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Solvothermal synthesis of theophylline and *N,N*'-(ethane-1,2-diyl)diformamide co-crystals from DMF decomposition and N-formylation trough catalytic effect of 3-carboxyphenylboronic acid and cadmium acetate

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Here we present the unexpected production of *N,N*'-(ethane-1,2-diyl)diformamide. The solvothermal reaction was conducted in DMF at 100 °C with starting compounds cadmium acetate, 3-carboxyhenylboronic acid and aminophylline (2:1 mixture of theophylline and ethylenediamine). The *N,N*'-(ethane-1,2-diyl)diformamide is obtained as a result of a formylation reaction, catalyzed by Cd^{2+} and the high temperature. The *N,N*'-(ethane-1,2-diyl)diformamide co-crystallized with theophylline in the triclinic space group $P\bar{1}$, with unit cell parameters a = 6.7437(8), b = 8.7847(14), c = 9.4656(15), α = 91.825(13)°, β = 103.313(12)°, γ = 98.054(12)°, and Z = 2. The co-crystal structure is stabilized by intermolecular hydrogen bonds between the *N,N*'-(ethane-1,2-diyl)diformamide and theophylline. The excesses of theophylline crystallized in a new polymorphic form in space group *Pn,* with unit cell parameters a = 3.8744(4), b = 12.8898(9), c = 8.1167(6), β = 98.965(8)° and Z = 2.

Key words: theophylline, polymorphism, single crystal, isotopically, N-formylation.

INTRODUCTION

Formamides are extensively used in organic synthesis as intermediates in the preparation of pharmaceuticals, as protecting groups in peptides synthesis, Lewis base catalysts in organic transformations, for Vilsmeier formylation etc. [1–6]. Nowadays, formylation methods are dependent on the used formylating reagent [7–11] the most common being formyl acetate [12]. Many of these methods suffer from different drawbacks such as the use of a costly and harmful formylating agents or catalysts, long reaction times accompanied by high temperatures and the formation of side products. More recent investigations on N-formylation of amines have been focused on the use of inorganic solid oxides as catalysts [13–15], the reaction media and conditions [16]. The studies are needed in order to minimize the unwanted drawbacks and to reduce the costs. We report herein the unexpected synthesis of N,N'-(ethane-1,2-diyl)diformamide from ethylenediamine (**en**) and N,N'-dimethylformamide using cadmium acetate and 4-carboxyphenylboronic acid as catalysts (Scheme 1).

EXPERIMENTAL SECTION

Synthesis of the title compounds

The Aminophylline was kindly provided by Sopharma AD, (Bulgaria) while all other chemicals were commercially available and used without additional purification. Co-crystals of *N,N*'-(ethane-1,2-diyl)diformamide (**edd**), and theophylline (**teo**) were obtained by solvothermal method. Aminophylline (126 mg, 0.3 mmol), 4-carboxyphenylboronic acid (49 mg, 0.3 mmol), $Cd(CH_3CO_2)_2$ x $2H_2O$ (40 mg, 0.15 mmol), were dissolved in 8 ml N,N'-dimethylformamide (DMF), 2 ml methanol and 0.5 ml of $_{dd}H_2O$ (double distilled water) and reacted in 20 ml Teflon lined autoclaves at 100 °C for 24 h. The autoclaves were quenched to room temperature in a water bath and the solution was collected by filtration. A mixture of prismatic (plate like) colorless crystals was obtained by slow evaporation of the solution. Single crystal studies revealed the presence of two new crystal phases. Theophylline and a co-crystal of theophylline and *N,N*'-(ethane-1,2-diyl)diformamide.

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X-ray data collection and structure determination

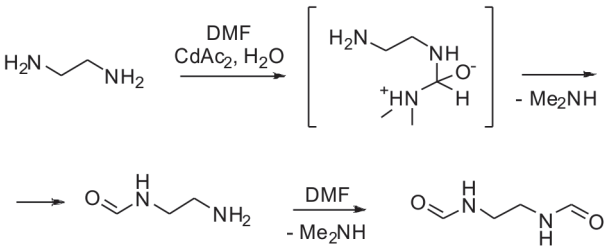
Crystallographic measurements and data collection were performed on an Agilent SupernovaDual diffractometer equipped with an Atlas CCD detector using micro-focus Mo Kα radiation (λ = 0.71073 Å) at 290 K. The determinations of the unit cell parameters, data collection and reduction were performed with Crysalis-Pro software [17]. The structures were solved by direct methods ShelxS [18] and refined by the full-matrix least-squares method with the ShelxL-2013 programs [18]. All non-hydrogen atoms, were located successfully from Fourier maps and were refined anisotropically. H atoms on C and N atoms were generated geometrically and their positional parameters were refined with C—H = 0.9600, N—H = 0.9300 Å with U_{iso}(H) = 1.2U_{eq}(C or N) Most important crystallographic and refinement indicators are listed in Table 1. Complete crystallographic data for the structure reported in this paper have been deposited in the CIF format with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 1039797 and 1039798. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

