BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
DEPARTMENT OF INORGANIC AND ANALYTICAL CHEMISTRY

Theses of the Ph.D. dissertation

Preparation, thermal, analytical and structural study on new lattice compounds of theophylline

By

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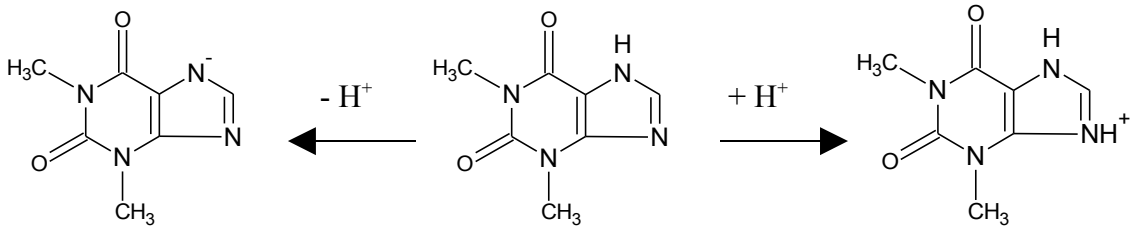
1. Introduction

Theophylline - one of the methyl-xanthines - is a drug used in treatment of acute asthma and as diuretics that is produced in form as solid medicament and injection as well.

Its application hampered by its low water solubility can be improved by addition of various acid or base molecules of organic solubilizers. Aminophylline – stoichiometric ratio of that is theophylline : ethylenediamine : water = 2 : 1 : 1 – contains ethylenediamine to rise the water solubility of theophylline, but a lot of people, especially Caucasian women are sensitive for that. For this reason, more and more scientific studies and researches are interested in new effectual medicaments taking effect acute asthma, and there are more and more experiments with additional solubilizers to prepare new molecular compounds containing theophylline. Expected values of solubility of the new inclusion compounds may be between that of the starting materials.

The theophylline as amphoteric unit might occur either as neutral, anionic or cationic constituent in lattice compounds depending on both the strength of acid/base character of organic solubilizer and opportunities for stabilization by hydrogen bonding system.



theophyllinate anion theophylline theophyllinium cation

2. Aims

The aim of my work was to prepare and to study analytical, thermal and structural properties of new molecular compounds containing theophylline, moreover to describe the thermal decomposition of starting materials and aminophylline as model compound. It was an interesting aim of my work to clear up the amphoteric features of theophylline in the inclusion compounds. Analytical properties, thermal behaviours and structures of the new molecular compounds, co-crystals and other samples have been prepared by myself have been investigated by several up-to-date analytical methods. My work was also aimed at finding correlations among structures and analytical features.

My primary aim was to find solubilizers being suitable for preparation of solid molecular compounds and co-crystals. Physiological effects of the solubilizers have been left out of consideration in my experiments.

The investigation of secondary adhesive force in the lattice compounds and of theophylline's amphoteric properties was in the middle of my research. The strength of adhesive force in molecular compounds was examined by means of thermal behaviour and stability of solid samples, as well.

Goal of mine was also to reproduce some molecular compounds on the basis of literary data and to investigate them to complete my experiences and my FTIR database related to inclusion compounds containing theophylline.

My work was aimed at finding and describing a crystal structure that could be model for the structure of aminophylline as well, because up to the present the crystal structure of aminophylline is not described yet in the literature by single crystal X-ray diffraction. For this reason I have tried to prepare new inclusion compounds containing ethylenediamine and its analogues as well.

3. Preparation of new molecular compounds containing theophylline and applied analytical methods

In the course of my experiments the quantity of the starting materials, *i.e.* anhydrous theophylline and one of the 29 solubilizers, was 1-1 mmol. Generally the solvent was distilled water except in the case of urea and its derivatives, where used both distilled water and ethanol based on literary data. Several times the molar ratio of the starting materials was different compared to the previously mentioned values.

At first, on the basis of both FTIR spectra and powder X-ray diffraction patterns the quality of the samples could be determined. I have drawn structural conclusion from positions, intensities and existence of characteristic bands in FTIR spectra.

