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Thermal and structural study on the lattice compound 1,4-diammoniumbutane bis(theophyllinate)

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Abstract

Crystalline title compound (**1**) prepared from aqueous solution of theophylline and 1,4-diaminobutane has been structurally and thermally characterized. Both the two-step TG decomposition curve and elemental analysis of the hexagonal crystals show that it consists of theophylline and 1,4-diaminobutane in 2:1 molar ratio. Actually, presence of one type of both theophyllinate anions and 1,4-diammoniumbutane dication have been indicated by FTIR spectroscopy. The molecular structure of lattice compound (**1**) has been determined by single crystal X-ray diffraction, where the hydrogen positions have been obtained from differential Fourier maps. It has confirmed that the crystal is really built up from these ionic constituents bound together with an extensive net of hydrogen bonds. The coupled TG-FTIR analysis of the evolved gases has revealed that the diamine is released as a whole molecule in the first decomposition step. Clathrate **1** and the proton migration in it might serve as a structural model of solid aminophylline whose crystal structure is still unknown.

Keywords: Theophylline; Putrescine; Simultaneous TG-DTA; Single crystal X-ray diffraction; Coupled TG-EGA-FTIR

1. Introduction

Theophylline is a drug used in treatment of acute asthma, in tremor therapy and as diuretics. Its application hampered by its low water solubility can be improved by addition of various acid or base molecules of organic solubilizers. Injection of aminophylline containing both theophylline and ethylenediamine is already incorporated as a drug formulation into several Pharmacopoeias [1–3]. Various efforts to prepare this solid lattice compound of theophylline, ethylenediamine and water in 2:1:1 molar ratio were already taken [4,5]. FTIR spectroscopy on this substance shows that theophyllinate anions and ethyleneammonium cations are present, but the crystal structure of solid aminophylline has not been published yet. Detailed investigation of thermal decomposition products of solid aminophylline by TG-DTA, FTIR spectroscopy and powder X-ray diffraction was carried out by Nishijo and Takenaka [5].

There are also several attempts on replacement of ethylenediamine with other solubilizers, because a few people are sensitive to this drug's component [6–9]. Nishijo *et al.* synthesized theophylline complexes with a series of α,ω-alkanediamines including 1,4-diaminobutane as well, and examined them by TG and DTA, powder XRD and FTIR spectroscopy. They found that theophylline was present in double molar ratio compared to the diamine in these lattice compounds [10]. They have also attempted to prepare further solid molecular compounds with several aliphatic and aromatic monoamines. The synthesized substances obtained in 1:1 molar ratio were investigated with the same methods [3,11]. As part of our ongoing research on lattice compound formation of theophylline with alkaline, neutral and acidic organic molecules we have recently reported, among others, a successful preparation of crystalline compounds with 2-aminoethanol, ethylenediamine carbamate and 5-sulfosalicylic acid [12], whose crystal and molecular structures have also been determined by single crystal X-ray diffraction showing the presence of theophylline in three different forms, as theophyllinate anion, neutral molecule and theophyllinium cation, respectively [13,14].

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Here we report preparation, detailed structural (FTIR spectroscopy, single crystal X-ray diffraction), and thermoanalytical (simultaneous TG/DTA, coupled TG–EGA–FTIR) study of crystalline 1,4-diammoniumbutane bis(theophyllinate), which may serve as a structural model for the solid aminophylline.

2. Experimental

2.1. Preparation of lattice compound of theophylline with 1,4-diaminobutane

Anhydrous theophylline (180.2 mg, 1 mmol) was dissolved by intense stirring in 8 ml aqueous solution of 1,4-diaminobutane (0.5 ml, 4.97 mmol). Two solutions were prepared in this way, one of them was held in a refrigerator, while the other one was left at room temperature. Both solutions were covered by punched parafilm to slow down evaporation of the solvent, and in a week hexagonal shape crystals appeared in the solutions. They were filtered on glass filter, washed with absolute ethanol and dried in open air at room temperature.

