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Study on the molecular structure and thermal stability of purine nucleoside analogs

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ABSTRACT

The thermal decomposition processes of eight purine nucleoside analogs were measured with thermogravimetry (TG) and differential scanning calorimetry (DSC). The IR spectra and high-performance liquid chromatography (HPLC) of purine nucleoside analogs and their residues from thermal decomposition at various temperatures were determined. The molecular bond orders were calculated with an ab initio method from the GAMESS program. The mechanisms of thermal decomposition for purine nucleoside analogs were discussed. The results indicate that the main decomposition pathway of purine nucleoside analogs is the fracture of the *N*-glycosidic bond first, and the residues of the initial stage of decomposition are mainly corresponding purines. A part of purine nucleoside analogs decomposes directly to small molecules and insoluble substances at the first stage. When the *N*-glycosidic bond order is close to that of the weakest bond within purine ring, most of purine nucleoside analogs will decompose directly. The amino group at purine ring is easy to be oxidized, some oxidation products can be found in the residues of some purine nucleoside analogs. There is a positive correlation between the calculated weakest bond orders and the decomposition temperatures of purine nucleoside analogs. The stronger the weakest bond order, the higher the decomposition temperature. The molecular bond orders can serve as the basis to judge molecular thermal stability for analog compounds with similar molecular structure, size, and energy. The substituent group affects the thermal stability of the purine nucleoside analogs. Increasing the number of electron-donating groups on the purine ring and furanose ring will enhance the *N*-glycosidic bond, will increase the temperature of thermal decomposition, and be likely to change the mechanism of thermal decomposition.

1. Introduction

The natural nucleosides are the main compositions of nucleic acids, they include purine nucleosides and pyrimidine nucleosides, and they also can be divided into ribonucleosides and deoxyribonucleoside. Most of natural nucleosides have significant physiological functions and clinical significance. For example, hypoxanthine ribonucleoside (inosine) can be used in the treatment of acute and chronic hepatitis, rheumatic heart disease, oligoleukocythemia, thrombocytopenia, and in the adjunctive therapy of central retinitis and optic atrophy [1]. It has been proposed for spinal cord injury [2]. Uridine can be used in the treatment of giant red blood cell anemia, liver, cerebrovascular and cardiovascular diseases [3]. Adenosine can be used in the treatment of paroxysmal supraventricular tachycardias [4] and acute myocardial infarction [5].

In recent years, the researches on the synthetic nucleoside compounds as antiviral and antineoplastic drugs have been paid more and more attention [6–11]. Nearly 50% of the antiviral drugs are nucleoside compounds [7]. There are 15% of antitumor drugs are antimetabolite, most of them are nucleoside analogs [11]. Including: zidovudine (AZT) [12], stavudine (d4T) [13] and didanosine [14] for AIDS treatment, lamivudine (3TC) [15] and telbivudine (LdT) [16] for hepatitis B treatment, brivudine (BVDU) [17] for herpes zoster treatment, cladribine [18] and clofarabine [19] for anticancer treatment, nelarabine [20] for T-cell acute lymphoblastic leukemia treatment, 2-chloroadenosine [21] for prostate cancer treatment, and so on.

In our previous studies [22–26], we have found that there is some regularity in the thermal decomposition mechanisms of pyrimidine nucleoside analogs. The decomposition processes of some analogs are that the *N*-glycosidic bond ruptures first, and the residue of the decomposition is mainly corresponding pyrimidine. While, others are that the rupture of the *N*-glycosidic bond and the decomposition of pyrimidine ring synchronize,

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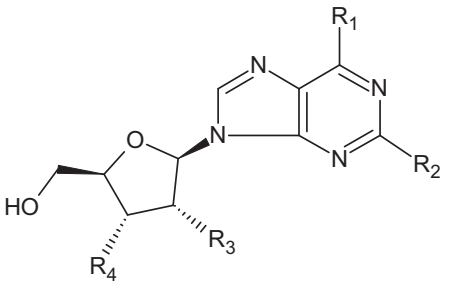

Inosine: R_1 = -OH, R_2 = -H, R_3 = R_4= -OH
2'-Deoxyinosine: R_1 = -OH, R_2 = R_3= -H, R_4= -OH
Guanosine: R_1 = -OH, R_2 = NH_2, R_3 = R_4= -OH
2'-Deoxyguanosine: R_1 = -OH, R_2 = NH_2, R_3 = H, R_4 = -OH
Adenosine: R_1 = -NH_2, R_2 = -H, R_3 = R_4= -OH
2-Deoxyadenosine: R_1 = -NH_2, R_2 = -H, R_3 =H, R_4= -OH
2-Aminoadenosine: R_1 = -NH_2, R_2 = -NH_2, R_3 = R_4= -OH
2-Chloroadenosine: R_1 = -NH_2, R_2 = -Cl, R_3 = R_4 = -OH

Scheme 1. Molecular structures of purine nucleoside analogs.

and the residue of the decomposition contain small amount of corresponding pyrimidine. The molecular structure and the groups on pyrimidine ring and furanose ring impact the distribution of charges and molecular bond orders, and lead to different thermal decomposition mechanism.

