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THERMAL, FTIR AND XRD STUDY ON SOME 1:1 MOLECULAR COMPOUNDS OF THEOPHYLLINE

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Abstract

Thermal stability and structural features of three newly synthesized 1:1 lattice compounds of theophylline (**th**) with ethylenediamine carbamate (**enCO$_2$**), 1,10-phenanthroline (**phen**), and 5-sulfosalicylic acid (**sa-5-SO$_3$H**) have been studied in comparison with those of the theophylline compounds with ethanolamine (**ea**) and salicylic acid (**sa**). Simultaneous TG-DTA measurements, FTIR spectroscopy and X-ray diffraction have been carried out to get information on the various structural units of these solid inclusions, especially on the actual form (molecule, anion or cation) of theophylline moieties built in. Theophyllinate and theophyllinium ions have been found in the ethanolammonium-theophyllinate (1:1) (**1, eaH$^+$·th$^-$**) and the theophyllinium salicylic acid 5-sulfonate monohydrate (1:1:1), (**5, thH$^+$·saSO$_3^-$·H$_2$O**), respectively. Whilst the 1:1 complexes with 1,10-phenanthroline (**2, th·phen**), ethylenediamine carbamate (**3, th·enCO$_2$**), and salicylic acid (**4, th·sa**) contain neutral theophylline moieties associated with H-bonds. In compound (**3**) the zwitterion of N-(2-ammonium-ethyl)carbamate (NH_3^+-CH_2-CH_2-NH-CO_2^-) is present.

Keywords: ethanolamine, FTIR, 1,10-phenanthroline, salicylic acid and 5-sulfosalicylic acid, simultaneous TG-DTA, theophylline lattice compounds, ethylenediamine carbamate, unit cell parameters, XRD

Introduction

The solubility of drug theophylline in water can be increased by either basic or acidic additives. In medical injections used for treatment of acute asthma usually the base ethylenediamine (**en**) is applied, anyhow there are efforts on further improvement of this medicine based on theophylline [1]. The hydrated solid molecular compound of theophylline with ethylenediamine (in 2:1 molar ratio), called aminophylline, is a drug described in several Pharmacopeias. From the solutions prepared with additives enhanc-

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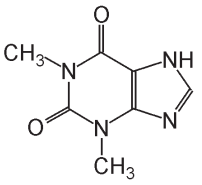
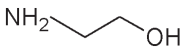
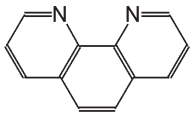
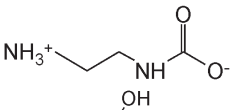
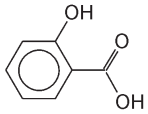
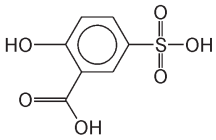
ing solubility, usually various lattice compounds of theophylline can be crystallized. Nishijo and co-workers synthesized a series of 2:1 theophylline complexes with α,ω-alkanediamines (n = 4–8) and characterized by TG-DTA, powder XRD, and IR spectroscopy [2]. They also looked for similar solid molecular compounds with several aliphatic and aromatic monoamines and aminoalcohols. The theophylline compounds formed with 1:1 molar ratio (including that of ethanolamine, **ea**) were also characterized, and a scheme for their H bonds was proposed based on their IR data [3, 4].

Table 1 Thermal behaviour and dissociation exponent(s) of the pure constituent compounds

Compounds	Name	pK_s, pK_b, pI
	Theophylline (*m.p.*: 269–270°C)	amphoteric: $pK_s = 8.6$ ($pK_b^{corr} = 5.4$) $pK_b = 13.72$ ($pK_s^{corr} = 0.28$)
	ethanolamine (*b.p.*:170°C)	$pK_b = 4.5$ ($pK_s^{corr} = 9.5$
	1,10-phenanthroline (*m.p.*: 114–117°C) 1,10-phenanthroline·H_2O (*m.p.*: 100–104°C, dec.)	$pK_{b,1} = 5.05$ ($pK_{s,1}^{corr}$ =8.95) $pK_{b,2} = 14.5$ ($pK_{s,2}^{corr} = -0.5$)
	ethylenediamine carbamate (subl.; *m.p.*: 171°C in sealed capillary [16])	isoelectric pH: $pI = 8.4$ [17]
	salicylic acid (*m.p.*: 159–161°C)	$pK_{s,1} = 3.0$ ($pK_{b,1}^{corr} = 11.0$) $pK_{s,2} = 13.4$ ($pK_{b,2}^{corr} = 0.6$)
	5-sulfosalicylic acid·$2H_2O$ (*m.p.*: 110°C, dec.)	$pK_{s,1} = 2.49$ ($pK_{b,1}^{corr} = 11.51$) $pK_{s,2} = 11.74$ ($pK_{b,2}^{corr} = 2.24$)