When the sample have been proved to be a molecular compound, or when I could not preclude the possibility of a mixture on the basis of results of FTIR spectroscopy and X-ray diffraction methods, then I have verified my assumptions by means of combustion (Mrs. Kálmán Medzihradszky DSc – ELTE) and thermal analyses, and I have confirmed the stoichiometric ratio and investigated the thermal behaviour as well.

Thermal stabilities of the lattice compounds were investigated by simultaneous thermogravimetry and differential thermal analysis coupled online with in situ evolved gas analysis (TG/DTA-MS and TG-FTIR).

My conclusions for structures of inclusion compounds have been confirmed by results of single crystal X-ray diffraction methods (Petra Bombicz PhD– MTA) if suitable single crystals have developed during preparation processes, and so I could confirm my structural assumptions as well.

There are some photos from some crystals by optical and scanning electron microscopy, and for good cause NMR spectra of some samples have been measured (András Simon PhD– BME), too.

Applied analytical methods and apparatuses

Powder X-ray diffraction (XRD)

Jena-Zeiss HZG4 Freiberger Präzisions Mechanik

PANalytical X'Pert Pro MPD

Fourier transform infrared spectroscopy (FTIR)

Bio-Rad Excalibur Series FTS 300

Simultaneous DTA-TGA (TG/DTA)

TA Instruments SDT 2960 Simultaneous DTA-TGA

Combustion analysis (CHN)

Heraeus CHN-O-RAPID (ELTE, Mrs. Kálmán Medzihradszky DSc)

Evolved gas analytical methods

TG/DTA-MS (Evolved gas analyses by online coupled TG/DTA-MS)

TA Instruments SDT 2960 Simultaneous DTA-TGA

Balzers Instruments Thermostar GSD 300 T3

TG-FTIR (Evolved gas analyses by online coupled TG-FTIR):

TGA 2050 Thermogravimetric Analyzer

Bio-Rad Excalibur Series FTS 300

Single Crystal X-ray diffraction (Single Crystal XRD)

Enraf-Nonius CAD4

Rigaku RAXis Rapid Image Plate

(MTA, Petra Bombicz PhD)

Nuclear magnetic resonance spectroscopy (NMR)

Bruker Avance DRX-500

(BME, András Simon PhD)

Scanning electron microscopy (SEM)

JEOL JSM-5500 LV Scanning Electron Microscope

(BME, Máté Dervarics)

Optical microscopy (OM)

LEICA MZ6 optical microscope and JVC GCX3 digital camera

4. New scientific results

New scientific results in connection with solid aminophylline

4.1. The strength of linkage among water, ethylenediamine and theophylline in the solid aminophylline has been cleared up by evolved gas analysis methods (TG/DTA-MS and TG-FTIR). On the basis of dynamics of gaseous species' evolution has been established that the evolution rate of water of crystallization from aminophylline reaches a maximum at lower temperature than that of ethylenediamine, so the water of crystallization leaves easier from molecular compound [1].

4.2. *Trans*-1,4,5,8-tetraazadecaline has been found and identified by several analytical methods (XRD, FTIR, NMR, TG/DTA-MS and TG-FTIR) as a crystal appearing occasionally in preparation of aminophylline. The finding and the identification of this previously not published, potential contamination confirm the necessity of storage of diamines excepting carbon-dioxide [2].

4.3. Thermal stability and thermal degradation processes of α,ω-alkanediamine carbamates ($[^{+}NH_3(CH_2)_nNHCOO^{-}]$, where n = 2, 3, 4 and 6) have been determined by evolved gas analysis methods (TG/DTA-MS and TG-FTIR). It has established that elimination of carbon-dioxide at about 140˚C almost independent from length of carbon-chain [1].

Preparation and analytical, structural, thermal study of new inclusion compounds containing theophylline

4.4. Seven pieces of new molecular compound containing theophylline have been prepared (*Figure 1*) which have contained the theophylline as either neutral or ionic form.

The structures of the co-crystals (*Figure 1*) have been described on the basis of results of several analytical methods (XRD, FTIR, TG/DTA and combustion analysis). By managing to prepare single crystals, we could confirm my conclusions from analytical results for crystal structures by single crystal X-ray diffraction analyses, as well [3-7].

Results collected in the course of my researches have been used for determination of structure of solid aminophylline.

