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

S. W. Shah¹, Fuad A. Al-Darabi², A. U. Rahman² and S. I. Shah³

¹Center of Excellence in Analytical Chemistry, University of Sindh, Jamshoro-76080, Sindh, Pakistan
²M. A. Kazi Institute of Chemistry, University of Sindh, Jamshoro-76080, Sindh, Pakistan
³Medical Physics Section, Department of Physics, University of Sindh, Jamshoro-76080, Sindh, Pakistan

Abstract: Thermoanalytical behaviour of 2-amino- and 2-oxo- substituted pyrimidines studied in an inert atmosphere (N₂) 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 for a biologically and pharmaceutically important group of compounds (Youssef et al., 1989; Gaye-Saye & 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) (Tamankova & 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-Saye & Aaron, 1994), thin layer and liquid chromatography (Simek et al., 1994; Simanov, 1994; Guerrieri et al., 1994; Hiroshi et al., 1990; Tomankova & 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; Hanies, 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 α-cyclodextrin and pyrimidine derivatives by thermogravimetry and infrared spectroscopy. Surya et al. (1995), have studied some coordination compounds of 2-mercapto pyrimidines.

In the present paper, we report thermoanalytical behaviour of some 2-amino- and 2-oxo-pyrimidines in a dynamic N₂ 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-amine-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-propan-1-ones (2: 1 molar ratio) were mixed in dry ethanol. The mixture was made alkaline using KOH pellets, 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 solution 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 EC) 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 EC and a heating rate of 10
EC/ min. The `AlO powder was used as a reference material
for DTA. The samples were accurately weighed (10 ± 0.01
mg) in platinum cells using Mettler M-S microbalance.

Results and Discussion
Thermoanalytical Behaviour: The simultaneous TG-DTA curves
for 2-amino- and 2-oxo-substituted pyrimidines studied here
are shown in Figures 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 EC and is completed up to 388 EC. Second loss (11
%) occurs between 388-540 EC, followed by another 39.5 %
mass loss up to 660 EC. While on DTA curve, two
endothermic peaks appear at 362 EC and 650 EC. The peak
at 650 EC 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 EC and ends at
380 EC. Second loss (3.5 %) is rather slow, which occurs
between 380-548 EC, followed by third 17.5 % loss up to
628 EC, leaving behind 3 % carbonaceous residue. While the
DTA trace shows an exothermic peak at 128 EC, and two
endothermic peaks at 388 EC and 588 EC.

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

<table>
<thead>
<tr>
<th>Pyrimidine</th>
<th>Mass Loss (%)</th>
<th>T EC (T1,T2)</th>
<th>DTA Peak</th>
<th>T EC (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>49 5</td>
<td>160-388</td>
<td>-</td>
<td>362</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>388-540</td>
<td>-</td>
<td>650</td>
</tr>
<tr>
<td></td>
<td>39 5</td>
<td>540-660</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>76</td>
<td>142-380</td>
<td>+</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>380-548</td>
<td>-</td>
<td>388</td>
</tr>
<tr>
<td></td>
<td>17 5</td>
<td>548-628</td>
<td>-</td>
<td>588</td>
</tr>
<tr>
<td>P3</td>
<td>95</td>
<td>190-338</td>
<td>+</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>338-454</td>
<td>+</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>454-505</td>
<td>+</td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>530-570</td>
<td>-</td>
<td>490</td>
</tr>
<tr>
<td>P4</td>
<td>71</td>
<td>170-350</td>
<td>+</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>350-528</td>
<td>-</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>528-670</td>
<td>-</td>
<td>410</td>
</tr>
</tbody>
</table>

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 N2.
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trace of P3 displays (Fig. 3) 100 % mass loss in three steps. First major loss is observed between 190-338 EC (95 %), followed by another, quite a slow loss (1 %) up to 454 EC. Third mass loss is also a slow loss which occurs over the range 454-505 EC. DTA curve shows a series of exothermic peaks at 82 EC, 104 EC and 330 EC, and a large endothermic peak at 490 EC.

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 EC, followed by second loss (6 %), rather a slow loss up to 528 EC. Third step shows 22 % loss over the range 528-670 EC. DTA curve records an exothermic peak at 108 EC, and three endothermic peaks at 360 EC, 410 EC (shoulder) and a large at 625 EC. From the thermal curves data, it is observed that the first mass loss is detectable between 142-190 EC, 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 (Tm) values observed are 650 EC, 588 EC, 490 EC and 625 EC. These values are the thermal stability indicators, and determine the stability order of 2-amino- and 2-oxo-pyrimidines as: P3 < P2 < P4 < P1

References
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