Sekiya and co-workers [5] found new theophylline complexes with eight differently substituted aromatic acids (including salicylic acid, **sa**) and phenols. They characterized the 1:1 compounds by elemental analyses, melting temperature ranges, and IR spectra. Structural information based on single crystal X-ray diffraction are available on non-ionic 1:1 molecular compounds with *p*-nitroaniline [6], urea [7], sulfathiazol [8], and 5-chlorosalicylic acid [9] in comparison with theophylline monohydrate [10] and anhydrous theophylline [11]. Presence of theophyllinium cat-

ion is structurally proved only in theophylline hydrochloride [12]. Crystal and molecular structure of 2:1 type compounds are known already for bis(theophylline) phenobarbital [13] and bis(theophylline) 5-fluorouracyl monohydrate [14].

As part of our ongoing research on preparation and structural characterization of lattice compounds and metal complexes [15] of theophylline, we report here the results of our investigation on five 1:1 type solid compounds of theophylline and various organic bases and acids (Table 1) by simultaneous TG-DTA, powder X-ray diffraction and FTIR spectroscopy prior to their single crystal X-ray diffraction studies [18].

Experimental

*Preparation of **1** (**eaH$^+$·th$^-$**) and **3** (**th·enCO$_2$**) crystals*

Well-grown colourless crystals of ethanolammonium theophyllinate (1:1 compound of ethanolamine and theophylline, **1, eaH$^+$·th$^-$**) and theophylline N-(2-ammonium -ethyl)carbamate (1:1 compound of theophylline and ethylenediamine carbamate, **3, th·enCO$_2$**) have been obtained in partially covered vessels at ambient circumstances in the laboratory after 2 weeks by slow evaporation of 6 mL aqueous solutions of theophylline (**th**, 180.2 mg, 1 mmol) and 1 mL of ethanolamine (**ea**, ca. 16.5 mmol) or ethylenediamine (**en**, ca. 15 mmol), respectively. In the latter case the ethylenediamine carbamate (**enCO$_2$**) formed slowly and spontaneously over the solution surface as reaction product of **en** and CO_2 from air and than this air-born fine white powder was dissolved in the solution, as well.

*Preparation of crystalline **2** (**th·phen**), **4** (**th·sa**) and **5** (**thH$^+$·saSO$_3^-$·H$_2$O**)*

Anhydrous theophylline (180.2 mg, 1 mmol) was dissolved in 5 mL warm aqueous solutions containing stoichiometric amount of 1,10-phenanthroline monohydrate (198.3 mg, 1 mmol), salicylic acid (138.2 mg, 1 mmol), or 5-sulfosalicylic acid dihydrate (254.2 mg, 1 mmol), respectively. The compound with 1,10-phenanthroline (**2, th·phen**) was obtained immediately as fine fibers, while the compounds with salicylic acids (**4, th·sa** and **5, thH$^+$·saSO$_3^-$·H$_2$O**) crystallized as fine needles after few days or a week.

*Elemental analysis of **1**–**5***

C, H, and N analyses of samples **1**–**5** were carried out at the Microanalytical Laboratory of Loránd Eötvös University of Budapest (ELTE-TTK, Budapest, Hungary) in a Heraeus-CHN-O-Rapid analyzer.

FTIR spectroscopy

Fourier transformed infrared spectra of compounds **1**–**5** and the starting substances were recorded on a Perkin Elmer FTIR System 2000 and a Biorad Excalibur FTS 3000 spectrometer in the range of 4000–400 cm^{-1} using KBr pellets.

Thermal analysis

Thermal behaviour of theophylline compounds and their pure constituents were investigated to 600°C by simultaneous TG/DTA apparatus (SDT 2960, TA Instruments). Sample size of 9–19 mg, open Pt crucibles, Al_2O_3 as reference material and a heating rate of 10°C min^{-1} were used. The measurements were carried out in flowing air atmosphere at a rate of 130 mL min^{-1}.

