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Thermal decomposition mechanism and kinetics of gemcitabine

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ABSTRACT

Gemcitabine (GTB) is a nucleoside drug used in chemotherapy for various carcinomas. In order to know why does GTB have good thermal stability, and to further understand the relationship between thermal stability and molecular structure. The thermal decomposition of GTB was measured with various thermal analytical techniques, the gaseous products and the residues of thermal decomposition were determined and identified. The molecular bond orders were calculated. The thermal decomposition mechanism of GTB was discussed. The thermal decomposition kinetics and the prospective lifetime of GTB were studied using the ATSM method. The results indicated that two strong electronegative fluorine atoms on furan ring make the strong charge-transfer (CT) structure to be formed, this strong CT structure remarkably enhance the N-glycosidic bond and the weakest bond, and lead to higher thermal stability and distinctive thermal decomposition mechanism. The thermal decomposition of GTB is a three-stage process. The initial step of decomposition is likely due to the loss of a furan ring. Most of GTB decompose and carbonizes directly to form insoluble substance and small molecules and just part of GTB decompose by way of cytosine stage. The initial decomposition temperature in either nitrogen or air is 235 °C. For decomposition in nitrogen, the apparent activation energy E_a and pre-exponential factor A for the initial thermal decomposition are 123.4 kJ mol^{-1} and 3.80×10^{10} min^{-1}, respectively. For decomposition in air, the corresponding E_a and A are 126.3 kJ mol^{-1} and 7.94×10^{10} min^{-1}, respectively. GTB has very good thermal stability under routine temperature and dry air atmosphere.

1. Introduction

Gemcitabine (GTB) with chemical name 2′,2′-Difluorodeoxycytidine is a nucleoside analogue used in chemotherapy. It is marketed as Gemzar by Eli Lilly and Company. GTB is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system [1] and is used in various carcinomas: non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer [2–6]. GTB is investigated for use in esophageal cancer, and is used experimentally in lymphomas and various other tumor types [7,8]. GTB is administered by the intravenous route, since it is extensively metabolized by the gastrointestinal tract [9].

GTB is easy to degrade in acidic aqueous solution. Some studies have confirmed that the hydrolysis products mainly are uridine analogue and has not observed the cleavage of the N-glycosidic bond [10,11] which connects the cytosine ring and furan ring. But the thermal stability of GTB in the solid state is remarkably better than other cytidine nucleoside drugs, such as emtricitabine, capecitabine, zalcitibine, and lamivudine. Why does GTB have such good thermal stability?

Thermoanalytical methods have been widely applied in the medicine field for several purposes including purity determination, compositional analysis, melting point testing, crystal formation and change tests, thermal stability of medicines, evaluation of the validity, thermal decomposition kinetics, identification of natural drugs, and process optimization for production of drugs [12–16].

The studies on the mechanism and kinetics of thermal degradation of GTB have important theoretical significance for knowing why does GTB have such good thermal stability, and further understanding the relationship between thermal stability and molecular structure, but little information has been published on the thermal decomposition of GTB. Now, the thermal decomposition processes for GTB in nitrogen and air atmospheres have been examined using thermogravimetric analysis (TG) and differential scanning calorimetry (DSC). The identity of volatile species that evolved during thermogravimetric decomposition was analyzed using coupled with infrared spectroscopy (TG–FTIR). Residues of thermal decomposition at different stages were examined using IR spectrometry, high-performance liquid chromatography (HPLC), and liquid chromatography mass-spectrometry (LC–MS). Molecular bond orders of GTB were calculated using an ab initio quantum chemistry program [17,18]. The reasons of thermal stability and thermal degradation mechanism of GTB were discussed and

