Journal of Molecular Structure 1075 (2014) 178–186

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

# Supramolecular self assemblies in polymorphs/solvates of aminopyrimidine and amino-s-triazines derivatives

Gomathi Sundaramoorthy, Jeyaraman Selvaraj Nirmalram, Samuel Ebenezer, Packianathan Thomas Muthiah *

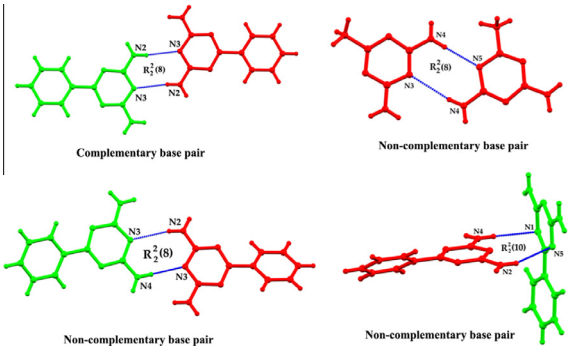
*School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, India*

## HIGHLIGHTS

- Polymorph of 2-amino-4,6-dimethoxypyrimidine and 2,4-diamino-6-phenyl-1,3,5-triazine.
- Solvates of 2,4-diamino-6-R-1,3,5-triazine, R is methyl/phenyl.
- Analysis of supramolecular patterns and frequency of occurrence of polymorphs.
- Complementary and non-complementary N–H···N base pair motifs - $R_2^2(8)$ and $R_2^2(10)$.

## GRAPHICAL ABSTRACT

The complementary $R_2^2(8)$ and non-complementary $R_2^2(10)$ base pairing motifs present in the new polymorphic forms of 2-amino-4,6-dimethoxypyrimidine [ADMP], 2,4-diamino-6-methyl-1,3,5-triazine [DAMT] and 2,4-diamino-6-phenyl-1,3,5-triazine [DAPT].




## ARTICLE INFO

*Article history:*
Received 29 May 2014
Received in revised form 19 June 2014
Accepted 20 June 2014
Available online 26 June 2014

*Keywords:*
Polymorph
Solvate
Non-covalent interaction
Complementary and non-complementary base pairing motifs

## ABSTRACT

Polymorphs of 2-amino-4,6-dimethoxypyrimidine [ADMP (1)], 2,4-diamino-6-methyl-1,3,5-triazine [DAMT (**2**)], 2,4-diamino-6-phenyl-1,3,5-triazine [DAPT (**3**)] and a solvate of DAPT with DMF solvent, [DAPT·DMF (**4**)] were obtained either during a systematic screening using various solvents or by serendipity. These polymorphs and solvates were then characterized using single crystal X-ray diffraction technique and their structural and supramolecular aspects are analyzed. The supramolecular architecture of compounds (**1**–**4**) are predominantly hydrogen bonded *via* N–H···N base pairs. These base pairs are formed either between crystallographically independent molecules in the lattice or between symmetry related molecules. The molecular self assembly process involved in **2**, **3** and **4**, facilitates the formation of some base pair motifs with graph-set of $R_2^2(8)$ and a rare non-complementary base pair motif with graph-set $R_2^2(10)$. The other interesting supramolecular patterns and non-covalent interactions which lead to the formation of new forms are discussed in detail.



## Introduction

The term polymorphism [1–3] among pharmaceuticals is a common phenomenon. Each polymorphic form of a drug molecule exhibits different physio chemical properties and biological performances. A widespread interest in understanding the polymorphic

* Corresponding author. Tel.: +91 0431 2407053.
*E-mail address:* tommtrichy@yahoo.co.in (P.T. Muthiah).

http://dx.doi.org/10.1016/j.molstruc.2014.06.063
0022-2860/

behavior of pharmaceutical drugs grew after performance failures of several marketed drugs [4–7]. The occurrence of undesired forms (in terms of performance), during manufacturing and storage has made polymorph screening a mandatory exercise for drug developing companies.

Several techniques are adopted for the preparation of polymorphs. Among them, sublimation, crystallization from supercritical fluids, crystallization from single solvent, crystallization from the melt, evaporation from a binary mixture of solvents, vapor diffusion, thermal treatment, thermal desolvation of crystalline solvates, growth in the presence of additives, grinding and rapid alteration of pH are the commonest methods [8–11].

Though many efforts have gone into the prediction of new forms through experimental and theoretical approaches [12,13], there seems to be no definite procedure to obtain a new polymorph. This fact supports the statement made by McCrone that "every compound has different polymorphic form and that, the number of forms known for a given compound is proportional to the time and energy spent in research on that compound" [14]. Of the polymorphs available in the literature some of them are reported to have been obtained by serendipity rather than through a systematic study [15–24]. Recording such serendipitous occurrences and analyzing their experimental and mechanistic pathways is also of immense interest for they pave way for designing new strategies for polymorph preparation.

