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THERMAL STABILITY AND STRUCTURE OF A NEW CO-CRYSTAL OF THEOPHYLLINE FORMED WITH PHTHALIC ACID TG/DTA-EGA-MS and TG-EGA-FTIR study

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A new co-crystal of theophylline and phthalic acid with 1:1 molar ratio has been prepared. It crystallises in the monoclinic crystal system, space group $P2_1/c$, a=11.5258(9), b=10.1405(6), c=13.9066(12) Å, β=106.827(4)°. The structure of the co-crystal has been revealed by single crystal X-ray diffraction. An infinite helical polymeric chain is formed by intermolecular hydrogen bonds of the two neutral constituents. The hydroxyl group and carbonyl oxygen atom in one of the carboxyl groups of phthalic acid form hydrogen bonds to O6 and to N(7)H atoms of theophylline, respectively, while the other carboxyl OH group of phthalic acid is in hydrogen bond to N9 atom of theophylline by very strong intermolecular interactions proven by 1883 cm^{-1} centred peak in FTIR spectrum.

Thermal degradation of this new supramolecular compound is a two-step process in air. At first phthalic acid (47.4%) released up to 230°C, meanwhile it loses water and transforms into phthalic anhydride. In EGA-MS spectra, the characteristic fragments of water (m/z=17, 18) appear from about 180°C, while absorption bands of phthalic anhydride are shown in EGA-FTIR spectrum at about 210°C. In the second step theophylline begins to sublime, melts at 276°C, and then evaporates up to 315°C with minute residues.

Keywords: *acute asthma, evolved gas analysis, FTIR spectroscopy, mass spectrometry (MS), phthalic acid, simultaneous TG/DTA, TG/DTA-MS, TG-FTIR, theophylline, XRD*

Introduction

Theophylline (dimethylxantine) is an effective drug used in treatment of acute asthma, beyond its use in tremor therapy and as diuretic as well. Effectual application of theophylline needs organic solubilizers (e.g.: ethylenediamine in the aminophylline [1, 2]) to raise its low water solubility. Solubility and dissolution characteristics of theophylline itself can be improved not only with alkaline type solubilizers [2], but also with acidic type ones like benzoic acid [3] because of amphoteric feature of theophylline. From concentrated solutions of theophylline with solubilizers, often new solid substances can be obtained as supramolecular compounds (co-crystals or salts) of theophylline [4, 5]. The theophylline unit might occur either as neutral, anionic [2], or cationic [6] constituent in such lattice compounds depending on both the strength of acid/base character of organic solubilizer and opportunities for stabilization by hydrogen bonding system of various crystalline environments [5]. Childs *et al.* [5], who have very recently reported single crystal structure of aminophylline (2:1=ethylenediamine:theophylline) and its monohydrate, suggest an approach that considers the co-crystals and salts as two end-members of a single continuum.

During our efforts to crystallize aminophylline or its hydrates as single crystals, which were failed, we have obtained and reported for the first time a co-crystal with ethylenediamine carbamate (WUYROX, [7–9]), whose single crystal structure contains neutral theophylline units and zwitter ionic carbamate. Nevertheless, we have also been seeking for structures similar or related to the aminophylline and formed with other alkaline compounds, and have successfully prepared single crystals of theophylline with 2-aminoethanol [7, 8] and 1,4-butanediamine as co-crystallized into ionic compounds [8, 10], and deposited the corresponding single crystal X-ray diffraction data on the crystal and molecular structure of ethanolammonium theophyllinate (WUYRIR, [7–9]) and 1,4-diammoniumbutane *bis*(theophyllinate) (YAHQII, [8–10] in the Cambridge Structural Database [9]. Both crystal structures confirm, that theophyllinate anions and primary ammonium cations are present in the lattices stabilized by extended hydrogen bonding systems [7, 8, 10–12]. Simultaneous thermogravimetric and differential thermal analysis (TG/DTA) [7, 11, 12] have shown that the above salts containing theophylline anions release the volatile primary amine partners as neutral vapor molecules at relatively low temperatures, while the theophylline itself, after regeneration by regaining its N(7) proton,

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recrystallizes gradually, slowly and at least partially showing endothermic heat effect at the expected melting point range [7]. Similar thermally induced proton shifts [5] might occur slowly at certain combinations of relatively low temperature and long time period, as well.