2.2. Elemental analysis

C, H and N analyses of the obtained crystals was carried out by a Heareus-CHN-O-Rapid analyzer in Microanalytical Laboratory of Loránd Eötvös University of Sciences (Budapest, Hungary) (calculated for 1,4-diammoniumbutane bis(theophyllinate) (**1**) $C_4H_{14}N_2{\cdot}2C_7H_7N_4O_2$: 48.21 C%, 6.29 H%, 31.23 N%; measured: 47.99 C%, 6.35 H%, 31.13 N%).

2.3. FTIR spectroscopy

The Fourier transform infrared spectra of the starting materials (1,4-diaminobutane, theophylline) and lattice compound (**1**) were measured by a Bio-Rad Excalibur Series FTS 3000 spectrometer in the range of 4000–400 cm^{-1} using KBr pellets.

2.4. Thermal analysis

Thermal behaviour of the starting substances and the lattice compound were investigated upto 500 °C by a simultaneous TG/DTA apparatus (STD 2960, TA Instruments). Sample sizes of about 8–12 mg, open Pt crucibles, a heating rate of 10 °C/min and Al_2O_3 as reference material were used. The measurements were carried out in flowing air atmosphere at a rate of 130 ml/min.

2.5. X-ray diffraction

X-ray powder patterns of lattice compound (**1**) and the starting anhydrous theophylline were performed on a HZG-4 diffractometer (Jena Zeiss, Freiberger Präzisions Mechanik) using Ni filtered Cu Kα radiation.

Single crystal X-ray data collection of 1,4-diammoniumbutane bis(theophyllinate) (**1**) was performed on an Enraf-Nonius CAD4 single crystal diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) and graphite monochromator at 293(2) K, in the range of $2.38^\circ \leq \theta \leq 34.94^\circ$ using ω–2θ scans. The intensity of three standard reflections were monitored every 60 min. They indicated a crystal decay of 2%, the data were corrected for decay. Cell parameters were determined by least-squares calculation of the setting angles of 25 reflections in the range of $14.99^\circ \leq \theta \leq 16.92^\circ$. A semi-empirical ψ-scan absorption correction was applied to the data, the minimum and maximum transmission factors were 0.941 and 0.950.

2.5.1. Crystal data

Formula $C_{18}H_{28}N_{10}O_4$, Fwt.: 448.50, colourless, block type crystals with the size of 0.45 mm × 0.30 mm × 0.20 mm, monoclinic crystal system, space group $P2_1/n$, $a = 10.595(1)$ Å, $b = 7.794(1)$ Å, $c = 13.221(1)$ Å, $\beta = 94.448(5)^\circ$, $V = 1088.5(2)$ Å^3, $Z = 2$, $F(0\,0\,0) = 476$, $D_x = 1.368$ Mg/m^3, $\mu = 0.101$ mm^{-1}. A total of 5071 reflections were collected of which 4775 were unique [$R(\text{int}) = 0.0085$, $R(\sigma) = 0.0342$]; 2667 reflections were $>2\sigma(I)$. Completeness to $2\theta = 1.000$. The structure was solved by direct methods by the program SHELXS-97 [15]. Anisotropic full-matrix least-squares refinement on F^2 by SHELXL-97 [16] for all non-hydrogen atoms yielded $R_1 = 0.0480$ and $wR_2 = 0.1491$ for 2667 [$I > 2\sigma(I)$] and $R_1 = 0.0945$ and $wR_2 = 0.1617$ for all (4775) intensity data (goodness-of-fit = 0.998; the maximum and mean shift/esd 0.034 and 0.001). Number of parameters = 152. The maximum and minimum residual electron density in the final difference map were 0.403 and −0.204 e Å^{-3}.

Hydrogen atomic positions were calculated from assumed geometries except amino hydrogens those 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 refined.

2.6. Evolved gas analysis

Gases evolved from compound (**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, $d_{\text{in}} = 4$ mm). The FTIR gas cell and the connecting stainless steel tube were kept at 180 °C. About 25 mg of samples was heated up to 500 °C in an open Pt crucible in flowing air atmosphere of 130 ml/min. The heating rate was 10 °C/min. Interferograms were accumulated in every 30 s and spectra of gaseous mixture are obtained at a resolution of 4 cm^{-1}.