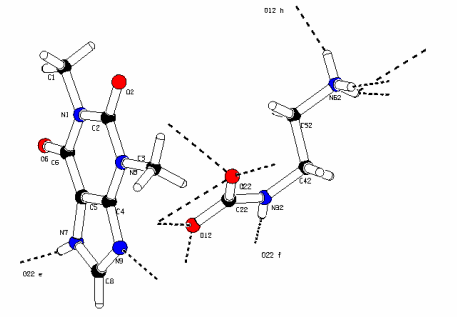
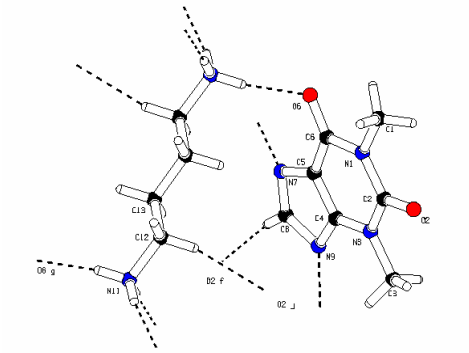
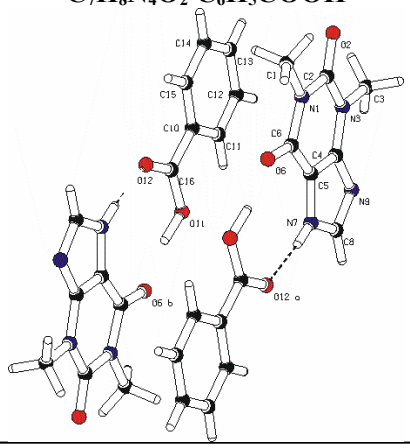
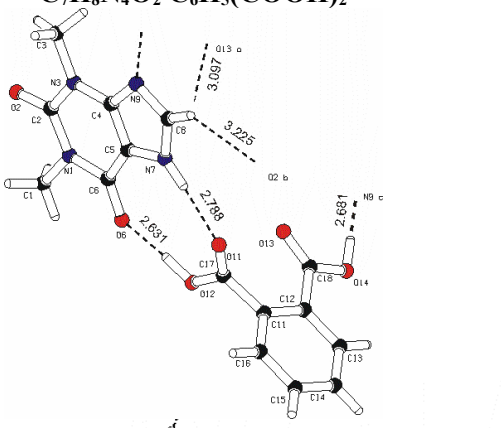
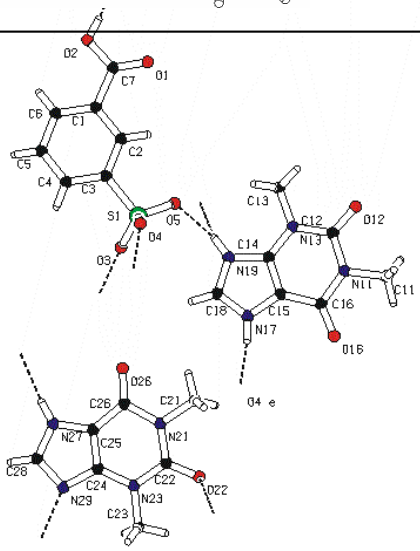
<table>
<tr><th colspan="2">Crystal structures proved by single crystal X-ray diffraction analyses</th></tr>
<tr><td>theophylline ethylenediamine carbamate [3]
$C_7H_8N_4O_2$·[NH_3^+-CH_2-CH_2-NH-COO^-]
  </td><td>1,4-diammoniumbutane bis(theophyllinate) [4]
[NH_3^+-$(CH_2)_4$-NH_3^+]·[$C_7H_7N_4O_2^-$]$_2$
  </td></tr>
<tr><td>theophylline–benzoic acid [5]
$C_7H_8N_4O_2$·C_6H_5COOH
  </td><td>theophylline–phthalic acid [6]
$C_7H_8N_4O_2$·$C_6H_5(COOH)_2$
  </td></tr>
<tr><td colspan="2">theophylline – theophyllinium – 3-carboxy-benzolsulfonate [7]
$C_7H_8N_4O_2$·[$C_7H_8N_4O_2^+$]·[HOOC-C_6H_4-SO_3^-]
  </td></tr>
<tr><th colspan="2">Crystal structures proved by other analytical measurements</th></tr>
<tr><td>inclusion compound of theophylline containing cytosine [5]
$C_7H_7N_4O_2^-$·$C_4H_6N_3O^+$</td><td>inclusion compound of theophylline containing benzotriazole [5]
$C_7H_8N_4O_2$·$C_6H_5N_3$·0.5H_2O</td></tr>
</table>