The initial intention was to produce a new metal organic framework (MOF) assembled in the same way as the reported metal-adenine bio-MOFs [19]. The concept was to employ the structural similarity of theophylline (**teo**) and adenine and to replace the dimethylcarbamate and pyridine by 3-carboxyhenylboronic acid and ethylene diamine (all three compounds coordinate Zn trough NH- and COOH moieties). The target was to obtain a "free" (e.g. not involved in Zn coordination) NH_2 and/or R-B$(OH)_2$ group, oriented towards the pores of the MOF. Thus an active center that could potentially trap CO_2 or other molecules and gazes would be present in the framework. Although, the conducted solvothermal synthesis produced two new crystal phases, single crystal data collection showed that the envisaged porous material was not produced. Instead, a co-crystal between theophylline and *N,N*'-(ethane-1,2-diyl)diformamide a new polymorph of theophylline were obtained. As **edd** was not one of the starting

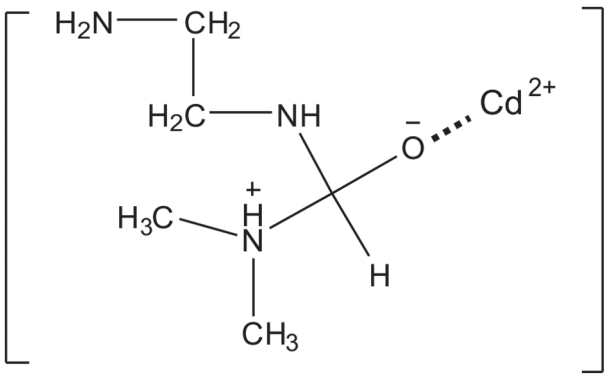
Table 1. Most important crystallographic and refinement details for compounds **1** and **2**

Compound reference	**teo:edd**	**teo**
Chemical formula	$C_9H_{12}N_5O_3$	$C_7H_8N_4O_2$
Formula Mass	238.24	176.17
Crystal system	Triclinic	Monoclinic
a/Å	6.7441(6)	3.8744(4)
b/Å	8.7826(11)	12.8898(9)
c/Å	9.4653(11)	8.1167(6)
α/°	91.834(10)	90
β/°	103.319(9)	98.965(8)
γ/°	98.035(9)	90
Unit cell volume/Å^3	539.00(11)	400.40(5)
Temperature/K	290(2)	290(2)
Space group	*P*1–	*Pn*
No. of formula units per unit cell, *Z*	2	2
Radiation type	MoKα	MoKα
Absorption coefficient, μ/mm^{-1}	0.114	0.106
No. of reflections measured	2543	2386
No. of independent reflections	1959	1499
R_{int}	0.0218	0.0240
Final R_1 values ($I > 2\sigma(I)$)	0.0578	0.0633
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1452	0.1644
Final R_1 values (all data)	0.0816	0.0828
Final $wR(F^2)$ values (all data)	0.1663	0.1786
Goodness of fit on F^2	1.152	1.068
CCDC number	1039797	1039798



Scheme 1.

compounds it has to be produced during the synthesis. A plausible mechanism for **edd** production is the N-formylation of **en** trough Cd^{2+} catalysis shown in Scheme 1. The reaction implicates the breakdown of DMF and thus the existence of a possible Cd^{2+} intermediate shown on Scheme 2. The DMF breakdown is supported by the occurrence of dimethyl ammonium $(CH_3)_2NH^{2+}$ cations in several MOF structures [20–30] also obtained by solvothermal method and featuring Cd^{2+}, Zn^{2+}, In^{3+}, La^{3+} etc. as metal centers. One should note that in those cases the presence of boric or boronic acid is lacking. The use of boric acid as catalyst for the formation of primary, secondary and tertiary amides is not so common but is not unknown [31–33]. Interestingly in [31], neither boric acid nor polyethylene glycol (PEG) 400 showed catalytic activity alone, e.g. without the help of each other. Thus one may envisage a synergy catalytic influence Metal and R-B(OH)$_2$.



