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Short communication

Thermal analysis of *N*-carbamoyl benzotriazole derivatives

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Thermal properties of *N*-carbamoyl benzotriazole derivatives and *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid were investigated using thermogravimetric analysis and differential scanning calorimetry. The results revealed a difference between structural analogs of *N*-carbamoyl benzotriazole derivatives. They seem to be in agreement with the previously proposed formation of *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid from 1-(*N*-benzyloxycarbamoyl) benzotriazole, *via* an intermediary *N*-benzyloxyisocyanate acid, during heating. Substantially different thermal properties were observed for structural analogues, 1-(*N*-methoxycarbamoyl) benzotriazole and 1-(*N*-ethoxycarbamoyl) benzotriazole. In contrast to *N*-benzyloxyisocyanate, no corresponding reactions were observed for their decomposition products, *i.e.*, methoxyisocyanate and ethoxyisocyanate.

Keywords: *N*-carbamoyl benzotriazole, *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid, thermogravimetric analysis, differential scanning calorimetry, ATR-FTIR

Hydroxyurea and its derivatives show versatile biological activities. Today, they are employed in the treatment of various neoplastic and non-neoplastic diseases such as various types of cancer (1, 2), sickle cell anemia (3), HIV infection (4, 5), thrombocythemia (6) and psoriasis (7). *N*-substituted benzotriazoles are well known as useful synthons in the synthesis of carbamates, ureas, semicarbazides and carbazides (8, 9). Recent reports on 1-(*N*-benzyloxycarbamoyl) benzotriazole revealed its crystal structure (10) and usage in the synthesis of hydroxyurea derivatives (11, 12). Butula and Jadrijević-Mladar Takač (11) reported the preparation of *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid from 1-(*N*-benzyloxycarbamoyl) benzotriazole after its thermal decomposition in the presence of a catalytic amount of imidazole, *via* *N*-benzyloxyisocyanate as an intermediary product. In the current paper, we explore thermal decomposition of 1-*(N*-benzyloxycarbamoyl*)* benzotriazole, its structural analogues 1-(*N*-methoxycarbamoyl) benzotriazole and 1-(*N*-ethoxycarbamoyl) benzotriazole, as well as thermal properties of *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid

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† Dedicated to the memory of our dear friend and colleague, Prof. Ivan Kos.

(all structures are given in Fig. 1). These compounds were recently proven to be cytotoxic agents against monocytic THP-1 cell lines, whereas *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid exerted antimicrobial activity against *E. coli* strains (12).

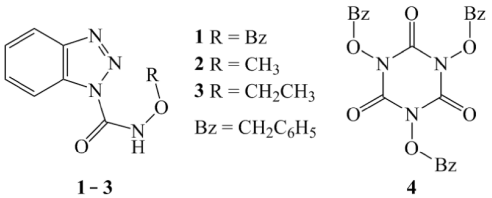


Fig. 1. Structures of 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**), 1-(*N*-methoxycarbamoyl) benzotriazole (**2**), 1-(*N*-ethoxycarbamoyl) benzotriazole (**3**) and *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid (**4**).

EXPERIMENTAL

1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**), 1-(*N*-methoxycarbamoyl) benzotriazole (**2**), 1-(*N*-ethoxycarbamoyl) benzotriazole (**3**) and *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid (**4**) were synthesized according to previously published procedures (11, 12).

Methods

Thermogravimetric analysis (TGA). – Thermogravimetric (TG) experiments were carried out using a Perkin Elmer (USA) Pyris 1 TGA thermogravimetric analyzer. Analysis was performed in an open aluminum pan with samples weighing approximately 5 mg. All samples were measured at 30 to 500 °C at the heating rate of 10 °C min^{-1} under a continuous nitrogen flow at a rate of 30 mL min^{-1}.

Attenuated total reflectance infrared spectroscopy (ATR-IR). – The samples were additionally analyzed using spectroscopy using a Perkin Elmer (USA) Spectrum 100 FT-IR spectrometer. For each sample, 4 scans at a resolution of 4 cm^{-1} were recorded between 4000 cm^{-1} and 450 cm^{-1}.

Differential scanning calorimetry (DSC). – DSC thermograms of solid products were recorded on a Perkin Elmer (USA) DSC 7 differential scanning calorimeter. The instrument was calibrated with indium and zinc prior to the analysis of samples under dry nitrogen purge at a flow rate of 35 mL min^{-1}. All samples (≈ 5 mg) were accurately weighed on a Mettler Toledo (Switzerland) MB microbalance, placed in a sealed aluminum pan with a pierced lid and scanned at a heating rate of 10 °C min^{-1} over the temperature range of 20 to 500 °C. An empty sealed aluminum pan with a pierced lid was used as a reference.