Despite the several lattice compounds, containing theophylline and various organic acids, prepared and characterized [4, 5], only two resolved single crystal structures with theophyllinium cation protonated on N(9) nitrogen, have been reported yet, that of theophyllinium chloride (THEOFI, R=0.122) [6, 9] and theophyllinium salicylic acid-5-sulfonate monohydrate (WUYRUD, R=0.0388) [7–9]. In the latter case, there is a water molecule in between the theophyllinium cations and the salicyl-5-sulfonate anion [8, 9]. Most of the cases, the acidic solubilizers have been built into the co-crystal as neutral molecule, as it is demonstrated in case of co-crystals of 5-chlorosalicylic acid – theophylline (CSATEO) whose structure was also solved by single crystal X-ray diffraction [9, 13]. Recently several 1:1 co-crystals of theophylline with malonic acid (XEJXAM), maleic acid (XEJXEQ), glutaric acid (XEJXIU) [9, 14, 15], sorbic acid, 4-hydroxy-benzoic acid, 1-hydroxy-naphthoic acid, salicylic acid [5, 7], and theophylline-2,4-dihydroxybenzoic acid–water (1:1:1) [16], furthermore 2:1 co-crystals of theophylline with oxalic acid (XEJWUF) [9, 14, 15], *DL*-tartaric acid (NEXWOD) and *L*-tartaric acid (NEYCIE) [9, 17] were prepared and their structure were solved by single crystal X-ray diffraction. In some cases, co-grinding of solid components as method of partial preparation were also reported [14, 17–19].

In this study, preparation, structure, analytical features and thermal behaviour of a new 1:1 co-crystal compound of theophylline with an acidic solubilizer, phthalic acid (**1**) is presented. It has been studied and characterized by elemental analysis, FTIR spectroscopy, powder and single crystal X-ray diffraction methods, while its thermal stability has been investigated by simultaneous thermogravimetry and differential thermal analysis coupled online with in situ evolved gas analyses (TG/DTA-MS and TG-FTIR).

Experimental

*Sample preparation of **1***

Anhydrous theophylline (th) (180.2 mg, 1 mmol, 99%, Sigma, T-1633) was dissolved by mild warming (about 50°C) and intense stirring in 30–50 mL aqueous solution of 1 mmol (166.1 mg, Aldrich, 88-99-3) phthalic acid. Solution was covered by punched paraffin film to slow down evaporation of the solvent and it was left on room temperature. In some weeks small solid crystals appeared in the solution, which were filtered on glass filter and dried in open air at room temperature.

Methods

Elemental analysis

C, H and N analysis of the filtered crystals were carried out by a Heareus-CHN-O-Rapid analyzer in Microanalytical Laboratory of Eötvös Loránd University of Sciences (Hungary). Calculated for $C_7H_7N_4O_2{\cdot}C_8H_6O_4$ (theophylline phthalic acid): 52.03 C%, 4.07 H%, 16.18 N%; measured: 52.73 C%, 3.67 H%, 16.27 N%.

FTIR spectroscopy

Fourier transform infrared spectra of starting materials and inclusion compound of **1**, theophylline phthalic acid were measured by a Bio-Rad Excalibur Series FTS 3000 spectrometer in the range of 4000–400 cm^{-1} using KBr pellets.

Powder X-ray diffraction

X-ray powder patterns of theophylline phthalic acid (**1**) and its starting materials (theophylline and phthalic acid) were recorded on a HZG-4 diffractometer (Jena Zeiss, Freiberger Präzisions Mechanik) using Ni filtered CuK_α radiation and on a X'Pert Pro MPD (PANalytical, The Nederlands) X-ray diffractometer with X'celerator detector.