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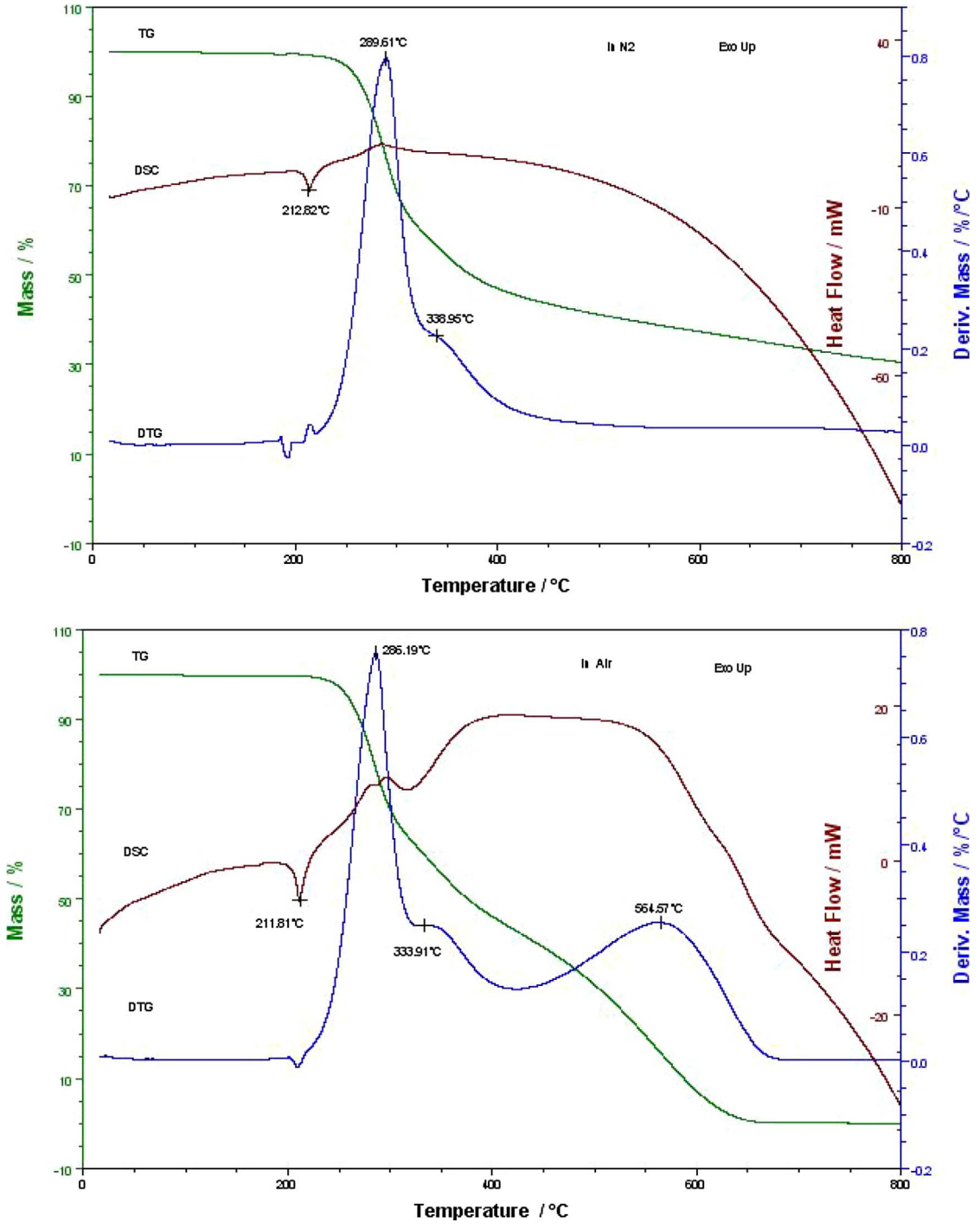

Fig. 1. The thermoanalytical curves of GTB obtained at $\beta = 10\ ^{\circ}\mathrm{C\,min^{-1}}$.

speculated based on the above results of analysis and calculation. The thermal decomposition kinetics of GTB was studied using the ASTM E1641 method [19–21]. The apparent activation energy E_a and pre-exponential factor A for thermal decomposition reactions were obtained from thermogravimetric data under different heating rates. The prospective lifetime of GTB at different temperatures was estimated to provide reference for the correct and reasonable use of this drug.

2. Experimental

2.1. Reagents

The GTB and cytosine were purchased from the Aladdin Chemistry Co. Ltd. (Shanghai, China). Their HPLC purities were 99.5% and were used without further purification. Acetonitrile (ACN) (HPLC purity