RESULTS AND DISCUSSION

Thermogravimetric analysis

Compound **1** evaporated in two steps, the first step taking place between 166 and 265 °C with the maximum rate at 232 °C (66 % loss of mass), and the second step between

265 and 328 °C with the maximum rate at 305 °C (98.4 % loss of mass), remaining further stable up to 500 °C. Compound **2** evaporated between 96 and 193 °C with the maximum rate at 180 °C, while compound **3** evaporated between 99 and 209 °C with the maximum rate at 200 °C. Isocyanuric acid derivative (**4**) lost 98 % of mass in a single step from 247 to 343 °C with the maximum rate at 288 °C and the remaining 2 % was stable up to 500 °C. TGA measurements for all compounds are given in Fig. 2. Section A in Fig. 2 denotes the temperature region corresponding to the second evaporation step of compound **1** and evaporation of compound **4**, indicating transition from **1** to **4** during the heating process.

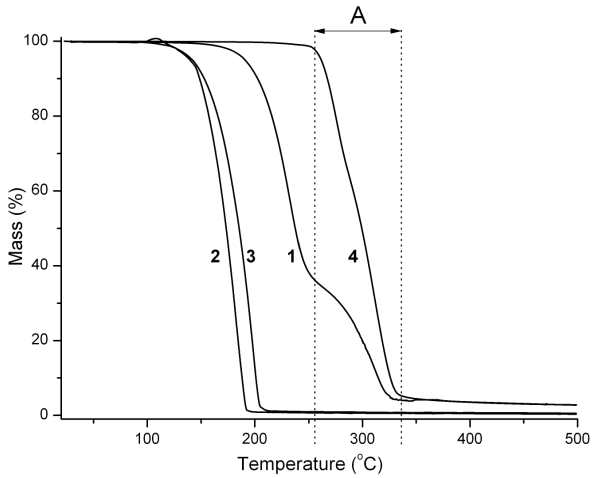


Fig. 2. TGA of 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**), 1-(*N*-methoxycarbamoyl) benzotriazole (**2**), 1-(*N*-ethoxycarbamoyl) benzotriazole (**3**) and *N*,*N*′,*N*′′-tribenzyloxyisocynauric acid (**4**).

TGA revealed a difference between structural analogs of *N*-carbamoyl benzotriazole derivatives. Compounds **2**, **3** and **4** evaporated in a single step, while compound **1** evaporated in two steps. The second step of evaporation of compound **1** was found with almost the same interval as the interval of evaporation of compound **4**, thus confirming a possible cyclization reaction taking place during the heating process, as suggested by Butula and Jadrijević-Mladar Takač (11). They reported the formation of compound **4** when compound **1** was heated at 120–130 °C in the presence of a catalytic amount of imidazole, and noted an exothermic reaction accompanied by an increase of reaction mixture temperature up to 150 °C.

Differential scanning calorimetry

Compound **1** showed a sharp endothermic peak at 122 °C (region 1a in Fig. 3a, dH = 108 J g^{-1}), and another exothermic process between 168 and 250 °C, characterized by a broad peak with the maximum at 235 °C (region 1b in Fig. 3a, dH = –233 J g^{-1}). Additional fluctuations in heat flow were observed from 250 to 330 °C (region 1c in Fig. 3a). Compound **4**, a suggested cyclization product of **1**, showed a sharp endothermic peak at 249 °C (region

4a in Fig. 3a, dH = 114 J g^{-1}), and a two-step exothermic process between 255 and 350 °C, with a peak maximum at 298 °C (regions 4b and 4c in Fig. 3a, dH = –889 J g^{-1}).

Compound **2** showed a sharp endothermic peak at 145 °C (region 2a in Fig. 3b, dH = 159 J g^{-1}), followed by a two-step endothermic process between 149 and 257 °C (regions 2b and 2c in Fig. 3b, dH = 355 J g^{-1}). Similar behavior was exerted by compound **3**, with a sharp endothermic peak at 119 °C (region 3a in Fig. 3b, dH = 121 J g^{-1}), and an endothermic process between 129 and 247 °C (regions 3b and 3c in Fig. 3b, dH = 275 J g^{-1}).