Simultaneous TG/DTA

Thermal behaviours of theophylline phthalic acid (**1**) and its starting materials were investigated up to 500°C by a simultaneous TG/DTA apparatus (STD 2960, TA Instruments). Sample size of about 6–15 mg, open Pt crucibles, a heating rate of 10°C min^{-1} and α-Al_2O_3 as reference material were used. The measurement was carried out in flowing air at a rate of 120 mL min^{-1}.

Evolved gas analysis by online coupled TG/DTA-MS

Gases evolved from theophylline phthalic acid (**1**) heated in furnace of a simultaneous TG/DTA apparatus (STD 2960, TA Instruments) are led to quadrupole MS spectrometer (Balzers Instruments Thermostar GSD 300 T3) through a heated quartz capillary (l=1 m, d_{in}=150 μm). EI ion-source of mass spectrometer and the connecting capillary were kept at 200°C. About 8 mg of crystals were heated up to 500°C in an open Pt crucible in flowing air of 120 mL min^{-1}. The heating rate was 10°C min^{-1}.

Evolved gas analysis by online coupled TG-FTIR

Gases evolved from theophylline phthalic acid (**1**) heated in the furnace of a TGA 2050 Thermogravimetric Analyzer (TA Instruments) are led to FTIR gas cell of TGA-IR Accessory Unit (Bio-Rad) attached to the above mentioned FTIR spectrometer through a heated steel tube (l=50 cm, d_{in}=3 mm). The FTIR gas cell and the connecting stainless steel tube were kept at 200°C. About 16 mg of theophylline phthalic was heated up to 500°C in an open Pt crucible in flowing air of 120 mL min^{-1}. The heating rate was 10°C min^{-1}. Interferograms were collected in every 30 s and spectra (4000–500 cm^{-1}) of gaseous mixture are obtained at a resolution of 4 cm^{-1}.

Single crystal X-ray diffraction

The crystals of theophylline phthalic acid (**1**) are colourless prisms. The size of the crystal selected for single crystal X-ray diffraction measurement is 0.60×0.50×0.40 mm. Formula is $C_7H_8N_4O_2+C_8H_6O_4$, formula mass is 346.30. It crystallises in the monoclinic crystal system, space group $P2_1/c$. The cell dimensions are a=11.5258(9), b=10.1405(6), c=13.9066(12) Å, α=γ=90°, β=106.827(4)°; V=1555.8(2) $Å^3$, Z=4, F(000)=720, D_x=1.478 Mg m^{-3}. A crystal was mounted on a loop in oil. The diffraction measurement was performed at room temperature T=293(2) K. Intensity data were collected on a Rigaku R-Axis Rapid diffractometer (graphite monochromator; CuK_α radiation, λ=1.54180 Å) in the range 6.65≤θ≤68.06°. Cell parameters were determined by least-squares of the setting angles of 3557 reflections. A total of 17403 reflections were collected of which 2748 were unique [R(int)=0.0314, R(σ)=0.0153]; 2455 reflections were >2σ(I). Completeness to 2θ=0.966. An empirical absorption correction was applied to the data, μ=0.996 mm^{-1}, the minimum and maximum transmission factors were 0.5864 and 0.6914. The structure was solved by direct methods with SHELXS97 [20]. Anisotropic full-matrix least-squares refinement with SHELXL97 [21] on F^2 for all non-hydrogen atoms yielded R1=0.0391 and wR2=0.1235 for 2455 [I>2σ(I)], R1 =0.0433 and wR2=0.1338 for all (2748) intensity data (goodness-of-fit=1.139; the maximum and mean shift/esd 0.000 and 0.000; extinction coefficient= 0.0061(7)). The extinction coefficient expression:

$$F_c^* = kF_c[1+0.001F_c^2\lambda^3/\sin(2\theta)]^{-1/4}$$

Number of parameters=241. The maximum and minimum residual electron density in the final difference map was 0.299 and –0.191 e $Å^{-3}$. The weighting scheme applied was

$$w=1/[\sigma^2(F_0^2)+(0.0697P)^2+0.4871P],$$
where $P=(F_0^2+2F_c^2)/3$

Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded.