In this article, the thermal decomposition processes of eight purine nucleoside analogs under nitrogen atmosphere were studied with thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The IR spectra and high-performance liquid chromatography (HPLC) of purine nucleoside analogs and residues of thermal decomposition at different stages were measured. The molecular bond orders of purine nucleoside analogs were calculated with ab initio methods of quantum chemistry (GAMESS package) [27–29]. Thermal decomposition mechanisms of purine nucleoside analogs were discussed. Thermal stability of purine nucleoside analogs were studied comparatively. The relationship between molecular structure and thermal properties of purine nucleoside analogs was explored.

There are three types of natural purines: hypoxanthine, guanine and adenine. In this article, we reported eight purine nucleoside analogs based on these three purines. These purine nucleoside analogs are all composed of two molecular fragments—a purine ring and a furanose ring. Two rings are connected with an *N*-glycosidic bond. The molecular structures of the purine nucleoside analogs are shown in Scheme 1.

2. Experimental

2.1. Reagents

All chemicals and reagents were purchased from market. Adenine (≥99.5%), adenosine (≥99.5%), 2′-deoxyadnosine (≥99%), hypoxanthine (99%), inosine (99%), guanine (99%), guanosine hydrate (99%), 2-chloroadenosine (99%), and 2′-deoxyinosine (≥98%) were purchased from Aladdin Chemistry Co., Ltd. (Shanghai, China). 2-aminoadenine (98%), and 2-chloroadenine (>98%) were purchased from Tokyo Chemical Industry Co., Ltd. (Japan). 2-aminoadenosine (98%) was purchased from J&K scientific Ltd. (Beijing, China). 2′-deoxyguanosine (≥99%) was purchased from Shanghai Jinsui Bio-Technology Co., Ltd. All chemicals were used without further purification. HPLC grade acetonitrile (ACN) and ultrapure water were used.

2.2. Measurements and calculations

The TG, DTG and DSC curves and the corresponding data of samples were obtained with an SDT-Q600 simultaneous thermal analyzer (TA Instruments Inc., USA) using an alumina ceramic crucible containing 10 mg of sample under nitrogen atmosphere (100 mL min^{-1}). The heating rate was 10.0 °C min^{-1} from ambient to 800 °C.

The residues of thermal decomposition were prepared in a SDT-Q600 simultaneous thermal analyzer using an alumina ceramic crucible containing sample under nitrogen atmosphere at a flow rate of 100 mL min^{-1} and heating rate of 10.0 °C min^{-1} from room temperature to the selected temperature. Endpoints included: beginning of weight loss, DTG peak, and bottom of the weight loss steps, etc.

The IR absorption spectra of samples and residues of thermal decomposition were carried out with a Nicolet iS 10 FT-IR spectrophotometer (Thermo Fisher Scientific Inc., USA) at room temperature. The spectra were collected by accumulating 32 scans and at a resolution of 4 cm^{-1} from 4000 to 400 cm^{-1} using a KBr pellet technique.

Separation studies were performed with an HPLC system from Hitachi High-Technologies Corporation of Japan. The instrument consisted of an LC 2130 quaternary gradient pump with a LC 2140 UV–vis detector. The data were acquired and processed using HS 2000 chromatography workstation (Hangzhou Science & Techn. Co., China). Reversed phase C-18 columns (200 mm × 4.6 mm i.d. size) containing 5 μm stationery phase were purchased from Dalian Elite Analytical Instruments Co., Ltd. The mobile phase was filtered through a 0.45 μm membrane and degassed before use via ultrasonication. The flow rate was kept constant at 1 mL min^{-1}. The 5.0 mg of samples (the standard samples or residues of thermal decomposition) were dissolved in 10 mL of mobile phase. A small amount of HAc dilute solution was used to help dissolution. The sample solution was filtered through a 0.45 μm membrane before injection. The injection volume was 5 μL and detection wavelength was 254 nm.

The mobile phase consisted of 50 mmol L^{-1} ammonium acetate solution as eluent A and ACN as eluent B. The mobile phase for separation of the inosine nucleoside analogs residues was 99% A and 1% B. The mobile phase for separation of guanosine nucleoside analogs residues was 94% A and 6% B. The mobile phase gradient for separation of adenosine nucleoside analogs residues was 0–7 min, 98% A and 2% B; 7–16 min, 85% A and 15% B. The mobile phase for separation of the residue of 2-aminoadenosine was 0–6 min, 95% A and 5% B; 6–15 min, 91% A and 9% B. The mobile phase for separation of the residues of 2-chloroadenosine were 90% A and 10% B.

The molecular structures of purines and purine nucleoside analogs were drawn and optimized with ChemDraw software attached to ChemOffice (Version: Ultra 11.0.1, Cambridgesoft, 2007). The GAMESS program is a general ab initio quantum chemistry package attached to ChemDraw and was used to calculate molecular energy, charge distribution and bond order. Program parameters include Job Type: Minimize [energy/geometry]; Method: HF; Basis Set: 3–21 G; Wave Function: R-Closed-Shell; Polarization: None; Diffuse: None; Exponent: POPLE; Opt. Algorithm: QA; Move Which: All Atoms. The program default values were adopted for the computational accuracy and convergence threshold; all calculations were completed on a personal computer.

3. Results and discussion

3.1. Thermal decomposition processes of purine nucleoside analogs

Fig. 1 presents the thermal decomposition curves of five purines and eight purine nucleoside analogs under nitrogen atmosphere.