3. Results and discussion

The powder XRD profile of the crystals of (**1**) has been different from that of theophylline or anhydrous theophylline monohydrate. It has indicated formation of a new lattice compound containing theophylline.

Fig. 1 shows the compounds TG and DTA curves measured simultaneously in flowing air atmosphere. Decomposition of 1,4-diammoniumbutane bis(theophyllinate) has occurred in two steps. Between 160 and 230 °C the more volatile 1,4-diaminobutane is likely released from the lattice compound and two fold molar amount of theophylline is left behind. The residual anhydrous theophylline sublimes till its melting point at about 275 °C (see DTA curves, Fig. 1) then evaporates without residue. Mass loss observed in the first step till 228 °C has been 19.69%, while the theoretical value corresponding to the elimination of the diamine molecule from (**1**) is 19.65%. At the same time the residual weight 80.31% corresponds to two molecules of anhydrous theophylline (theoretical value is 80.35%). The result of the elemental analysis is also in accordance with the expected composition of (**1**).

Analysis of FTIR spectrum of 1,4-diammoniumbutane bis(theophyllinate) (Fig. 2) has provided information on the actual molecular form of building units in lattice of (**1**). The characteristic absorption bands of carbonyl groups of theophylline have been observed at lower wavenumbers (1686 and 1631 cm^{-1}) than in pure theophylline molecule (1717 and 1667 cm^{-1}). It is a strong indication of N(7) deprotonated theophylline participating also in hydrogen bonds, i.e. theophyllinate anion is present in the crystal lattice as it was observed in the case of ethanolammonium theophyllinate [11–13] and coordination complexes of theophyllinate anion [17,18]. Characteristic absorption band of primary ammonium groups (RNH_3^+) has occurred at 2198 cm^{-1} showing that both amino groups of 1,4-diaminobutane are protonated and these ammonium groups take part in quite strong H-bonds in accordance with the findings of compound of 2-aminoethanol with theophylline [11–13].

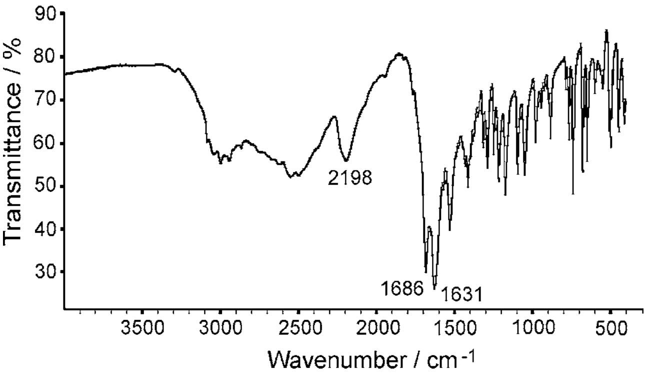

Fig. 2. FTIR spectrum of 1,4-diammoniumbutane bis(theophyllinate) (**1**) using KBr pellet.

The ionic structure of the moieties in (**1**) (Fig. 3) is confirmed by single crystal X-ray diffraction, where the amino hydrogen positions have been calculated from differential Fourier maps. The asymmetric unit contains one theophyllinate anion and a half of the diammoniumbutane dication. The 1,4-diammoniumbutane ion sits on a symmetry centre. Thus the stoichiometric ratio in the adduct is 2:1.