Aminopyrimidine and aminotriazine derivatives are quite well known for their antimalarial, antimicrobial, anti-tumor, anticancer and other biological activities [25–27]. Our group has worked extensively on the crystal engineering aspects of multicomponent salts/co crystals of some aminopyrimidines and aminotriazines derivatives [28–39]. During our search for some new multicomponent forms, we obtained polymorphic forms of 2-amino-4,6-dimethoxypyrimidine [ADMP (**1**)] and 2,4-diamino-6-phenyl-1,3,5-triazine [DAPT (**3**)] by serendipity. Since many biologically important solids are known to exist in different polymorphic forms, it intrigued us and we hunted for some possible polymorphic and solvate forms of ADMP, DAPT and 2,4-diamino-6-methyl-1,3,5-triazine [DAMT] (Scheme 1) using various polar and nonpolar solvents. Our search gave us a new unsolvated form of [DAMT (**2**)] and dimethyl formamide solvate of DAPT [DAPT·DMF (**4**)]. It is well known that polymorphic occurrences among pharmaceuticals are common phenomena and they are mostly influenced by contributions made by non-covalent interactions, molecular recognition process and packing modes [40–42]. Therefore studying their behavior in the crystalline state is of immense interest to design solids for specific needs [43,44]. In this paper we discuss the molecular geometries and supramolecular architectures assumed by new forms of (**1**–**4**) and compare them with the previously existing forms.

## Experimental section

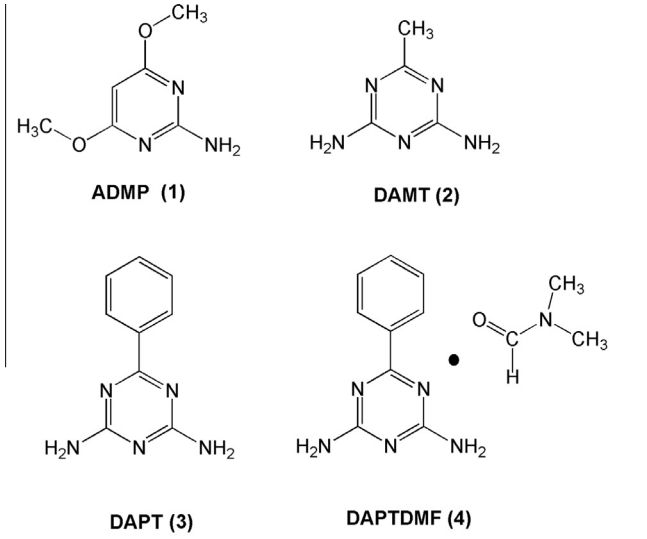
*Synthesis of polymorphs **1**–**4***

*2-Amino-4,6-dimethoxypyrimidine [ADMP (**1**)]*

ADMP (39 mg) and malonic acid (26 mg) were separately dissolved in 20 ml of methanol and then equimolar ratios of them were added together, warmed to 50 °C over the water bath for 20 min and kept for slow evaporation. Colorless prismatic crystals were obtained after 3 days.

*2,4-Diamino-6-methyl-1,3,5-triazine [DAMT (**2**)]*

DAMT (31 mg) was dissolved in 20 ml of nitromethane, warmed to 85 °C over the water bath for 20 min and kept for slow evaporation. Colorless prismatic crystals were obtained after 5 days.




**ADMP** = 2-amino-4,6-dimethoxypyrimidine

**DAMT** = 2,4-diamino-6-methyl-1,3,5-triazine

**DAPT** = 2,4-diamino-6-phenyl-1,3,5-triazine

**DAPTDMF** = 2,4-diamino-6-phenyl-1,3,5-triazine dimethyl formamide

**Scheme 1.** Molecular components of Polymorphs (**1**–**4**).

*2,4-Diamino-6-phenyl-1,3,5-triazine [DAPT (**3**)]*

DAPT (47 mg) and anthranilic acid (34 mg) were separately dissolved in 20 ml of methanol and then equimolar ratios of them were added together, warmed to 50 °C over the water bath for 20 min and kept for slow evaporation. Colorless prismatic crystals were obtained after 4 days.

*2,4-Diamino-6-phenyl-1,3,5-triazine dimethyl formamide [DAPT·DMF (**4**)]*

DAPT (47 mg) was dissolved in 20 ml of dimethyl formamide, warmed to 90 °C over the water bath for 20 min and kept for slow evaporation. Colorless prismatic crystals were obtained after 9 days.

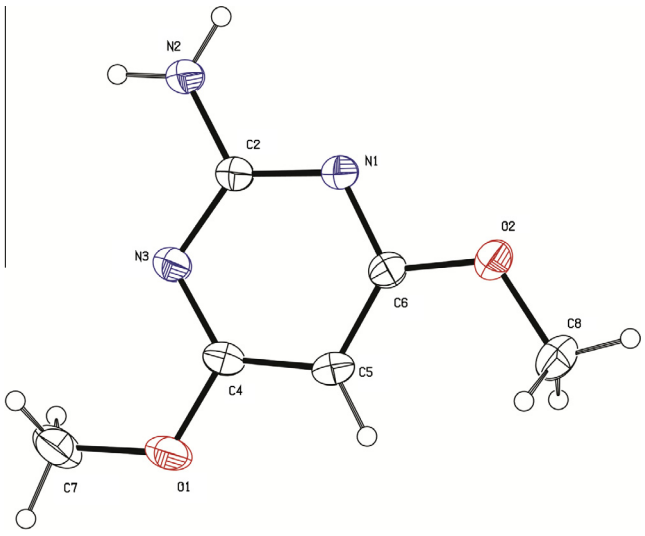



**Fig. 1.** ORTEP view of ADMP (**1**) with atom labelling scheme.