X-ray diffraction

Single crystal X-ray data collection of **1 ($eaH^+ \cdot th^-$), 3 ($th \cdot enCO_2$)**, and **5 ($thH^+ \cdot saSO_3^- \cdot H_2O$)** were performed on an Enraf-Nonius CAD4 single crystal diffractometer using CuK_α or MoK_α radiation. X-ray powder patterns of compounds **1**–**5** and their starting materials were recorded on an FPM HZG4 powder diffractometer using Ni filtered CuK_α radiation. Measured and calculated powder XRD patterns were compared and are available from the authors upon request.

Table 2 Elemental (C, H, and N) composition of 1:1 compounds of theophylline **1**–**5** in%

Lattice compounds	Formula and formula mass FW/g mol^{-1}	Calculated/%			Found/%		
		C	N	H	C	N	H
Ethanolammonium theophyllinate (**1, $eaH^+ \cdot th^-$**)	$C_9H_{15}N_5O_3$ 241.25	44.81	29.0	6.27	44.90	28.61	6.32
Theophylline 1,10-phenantroline: = 1:1 (**2, th·phen**)	$C_{19}H_{16}N_6O_2$ 360.38	63.33	23.32	4.48	62.78	22.64	4.73
Theophylline:ethylene diamine carbamate = 1:1 (**3, $th \cdot enCO_2$**)	$C_{10}H_{16}N_6O_4$ 287.24	42.25	29.56	5.67	42.26	29.19	6.07
Theophylline : salicylic acid = 1:1 (**4, th·sa**)	$C_{14}H_{14}N_4O_5$ 318.29	52.83	17.60	4.43	52.93	17.62	4.80
Theophyllinium salicylic acid 5-sulfonate monohydrate (1:1:1) (**5, $thH^+ \cdot saSO_3^- \cdot H_2O$**)	$C_{14}H_{14}N_4O_8S$ 416.37	40.39	13.46	3.87	40.45	13.49	3.87

Results and discussion

*Specific X-ray diffraction patterns of **1**–**5***

Powders of samples **1**–**5** gave unique X-ray diffraction patterns and no traces of the parent compounds were observed. The obtained C, H, and N content of the samples (Table 2). confirmed formation of substances with molar ratio of theophylline:additives = 1:1 (in the case of **5, thH$^+$·saSO$_3^-$·H$_2$O** one molecule of water of crystallization is also present).

In case of ethanolammonium theophyllinate (**1, eaH$^+$·th-**), theophylline N-(2-ammonium-ethyl)carbamate (**3, th·enCO$_2$**), and theophyllinium salicylic acid 5-sulfonate monohydrate (**5, thH$^+$·saSO$_3^-$·H$_2$O**) determination of unit cell parameters and crystal structures have been carried out by single crystal X-ray diffraction. The summary of crystal data of compound **1**, **3** and **5** is given in Table 3. Further details on the crystal and molecular structures of **1**, **3** and **5** will be published elsewhere [18].

Table 3 Crystal system, space group, unit cell data and *R*-factor of structure determination for lattice compounds **1**, **3** and **5**

Crystallographic data	Ethanolammonium theophyllinate (**1, eaH$^+$·th$^-$**)	Theophylline N-(2-ammonium-ethyl) carbamate (1:1) (**3, th·enCO$_2$**)	Theophyllinium salicylic acid 5-sulfonate monohydrate (1:1:1) (**5, thH$^+$·saSO$_3^-$·H$_2$O**)
Crystal system	triclinic	monoclinic	monoclinic
Space group	*P*-1 (No.2)	*Cc* (No.9)	*Cc* (No.9)
a/Å,	8.497(1)	8.949(2)	14.809(1)
b/Å,	8.581(1)	21.194(2)	8.779(1)
c/Å,	8.852(1)	7.339(2)	14.628(1)
α/°,	89.63(1)	90	90
β/°,	77.42(1)	117.85(2)	112.74(3)
γ/°,	63.53(1)	90	90
R	0.0450	0.0463	0.0388

*Structural comparison based on the FTIR spectra of **1**–**5***

The peak positions of some characteristic IR absorption bands of **1**–**5** and those of anhydrous theophylline are summarized in Table 4.