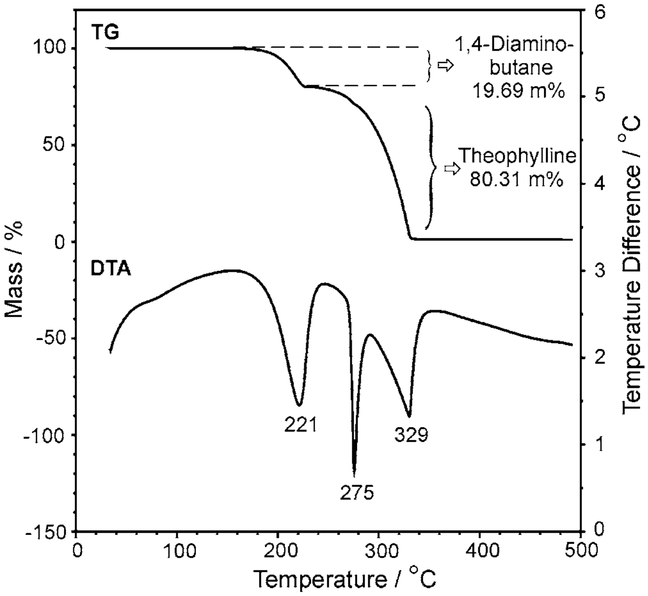

Fig. 1. Simultaneously measured TG and DTA curves of 1,4-diammoniumbutane bis(theophyllinate) (**1**) (initial mass: 10.4592 mg, heating rate: 10 °C/min, air flow of 130 ml/min, open Pt crucible, reference material: α-Al_2O_3).

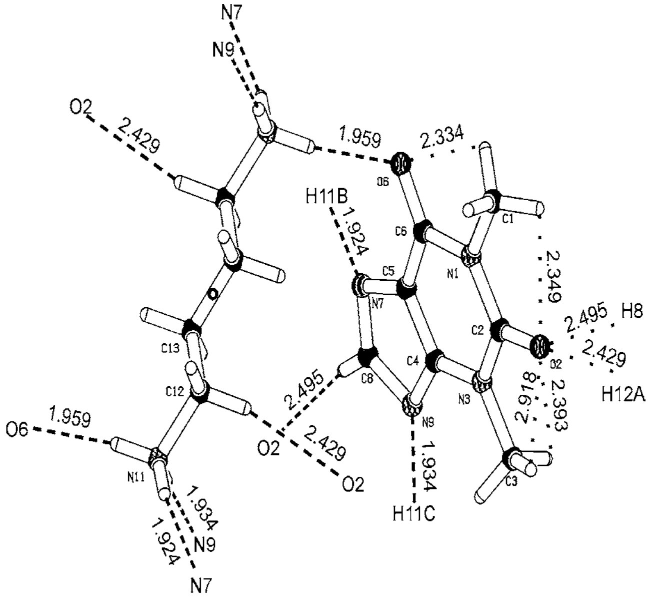

Fig. 3. Molecular structure of 1,4-diammoniumbutane bis(theophyllinate) (**1**). 1,4-Diammoniumbutane cation sits on a symmetry centre, half of this ion can be found in the asymmetric unit. Intermolecular interactions are shown with dotted line. The proton-acceptor (H...A) distances are given in Å.

Table 1
Geometric data of the shortest intermolecular contacts in the molecular lattice of 1,4-diammoniumbutane bis(theophyllinate)

Donor–H. . . acceptor		D–H (Å)	H. . . A (Å)	D. . . A (Å)	D–H. . . A (°)
N(11)–H(11A). . . O(6)	[$-x$, $1 - y$, $-z$]	0.8904	1.9590	2.827(1)	164.57
N(11)–H(11B). . . N(7)	[x, $1 + y$, z]	0.8898	1.9235	2.792(1)	164.65
N(11)–H(11C). . . N(9)	[$1/2 - x$, $1/2 + y$, $1/2 - z$]	0.8903	1.9335	2.817(1)	171.47
C(8)–H(8). . . O(2)	[$-1/2 + x$, $1/2 - y$, $1/2 + z$]	0.9305	2.4954	3.409(2)	167.02
C(12)–H(12A). . . O(2)	[$1 - x$, $1 - y$, $-z$]	0.9695	2.4285	3.379(1)	166.51

D: donor; A: acceptor; H: hydrogen.

Table 2
C−H. . . ring distances of the terminal methyl groups to the closest six- and five-membered ring (Cg(1): N7, C5, C4, N9, C8 and Cg(2): N1, C2, N3, C4, C5, C6)

X–H(*I*)	Cg(*I*)		H. . . Cg (Å)	X–H. . . Cg (°)	X. . . Cg (Å)
C(1)–H(1C)–>	Cg(1)	[$1 - x$, $-y$, $-z$]	3.1768	127.50	3.8375(16)
C(3)–H(3A)–>	Cg(2)	[$1 - x$, $1 - y$, $-z$]	3.3078	119.35	3.8702(17)
Cg(I)	*x*	*y*	*z*		
Cg(1)	0.31508(4)	0.17841(7)	0.12821(3)		
Cg(2)	0.41633(4)	0.20483(6)	−0.00066(3)		

Where the Cg(I) refer to the ring centre-of-gravity.

