

# Thermal and Structural Properties of Theophylline-7-acetic Acid

**Ferdinando Giordano**<sup>a</sup>, **Anastasia Foppoli**<sup>b</sup>, **Andrea Gazzaniga**<sup>b</sup>, **Mino R. Caira**<sup>c</sup>, **Sibulelo Vilakazi**<sup>c</sup>

<sup>a</sup> Dipartimento Farmaceutico, Università di Parma, Italia

<sup>b</sup> Istituto Chimico Farmaceutico, Università di Milano, Italia

<sup>c</sup> Department of Chemistry, University of Cape Town, South Africa

Theophylline-7-acetic acid (1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-acetic acid, TAA) is a derivative of theophylline, a xanthine extensively used for its diuretic, cardiac stimulant and smooth muscle relaxant pharmacological effects. With respect to the parent compound, TAA has a similar but more specific bronchodilator activity<sup>1</sup>.

The present work aims to give a comprehensive picture of the solid-state properties of TAA. Polymorphism and pseudopolymorphism of TAA were investigated by the usual analytical techniques such as thermal analysis (DSC, TGA, HSM), FTIR spectroscopy and X-ray diffractometry, both on powder and on single crystals to afford structural data.

An unsolvated crystal form and a monohydrate of TAA were recovered from recrystallisation trials. Anhydrate TAA [ $T_{\text{onset}} = 270.4(0.1) \text{ }^\circ\text{C}$ ,  $\Delta H_f = 198.1(5) \text{ J/g}$ , 10 scans] was isolated by crystallization from alcohols, acetone and methylene chloride, while the monohydrate separated from water and ethanol/water mixtures. TAA monohydrate transforms on heating into anhydrate TAA (Figures 1 and 2).

Suitable crystals of TAA for structural determination were grown from methanol solutions. Transparent, square to rectangular prisms [monoclinic, space group  $P2_1/n$ ,  $a = 9.5095(3) \text{ \AA}$ ,  $b = 7.1670(2) \text{ \AA}$ ,  $c = 14.4819(5) \text{ \AA}$ ,  $\beta = 98.569(1)^\circ$ ] developed after two days. The X-ray analysis (Figures 3 and 4) revealed a layered structure with interlayer  $\pi$ - $\pi$  interactions and unidirectional hydrogen bonding of the type  $\text{O-H}\cdots\text{N}$  between the TAA molecules within the layers.

Unfortunately, the recrystallization trials of  $\text{TAA}\cdot\text{H}_2\text{O}$  always led to fibrous crystals, thus precluding the X-ray structure determination of this species.

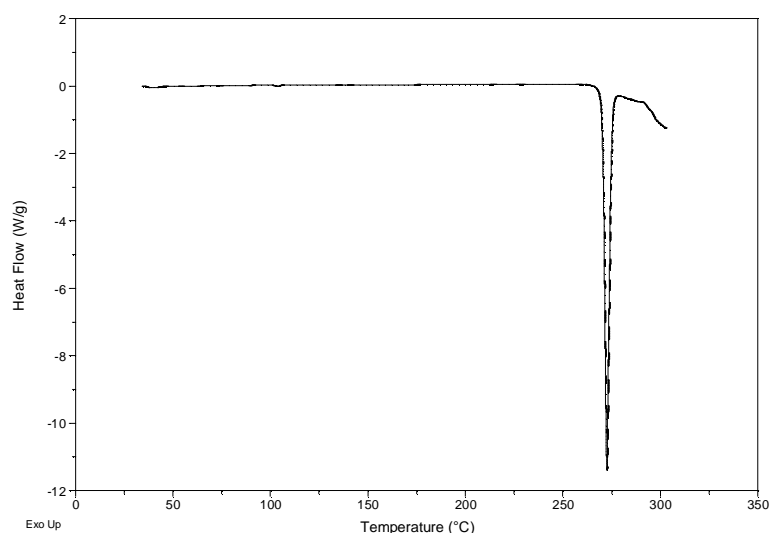


Fig. 1: DSC trace of TAA

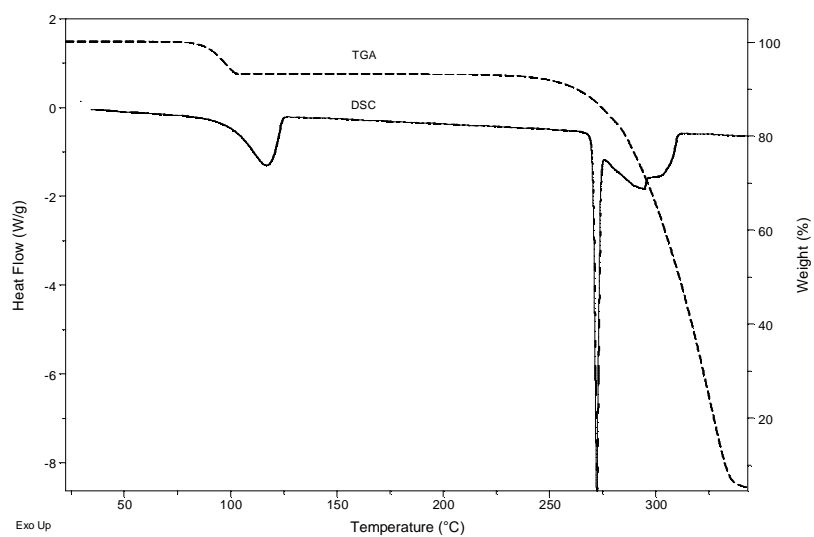


Fig. 2: DSC/TGA traces of TAA·H<sub>2</sub>O

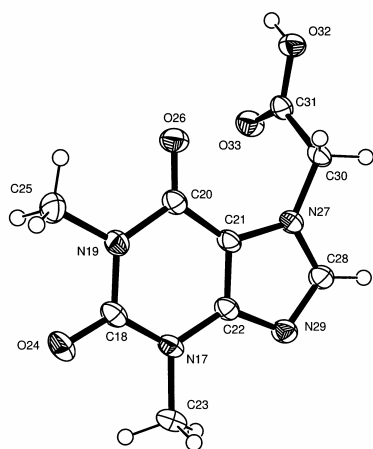


Fig. 3: ORTEP diagram of TAA with numbering scheme.

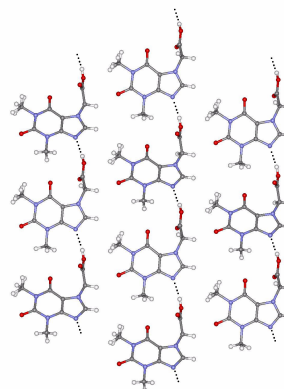


Fig. 4: POV-Ray diagram of TAA

## References

- 1 Ferretti, C.; Coppi, G.; Blengio, M.; Genazzani, E., Inhibitory effect of theophylline, theophylline-7-acetic acid, ambroxol and ambroxol-theophylline-7-acetate on rat lung cAMP phosphodiesterase isoenzymes, *Int. J. Tissue Reactions*, 1992, 14(1), 31-6.