves are reproducible for triplicate TG-DTA runs. The decomposition peak maximum temperature (T_m) values observed are 650°C, 588°C, 490°C and 625°C. These values are the thermal stability indicators, and determine the stability order of 2-amino- and 2-oxo- pyrimidines as: P3 < P2 < P4 < P1.

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