Crystallographic data (excluding structure factors) for the above crystal structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 684732.

Results and discussion

*Characterization of **1** by XRD, FTIR spectroscopy and simultaneous TG/DTA*

Both the powder XRD pattern and FTIR spectrum (Fig. 1) of crystals **1** have been found to be different from those of starting chemicals, or physical mixture of theirs, what has already given indication on formation of a novel lattice compound of theophylline with phthalic acid.

Because of the relatively strong acidic character of phthalic acid (pK_1= 2.89, pK_2=5.51 [22]) one might have expected formation of theophyllinium cations in the new co-crystal, but in the FTIR spectrum of **1** (Fig. 1), only slight negative shifts in wavenumbers of the carbonyl groups (1711 and 1650 cm^{-1}) has occurred compared to those of pure theophylline (1717 and 1667 cm^{-1}). Presence of neutral theophylline molecule seems to be more likely rather than that of its cationic form, when positive carbonyl shifts are expected [7]. Also the occurrence of phthalic acid in its neutral form can be in harmony with the FTIR spectrum of this compound [$\nu_{C=O}$ at 1689 cm^{-1}]. The structural prediction according to Childs *et al.* (Table 2 in [5], ΔpK_a=1.19) also suggests formation of co-crys-

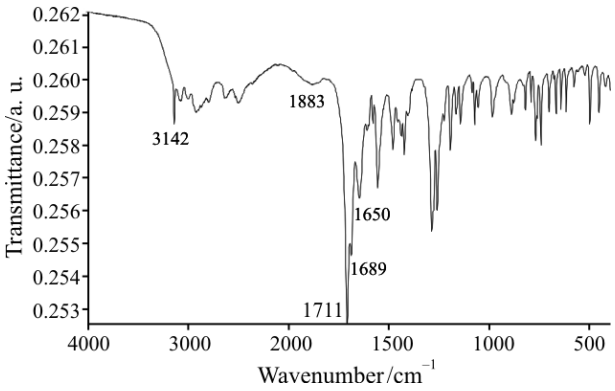

Fig. 1 FTIR (KBr) spectrum of theophylline phthalic acid co-crystal (**1**)

tals of neutral components. Anyhow, a broad peak at 1883 cm^{-1} indicates presence of a very strong hydrogen-bond beyond the band system between 2200 and 3300 cm^{-1} of hydrogen bonds (Fig. 1).

Thermal stability and decomposition processes of new inclusion compound have been shown in Fig. 2, measured by simultaneous TG/DTA in flowing air. The co-crystal is stable till 180°C. Decomposition of theophylline phthalic acid (**1**) has occurred in two steps without significant residue. Between 180 and 230°C phthalic acid has been released. The remaining anhydrous theophylline has melted at 276 and evaporated up to 315°C. Minute residues (ca. 1%) are burned out between 350 and 420°C.