The actual positions of stretching vibrations of the two carbonyl groups in the theophylline moiety have diagnostic value. Their wavenumbers are usually lowered if the carbonyl groups take part in stronger H-bonds compared to the anhydrous theophylline. Their value decreases much more if theophylline looses its N7 proton, and becomes theophyllinate anion [15]. The observed low $\nu_{C=O}$ values for ethanol-

ammonium theophyllinate **1** (**eaH$^+$·th$^-$**) indicated [3] the presence of theophyllinate anion what was confirmed by our single crystal study [18]. In molecules **2**, **3** and **4** the slightly lowered $\nu_{C=O}$ values are attributed to the effect of strong H-bonds in which the neutral theophylline moiety takes part, as can be seen in the crystal structure of theophylline N-(2-ammonium-ethyl)carbamate **3** [18] and implied also by the published IR spectra of theophylline : *p*-nitrophenol (1:1) compound [5]. The protonation of theophylline on N9 position causes only a slight upward shift of $\nu_{C=O}$ wavenumbers compared to the original values of theophylline. In case of theophyllinium salicylic acid 5-sulfonate monohydrate (**5**), the protonation is also confirmed by our single crystal X-ray study [18].

Table 4 Characteristic wavenumbers of IR absorption bands of compounds **1**–**5**

IR absorption	$\nu_{=NH}$ cm^{-1}	$\nu_{NH_3^+}$ cm^{-1}	$\nu_{C=O}$ cm^{-1}	$\nu_{C=O}$ cm^{-1}
Theophylline (anhydrous)	3122	–	1717	1668
Ethanolammonium theophyllinate (**1, eaH$^+$·th$^-$**)	– –	2140 –	– 1674 (1683 [3])	– 1630 1635 [3]
Theophylline : 1,10-phenantroline=1:1 (**2, th·phen**)	3157	–	1703	1651
Theophylline : N-(2-ammonium-ethyl) carbamate=1:1 (**3, th·enCO$_2$**)	3104 3385	– 2180	1702	1651
Theophylline : salicylic acid=1:1 (**4, th·sa**)	3110	–	1703 1679	1650
Theophyllinium salicylic acid 5-sulfonate monohydrate (**5, thH$^+$·saSO$_3^-$·H$_2$O**) (**1:1:1**)	3147	–	1717	1677

Stretching absorption bands of $-NH_3^+$ groups strongly bound by H-bonds were observed in the range of 2100–2200 cm^{-1} for compound **1** and **3**. These bands are originated from ethanolammonium and (2-ammonium-ethyl)carbamate ions, respectively. Specific vibration bands of N7-H7 bonds of the theophylline molecules usually showed various changes, as mentioned in [5], whilst totally disappeared from the theophyllinate compound **1**.

*Simultaneous TG-DTA study of **1**–**5***

The thermal behaviour of theophylline N-(2-ammonium-ethyl)carbamate **3 (th·enCO$_2$)** and theophylline-salicylic acid (1:1) **4 (th·sa)** has been found to be similar to that of ethanolammonium theophyllinate **1 (eaH$^+$·th$^-$)** [3]. Between 120 and 210°C these lattice compounds slowly release ethylenediamine carbamate, salicylic acid and ethanolamine, respectively (Fig. 1, for **1** [3]). All of these constituents, being fairly volatile in this temperature range, leave the system quantitatively, meanwhile anhydrous theophylline remains in the condensed phase. Above 200°C theophylline sublimes, then melts and evaporates, finally leaves the system without residue. The actual temperature range of elimination of the volatile constituents, the observed weight losses compared to the stoichiometric values, and the observed melting point of theophylline for **3**, **4** and **1**, are summarized in Table 5.

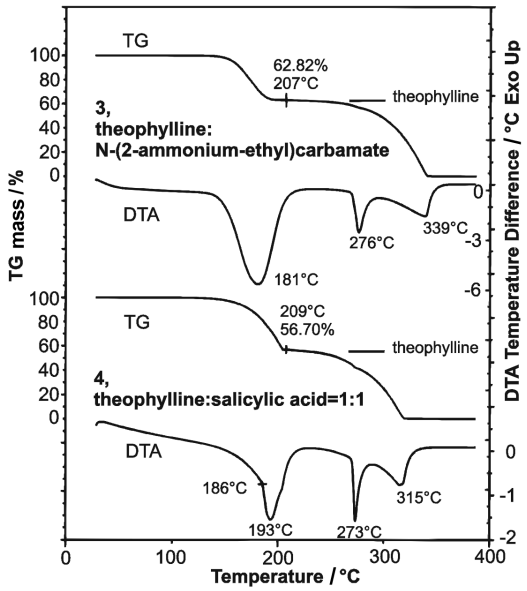


Fig. 1 Simultaneous TG-DTA curves of theophylline N-(2-ammonium-ethyl)-carbamate (1:1) **3** and theophylline salicylic acid (1:1) **4** measured in flowing air (130 mL min^{-1}) with heating rate 10 K min^{-1}, initial mass 18.77 mg and 9.45 mg for **3** and **4**, respectively