Scheme 2.

The **teo**:**edd** ration in the obtained co-crystals is 1:1 vs. 2:1 in aminophylline (Fig. 1). The molecular geometry (bond lengths and angles) of **teo** and **edd** are similar to those in the crystal structures of the f the compounds reported alone (Fig. 2). As one can expect the **teo**:**edd** co-crystal is successfully achieved through hydrogen bonding of **teo**

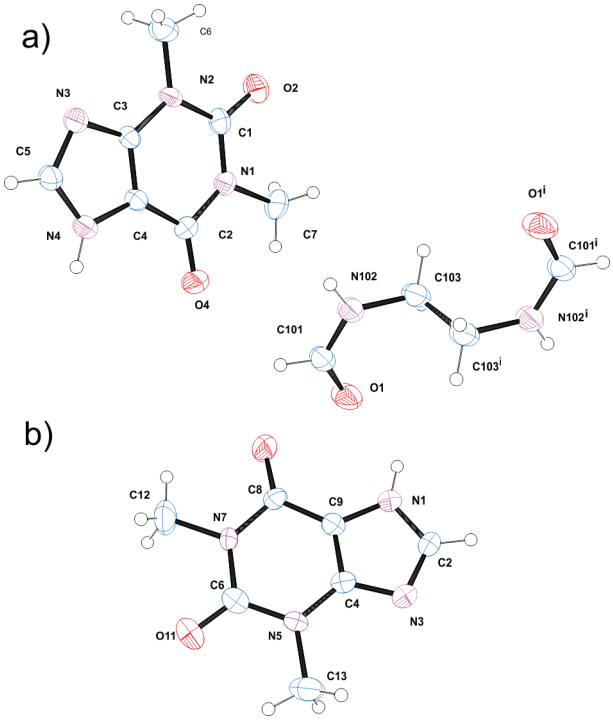


Fig. 1. *ORTEP* view of molecules present in the asymmetric unit of a) **teo:edd** co-crystal and b) **teo**; displacement ellipsoids are at 50% probability and hydrogen atoms are shown as spheres with arbitrary radii

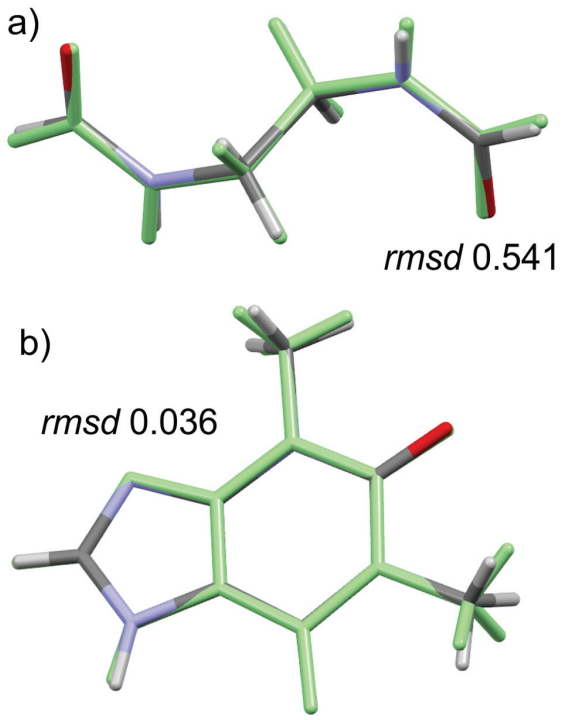


Fig. 2. Overlay of the molecules of a) **edd** and b) **teo** from co-crystal with those of compounds alone; the light (green) molecules are **enn** ref. [37] and **teo** ref. [35]