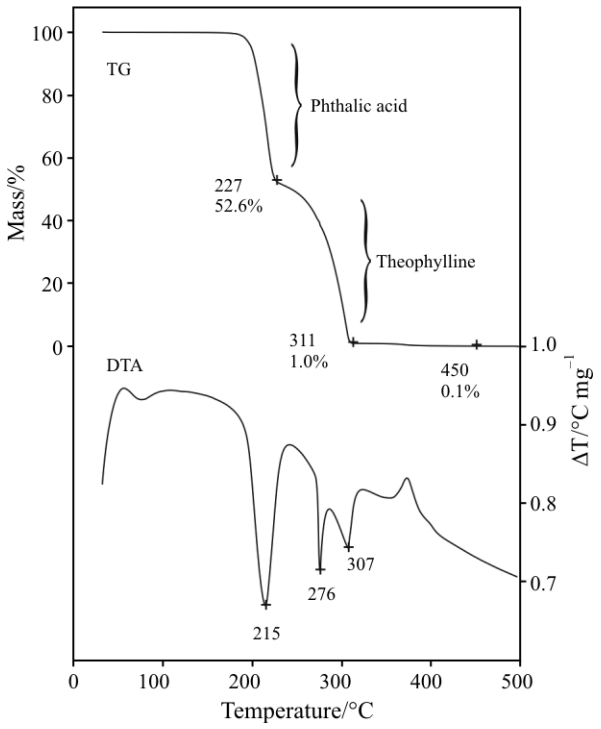

Fig. 2 Simultaneous TG/DTA curves of theophylline phthalic acid (**1**) in flowing air (120 mL min^{-1}, heating rate 10°C min^{-1}, initial mass 7.71 mg)

Mass loss in the first step has been 47.4%, while the theoretical value for phthalic acid is 48.0%. The residual mass 51.6% corresponds to anhydrous theophylline (theoretical value 52.0%). On the basis of both elemental analysis and TG curve the stoichiometric ratio of constituents is 1:1, i.e. really theophylline phthalic acid co-crystal is in hands.

*Crystal structure and secondary interactions in lattice of theophylline phthalic acid (**1**)*

In accordance with the FTIR study there is one neutral theophylline and one neutral phthalic acid molecule in the asymmetric unit of the crystal structure of theophylline and phthalic acid (Fig. 3). The hydrogen positions were determined from difference Fourier calculation. Weak C–H…O type intramolecular interactions (detailed also in Table 1) stabilise the molecular conformations.

There is an infinite helix (Fig. 4) constructed by alternating theophylline and phthalic acid molecules connected by strong hydrogen bonds (Table 1)in the crystal structure organised by the twofold screw axis parallel to the crystallographic b direction.

On one side of the theophylline there are two strong hydrogen bonds to a phthalic acid: N7–H7...O11 and O12–H12O...O6. On the other side of the theophylline N9…H14O–O14 strong intermolecular bond connects the next phthalic acid. Additionally, a week C8–H8A...O13 interaction contribute to the stability of the chain.

The parallel helices are intercalated (Fig. 5) like a zip arrangement. There is only one weak C8–H8A...O2 hydrogen bond between the helical columns (Table 1). As it can be observed in the middle of the cell in Fig. 5a

Table 1 Hydrogen bonds in the crystal structure of theophylline phthalic acid (**1**)

atoms	D–H	H…A	D…A	D–H…A	Symmetry operation
H–bonds forming the helix arrangement					
N7–H7...O11	0.91(2)	1.88(2)	2.788(3)	176(2)	–
O12–H12O...O6	0.99(4)	1.66(4)	2.631(2)	165(3)	–
O14–H14O...N9	0.97(3)	1.71(3)	2.681(2)	177(2)	1–*x*,–1/2+*y*,1/2–*z*
Weak H–bond in the helix					
C8–H8A...O13	0.9300	2.4800	3.097(3)	124.00	1–*x*,1/2+*y*,1/2–*z*
Weak H–bond between the chains					
C8–H8A...O2	0.9300	2.5000	3.225(3)	135.00	*x*,1/2–*y*,1/2+*z*
Weak intramolecular H–bonds stabilising the molecular conformation					
C1–H1A...O6	0.9600	2.2800	2.722(3)	107.00	–
C3–H3B...O2	0.9600	2.4000	2.768(3)	102.00	–
C13–H13...O14	0.9300	2.4400	2.750(3)	100.00	–

there is a column formed by two theophylline and two phthalic acid molecules belonging to two helices (Fig. 6). There is π...π intermolecular contact between the parallel theophylline molecules with the distance of 3.550(1) Å. The nearly parallel theophylline and phthalic acid molecules are out of the range of the interaction with the distance of 4.434(1) Å.