DSC analysis of compound **1** showed a broad exothermic peak between 168 and 250 °C, which is in excellent agreement with the first step of its thermal decomposition (region A

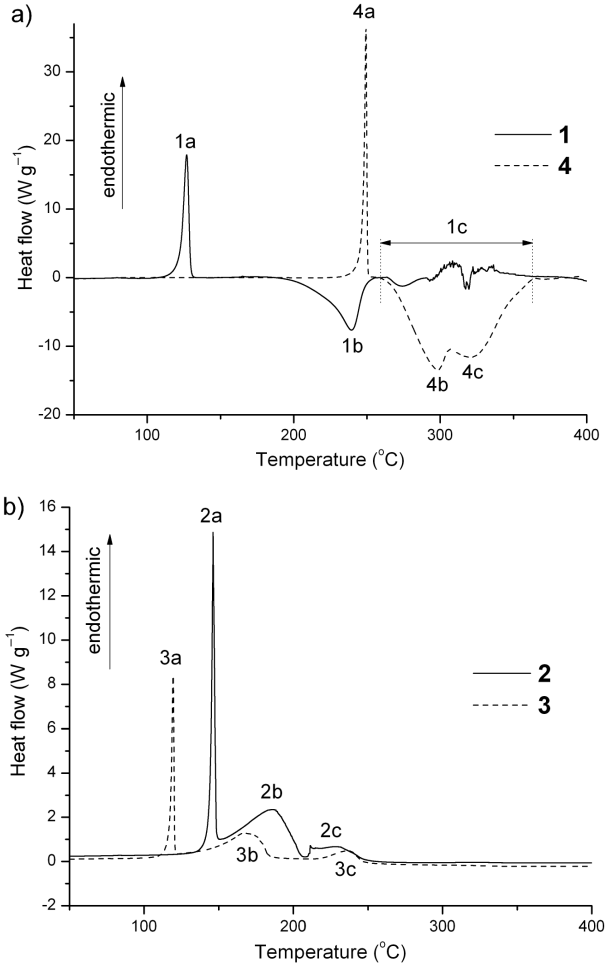


Fig. 3. DSC thermograms of: a) 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**) and *N*,*N*′,*N*′′-tribenziloxyisocyanuric acid (**4**); b) 1-(*N*-methoxycarbamoyl) benzotriazole (**2**) and 1-(*N*-ethoxycarbamoyl) benzotriazole (**3**).

in Fig. 4). Benzotriazole (BtH), a side-product of this decomposition, evaporated between 127 and 194 °C, followed by exothermal decomposition between 306 and 410 °C (13). This region corresponds roughly to the region of endothermic decomposition of compound **4** (255 to 350 °C, regions 4b and 4c, Fig. 3a), which may at least in part account for the complex features of DSC thermograms of compound **1** in this range (region B in Fig. 4). TGA curve of compound **4** corresponds to this range of temperatures as well (region A in Fig. 2).

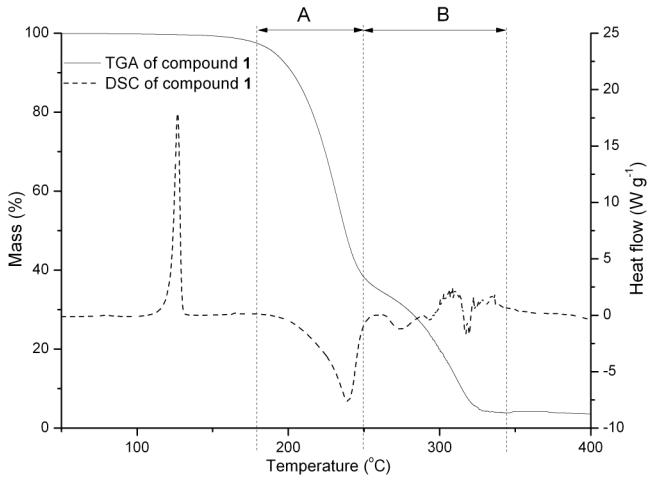


Fig. 4. TGA and DSC profiles of 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**).

When comparing the TGA or DSC data of compounds **2** and **3**, similar endothermic decomposition processes can be observed (regions 2b and 2c, and 3b and 3c in Fig. 3b). Further fate of the products, *i.e.* methoxyisocyanate and ethoxyisocyanate, is quite different from that of benzyloxyisocyanate, a decomposition product of compound **1**. Probably, it readily trimerizes to form compound **4** *via* an intermediary, *N*-benzyloxyisocyanate (11), according to the scheme given in Fig. 5.