Simultaneous TG-DTA curves of **3 (th·enCO$_2$)** and **4 (th·sa)** are shown in Fig. 1. For the salicylic acid lattice compound **4 (th·sa)** a melting point of 183–184°C was reported in [5]. At 186°C, in the middle of the decomposition process we have also observed a slight change in the slope of the DTA curve and which is attributable to the fusion of the non-decomposed fraction of **4**.

Table 5 Temperature range of the first elimination step, the observed and calculated mass losses for 1:1 compounds **1**, **3** and **4**, and the observed melting points of the residual theophylline

Compounds 1:1	Temperature range/°C	Observed mass loss/%	Calculated mass loss/%	Melting points observed for theophylline/°C
Ethanolammonium theophyllinate (**1, eaH$^+$·th$^-$**)	120–180	24.55	25.31 (1 mol ethanolamine)	274
Theophylline : N-(2-ammonium-ethyl)carbamate=1:1 (**3, th·enCO$_2$**)	130–195	37.18	36.62 (1 mol ethylenediamine carbamate)	276
Theophylline : salicylic acid=1:1 (**4, th·sa**)	135–210	43.30	43.40 (1 mol salicylic acid)	273

1,10-Phenanthroline compound **2 (th·phen)** showed a sharp endothermic peak of fusion at 190°C, while the theophyllinium salicylic acid 5-sulfonate monohydrate

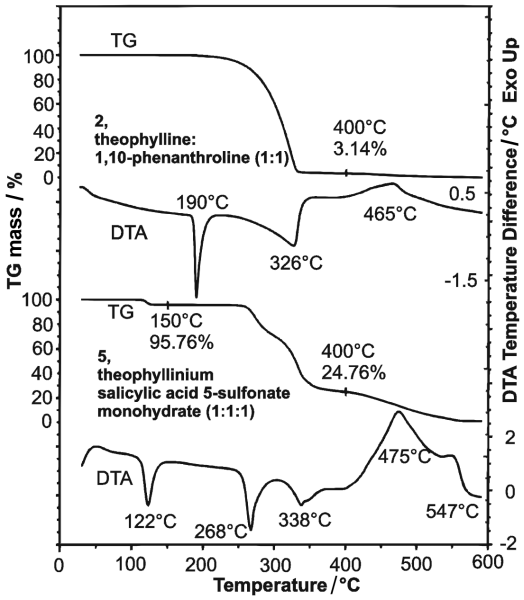


Fig. 2 Simultaneous TG-DTA curves of theophylline 1,10-phenanthroline (1:1) **2** and theophyllinium salicylic acid 5-sulfonate monohydrate (1:1:1) **5** measured in flowing air (130 mL min^{-1}) at heating rate 10 K min^{-1}, initial mass 9.67 and 9.31 mg for **2** and **5**, respectively

5 ($thH^+ \cdot saSO_3^- \cdot H_2O$) lost its one molecule of water of crystallisation between 110 and 135°C (mass loss observed 4.24, calculated 4.33%) and no additional melting of anhydrous 5 was observed (Fig. 2). Between 200 and 400°C both compounds **2** and **5** seemed to go through a complex degradation process, in which the theophylline moiety is also degraded. Neither stoichiometric mass losses nor melting point for theophylline occurred, although at 400°C 3.14 or 24.76% condensed phase residue of **2** and **5** were still present, respectively, which burned out only between 450–600°C.

Conclusions

Comparison of TG-DTA, XRD and FTIR data of compounds **1**–**5** and their parent substances gave indication on formation of new molecular compounds. Combination of TG mass losses with the results of elemental analysis helped us to determine the 1:1 composition of **1**–**5**. Actual form of the theophylline moieties were established according to FTIR spectra, while the structures were proven by single crystal X-ray diffraction studies. The extent of the basicity or acidity of the guest molecules is an important factor, but a certain complexity of structural features also need to stabilize the various ionic and molecular parts of the inclusion compounds [18]. Thermal stability of the five studied compounds seemed to corroborate mainly with the thermal behaviour of the guest molecules.

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