In the theophylline molecule the rotation of the terminal methyl groups C1 and C3 is blocked by the intramolecular C–H . . . O interactions to the neighbouring oxygen atoms O2 and O6 (O2. . . H(3A) 2.3487 Å; O2. . . H(1C) 2.3927 Å; O2. . . H(1A) 2.9183 Å; O6. . . H(1B) 2.3341 Å). The geometric data of these intermolecular contacts are summarized in Table 1. The system of hydrogen bonds built up three infinite two-dimensional networks (chains): N11-O6–N11-O6 approximately in the *a* crystallographic direction, N11-N7–N11-N7 approximately in the *b* crystallographic direction and N11-N9–N11-N9 approximately in the *c* crystallographic direction. Packing diagram is shown in Fig. 4. The distance of the six-membered ring of theophyllines along the *b* crystal axis is 3.651 and 4.930 Å, respectively. C–H. . . ring distances of the terminal methyl groups to the closest six- and five-membered ring are given in Table 2.

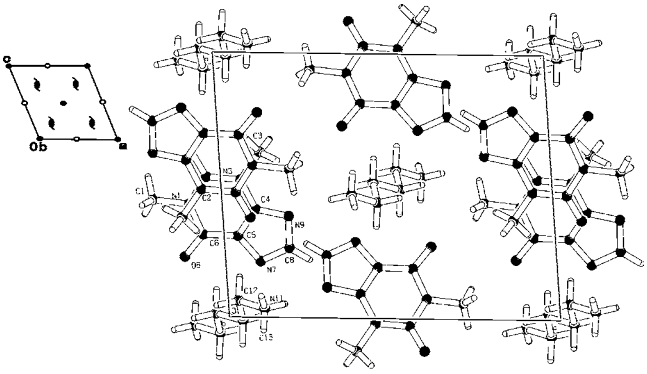

Fig. 4. The crystal structure viewed from the *b* crystallographic axis shows the columns of theophyllinate and diammonium-butane moieties, respectively perpendicular to the sheet. Every column is surrounded by four columns of the other organic ion. The symmetry centres drawn by a full circle on the inset represents those inversion centres that generate the diammonium-butane cations. The symmetry centres drawn by an open circle on the inset represents the inversion centres, which generates pairs of theophylline anions.

We have applied evolved gas analysis by coupled TG-FTIR spectroscopy to check the identity of the released gaseous species. With help of the public FTIR gas spectrum library of NIST [19] it can be seen that whole molecules of 1,4-diaminobutane are released in the first decomposition step of (**1**) even in flowing air, and no degradation or oxidation of the diamine occurred. Thus it has been confirmed that during the heating a migration of protons from the diammonium salt towards the theophyllinate anions takes place, and the neutral molecules of 1,4-diaminobutane leaves the lattice. After melting the residual anhydrous theophylline evaporates also as neutral molecule until 340 °C, as could be identified on the basis of its FTIR gas spectrum.

4. Conclusion

Crystalline powder and single crystals of a new lattice compound (**1**) containing theophylline and 1,4-diaminobutane has been prepared. Structure of the obtained 1,4-diammoniumbutane bis(theophyllinate) has been determined by single crystal X-ray diffraction. Both FTIR spectroscopy and single crystal X-ray diffraction have proved the presence of theophyllinate anions and diammonium cation formed from the starting components by proton migration. During a two-step thermal decomposition of (**1**) followed by simultaneous TG/DTA and EGA–FTIR spectroscopy, at first 1,4-diaminobutane as a neutral whole molecule has left the clathrate compound and anhydrous theophylline has remained in the solid state. That means also a solid state migration of proton backwards, i.e. from the diprotonated cation toward the theophyllinate moieties. The remaining anhydrous theophylline sublimes, melts and evaporates with the rising temperature.

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