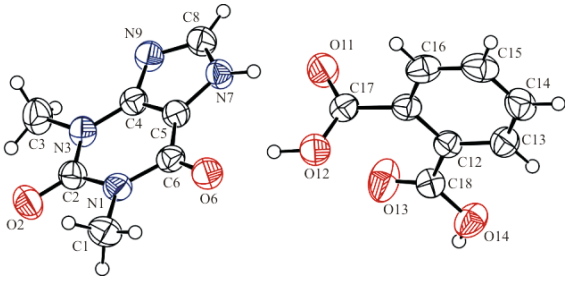

Fig. 3 The molecular structure and atom labelling of theophylline and phthalic acid in their co-crystal (**1**). The ORTEP [23] diagram is presented at 50% probability level

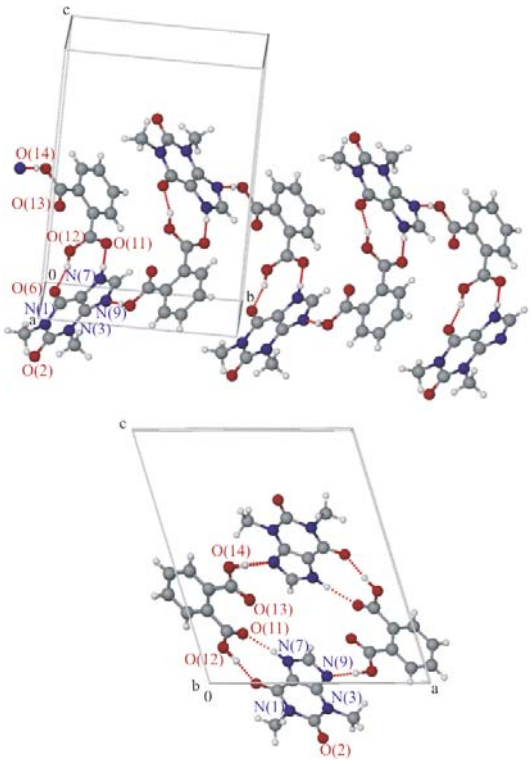

Fig. 4 Helix arrangement along the crystallographic *b* axis supported by hydrogen bonds [24]. a – View from the crystallographic *a* axis. b – View from the crystallographic *b* axis

*Evolved gas analyses (EGA-FTIR and EGA-MS) of theophylline phthalic acid (**1**)*

Release of phthalic acid from theophylline phthalic acid (**1**) between 180 and 230°C has been studied *in situ* by online coupled evolved gas analysis techniques, TG/DTA-MS and TG-FTIR. During the heating, phthalic acid partially loses water and transforms into phthalic anhydride. In FTIR gas-spectrum by TG-FTIR at 210°C (Fig. 7) absorption bands of phthalic anhydride have identified with help of the public FTIR gas spectrum library of NIST [26]. Fig-

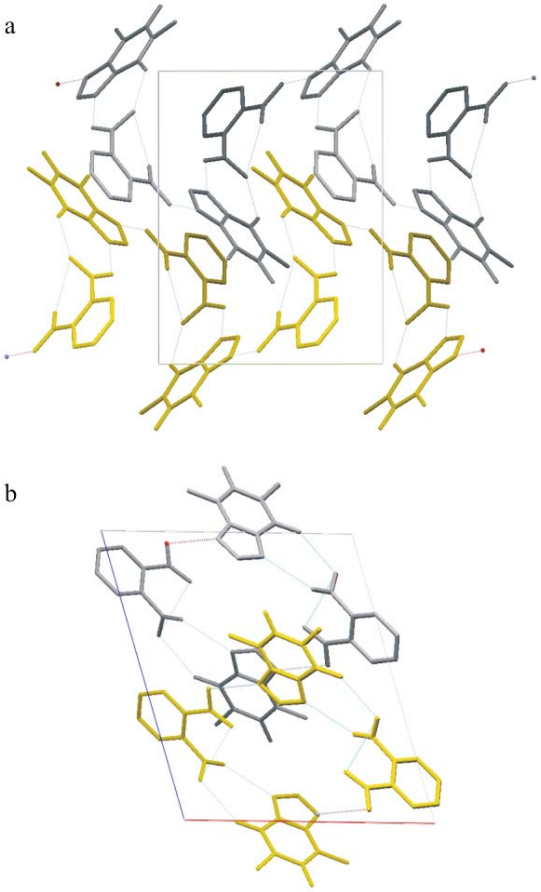

Fig. 5 The intercalated helices in the cell [25]. a – View from the crystallographic *a* axis. b – View from the crystallographic *b* axis