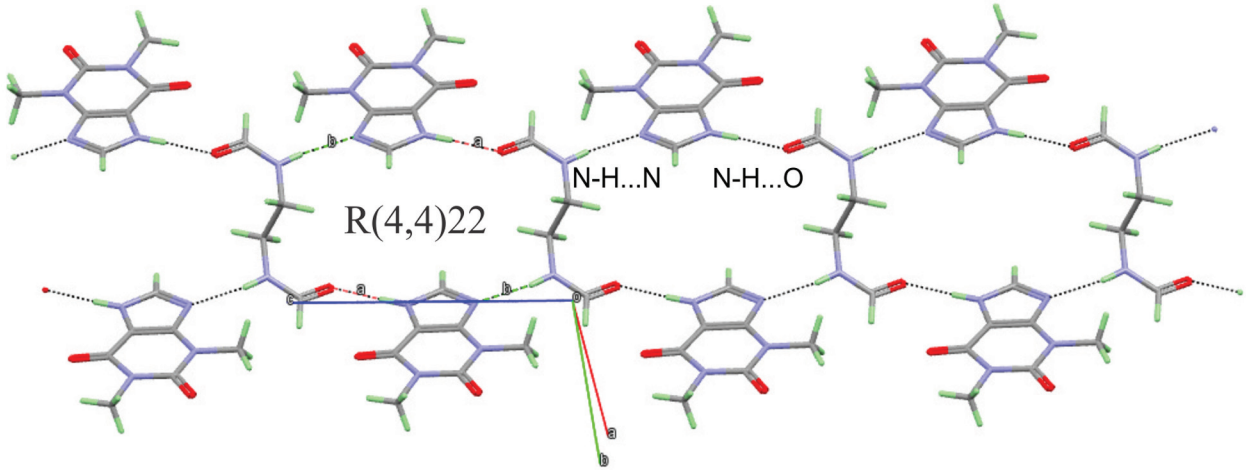


Fig. 3. Hydrogen bonding interactions (for details see Table 2) stabilizing the three-dimensional arrangement in **teo:edd** co-crystal

Table 2. Hydrogen-bond and CH_3…..O geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
teo : **edd**				
N4—H4···O6^{i}	0.93 (4)	1.78 (4)	2.708 (3)	177 (3)
N11—H11···N7	0.88 (4)	2.10 (4)	2.967 (3)	173 (4)
CH_3 ….. O				
C16—H16B···O6^{ii}	0.93 (3)	3.254 (4)	3.882 (5)	125 (2)
Symmetry codes: (i) *x, y, z+1;* (ii) *x, y−1, z.*				
teo				
N1—H1···N3^{i}	1.07 (9)	1.82 (9)	2.850 (6)	160 (7)
C2—H2···O10^{ii}	0.93	2.42	3.179 (7)	139 (5)
Symmetry codes: (i) *x−1/2, −y+2, z+1/2*; (ii) *x+1/2, −y+2, z−1/2.*				

and **edd** – resulting in a R(4,4)22 ring motif that extends into C(4,4)22 chains along *c* (Fig. 3 and Table 2). The two **teo** carbonyl oxygens are not involved in hydrogen bonding interaction and do not contribute to the three-dimensional stabilization of the structure. This is probably due to the molecular packing bringing in close proximity CH_3 and CH_2 groups and thus hindering the carbonyl oxygens. As **teo** is a purine it is not unexpected that week π….. π and CH_3….. π interactions additionally stabilize the crystal packing (Fig. 4). The excess of **teo** (the initially used Aminophylline is a **teo**: **en** in a 2:1 ratio) crystallizes in as a new polymorphic form (Fig. 1b). The structure features a pseudo-center of symmetry but the attempts to solve and refine the structure in a higher symmetry were not successful. As the bond

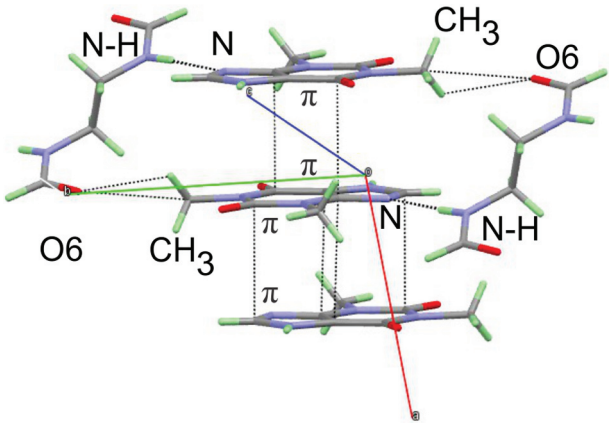


Fig. 4. Observed weak interactions (π….. π and CH_3…O) in the crystal structure of **teo:edd** co-crystal