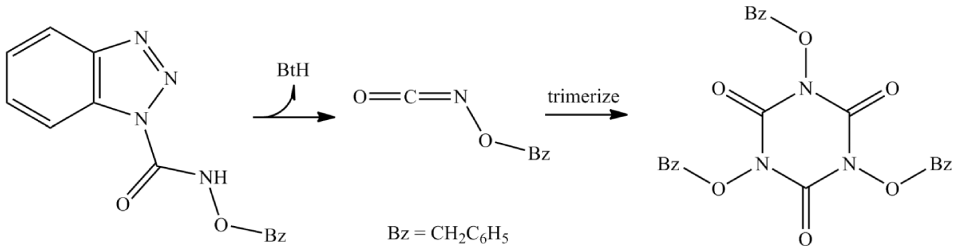


Fig. 5. The proposed scheme for the decomposition of 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**).

IR spectra

To support the proposed reaction scheme explaining the processes taking place during the DSC measurements of compound **1**, we measured the IR spectrum of the intermediate obtained by heating compound **1** to 250 °C. The obtained spectrum corresponds remarkably well to the spectrum of compound **4** obtained at 290 °C (Fig. 6), thus confirming the proposed formation of *N*,*N*′,*N*′′-tribenzyloxyisocynauric acid during heating of 1-(*N*-benzyloxycarbamoyl) benzotriazole. Additional confirmation is the presence of peaks at 1740, 1402, 1197, 1001 and 905 cm^{-1}, characteristic for *N*,*N*′,*N*′′-tribenzyloxyisocynauric acid (11, 12).

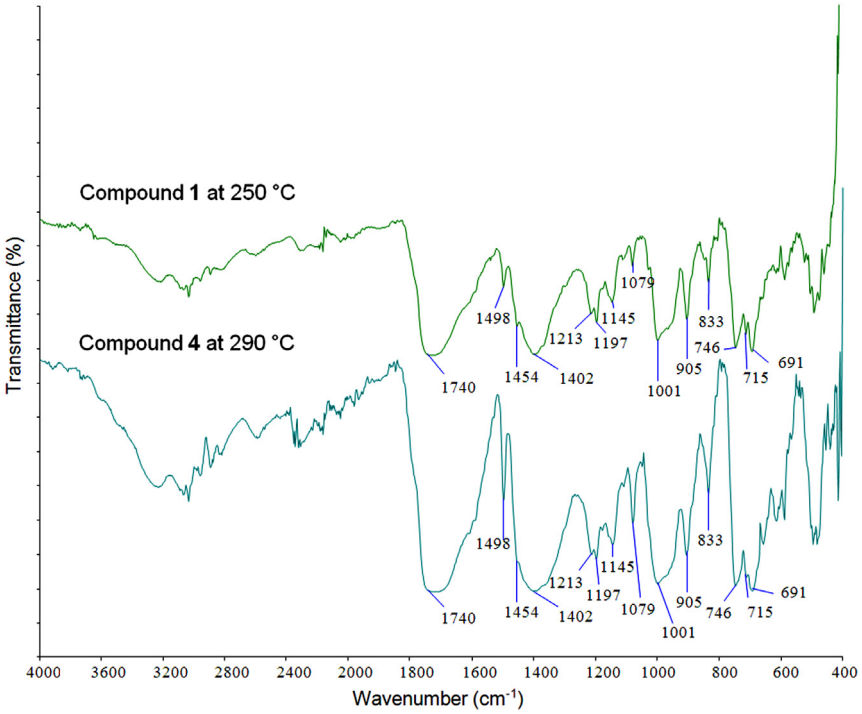


Fig. 6. IR spectra of the intermediate obtained by heating 1-(*N*-benzyloxycarbamoyl) benzotriazole (**1**) to 250 °C (top) and by heating *N*,*N*′,*N*′′-tribenzyloxyisocyanuric acid (**4**) to 290 °C (bottom).

CONCLUSIONS

All four compounds melted endothermically, with peaks at 122, 145, 119 and 249 °C for compounds **1**, **2**, **3**, and **4**, respectively. These findings are in good agreement with the previously reported melting points (15, 18). Melting is not accompanied by decomposition, as confirmed by TGA data. In adition, the results of TGA and DSC analyses seem to be in agreement with the previously proposed formation of *N*,*N*′,*N*′′-tribenzyloxyisocynauric

acid during the heating process of 1-(*N*-benzyloxycarbamoyl) benzotriazole. In contrast to *N*-benzyloxyisocyanate, no corresponding reactions were observed for methoxyisocyanate and ethoxyisocyanate, *i.e.*, the decomposition products of the structural analogues 1-(*N*-methoxycarbamoyl) benzotriazole and 1-(*N*-ethoxycarbamoyl) benzotriazole. Findings described in this work could be useful in the preparation of new and modification of the existing compounds, particularly in the light of the recently confirmed biological effects of these compounds (11, 12).

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