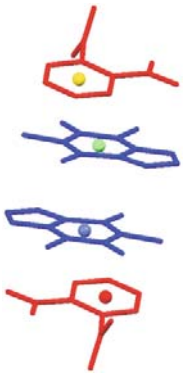

Fig. 6 The π…π intermolecular contact between the theophylline molecules in the column formed nearly in the diagonal of the *bc* crystallographic axes. The theophylline–phthalic acid distance is out of range

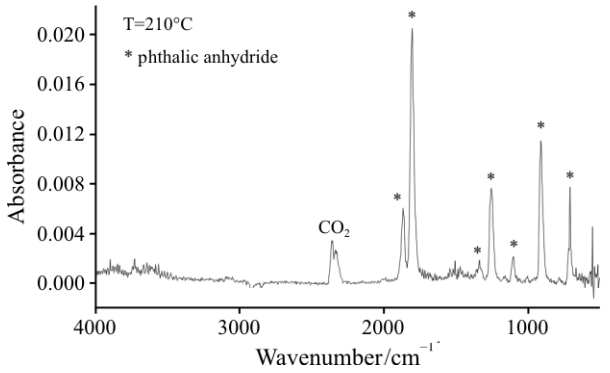

Fig. 7 FTIR gas-spectrum of evolved gas analysis (TG-FTIR) at 210°C of theophylline phthalic acid (**1**) in flowing air (120 mL min^{-1}, heating rate 10°C min^{-1}, initial mass 15.63 mg) [26]

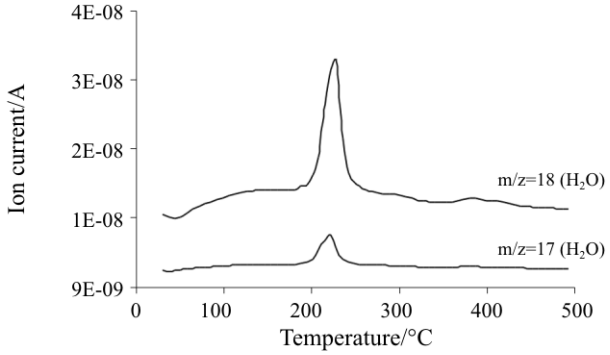

Fig. 8 Mass spectroscopic evolution curves of ion fragments of H_2O from theophylline–phthalic acid (**1**) in flowing air (120 mL min^{-1}, heating rate 10°C min^{-1}, initial mass 7.71 mg)

ure 8 shows mass spectrometric evolution curves of m/z=17 and 18 ion fragments from H_2O. Meanwhile phthalic acid vapour loses water, some further degradations, probably its decarboxylation has also taken place starting from 180°C, what is indicated by CO_2 evolution by both of the EGA methods.

Conclusions

Theophylline phthalic acid (**1**) have been prepared as a novel co-crystal of theophylline, with stoichiometric ratio of 1:1 according to elemental and thermal analysis. On the basis of FTIR spectrum and the crystal structure determined by single crystal X-ray diffraction, theophylline and phthalic acid exist as neutral molecules in their co-crystal, i.e. theophylline in solid-state is not protonated despite the acidic organic solubilizer.

The co-crystal is thermally stable up to 180°C, then a two-step thermal decomposition occurs according to the simultaneous TG-DTA measurements. The two components are released separately in two steps (first phthalic acid then theophylline). In the first degradation step phthalic acid transforms mainly to volatile phthalic anhydride identified in EGA-FTIR gas-spectra, while the released water was detected in the mass spectra, explicitly. Some degradation processes also occur resulting in CO_2 formation indicated by both TG/DTA-MS and TG-FTIR evolved gas analysis methods.

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