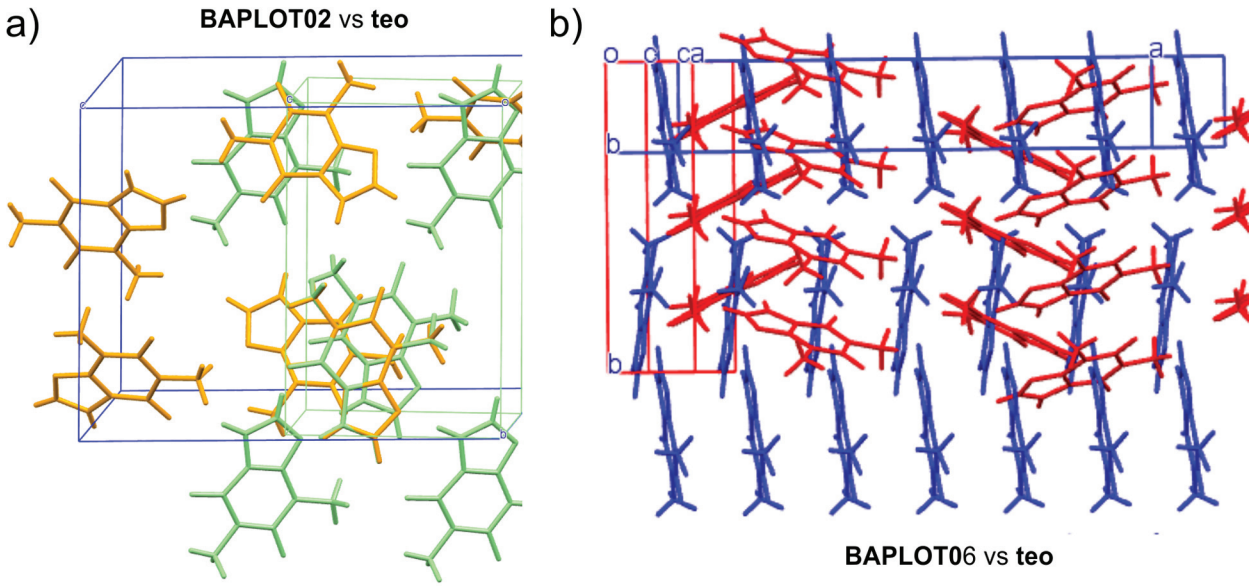


Fig. 5. The dissimilar molecular arrangement observed in the different polymorphic forms of Theophylline a) **teo** vs BAPLOT2 [34, 35] and b) **teo** and BAPLOT6 [36]

lengths and angles of the reported here polymorph and the already know modifications [34–36] are conserved, the differences between the three polymorphic forms (two monoclinic and one orthorhombic) are in the three-dimensional arrangement of the molecules (Fig. 5). This different three-dimensional packing is probably influenced by the presence of additional suitable hydrogen bonding partners as **edd** and 3-carboxyphenylboonic acid.

We have obtained a co-crystal of **teo**: **edd** and a new polymorph modification of theophylline. The N,N'-(ethane-1,2-diyl)diformamide (**edd**) is produced from ethylenediamine and DMF using cadmium acetate and 4-carboxyphenylboronic acid as catalysts. The breakup of DMF occurs in the presence of metal as catalyst while the N-formylation requires the presence of R-B$(OH)_2$.

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СОЛВОТЕРМАЛЕН СИНТЕЗ НА СЪКРИСТАЛИ НА ТЕОФИЛИН И N,N'-(ЕТАН-1,2-ДИИЛ) ДИФОРМАМИД ЧРЕЗ РАЗЛАГАНЕ НА ДМФ И N-ФОРМИЛИРАНЕ ПРИ КАТАЛИТИЧНО ДЕЙСТВИЕ НА 3-CARBOXYHENYLBORONIC КИСЕЛИНА И КАДМИЕВ АЦЕТАТ

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(Резюме)

Представяме неочакваното получаване на N,N'-(етан-1,2-диил)диформамид. Реакцията е проведена в ДМФ на 100 °C и изходните съединения са кадмиев ацетат, 3-карбоксифенилборна киселина и аминофилин (2:1 смес от 1,3-диметилксантин и етилендиамин). N,N'-(етан-1,2-диил)диформамид се получава в резултат на реакция на формилиране, катализирана от кадмий и висока температура. N,N'-(етан-1,2-диил)диформамид съкристализира с теофилин в триклинната пространствена група P1–, с параметри на единичната клетка a = 6.7437 (8), b = 8.7847 (14), c = 9.4656 (15), α = 91.825 (13)°, β = 103.313 (12)°, γ = 98.054 (12)°, и Z = 2. Структурата на съкристала е стабилизирана от между-молекулни водородни връзки. Останалият теофилин кристализира в нова полиморфна форма в пространствената група *Pn*, с параметри на елементарна клетка a = 3.8744 (4), b = 12.8898 (9), c = 8.1167 (6), β = 98.965 (8) и Z = 2.