Figure 1. New inclusion compounds prepared by myself

4.5. Correlation of analytical and structural features of new (*Figure 1.*) and two reproduced molecular compounds (inclusion compounds of theophylline containing cytosine and benzotriazole: {$C_7H_8N_4O_2 \cdot O{=}\ C(NH_2)_2$} and {$C_7H_8N_4O_2 \cdot C_5H_5N_5 \cdot 0.5H_2O$}) has been executed in the course of my researches.

Thermal degradation processes of inclusion compounds have been characterised by evolved gas analytical methods (TG/DTA-MS and TG-FTIR).

The correlations between analytical properties and structures of molecular compounds have been determined.

It has been shown that the shifts of characteristic FTIR bands of carbonyl groups of the theophylline depend on form of theophylline in the molecular compounds. In the case of theophyllinate anions the characteristic FTIR bands of carbonyl groups of the theophylline have appeared at lower wavenumbers than that of pure theophylline and in the case of presence of theophyllinium cations have been experienced increase of wavenumbers (*Table 1*).

Table 1.
Characteristic FTIR bands of carbonyl groups of theophylline in several molecular compounds
(Different forms of theophylline are indicated by different colours in the table. Blue: neutral theophylline molecule, green: theophyllinate anion, red: theophyllinium cation.)

Compound	$\nu_{C(2)=O}$ **(cm^{-1})**	$\nu_{C(6)=O}$ **(cm^{-1})**
Anhydrous theophylline $C_7H_8N_4O_2$	1717	1668
Theophylline ethylenediamine carbamate ($C_7H_8N_4O_2 \cdot [NH_3^+\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}COO^-]$)	1702	1651
1,4-diammoniumbutane bis(theophyllinate) ($[NH_3^+\text{-}(CH_2)_4\text{-}NH_3^+] \cdot [C_7H_7N_4O_2^-]_2$)	1686	1631
Theophylline–benzoic acid ($C_7H_8N_4O_2 \cdot C_6H_5COOH$)	1719	1671
Theophylline–phthalic acid ($C_7H_8N_4O_2 \cdot C_6H_5(COOH)_2$)	1710	1648
Theophylline – theophyllinium – 3-carboxy-benzolsulfonate ($C_7H_8N_4O_2 \cdot [C_7H_8N_4O_2^+] \cdot [HOOC\text{-}C_6H_4\text{-}SO_3^-]$)	1728 1712	1681 1653
Inclusion compounds of theophylline containing adenine ($C_7H_8N_4O_2 \cdot C_5H_5N_5$)	1703	1648
Inclusion compounds of theophylline containing cytosine ($C_7H_7N_4O_2^- \cdot C_4H_6N_3O^+$)	1687	1647
Inclusion compounds of theophylline containing benzotriazole ($C_7H_8N_4O_2 \cdot C_6H_5N_3 \cdot 0.5H_2O$)	1702	1658
Inclusion compounds of theophylline containing urea ($C_7H_8N_4O_2 \cdot O{=}C(NH_2)_2$)	1693	1649

4.6. Theophylline – theophyllinium – 3-carboxy-benzolsulfonate ($C_7H_8N_4O_2 \cdot [C_7H_8N_4O_2^+] \cdot [HOOC\text{-}C_6H_4\text{-}SO_3^-]$) has been prepared and investigated as a new crystal structure that has not published previously in the chemical literature.

The molar ratio of co-crystals has been determined as theophyllinium : 3-carboxy-benzolsulfonate = 2 : 1 first of all on the basis of results of FTIR spectroscopy and combustion analysis.

The twofold theophylline exist both neutral molecules and cations in the molecular compound.

In the crystal lattice the layers of neutral theophylline molecules alternate the ionic layers of theophyllinium cations and 3-carboxy-benzol-sulfonate anions which has been determined by single crystal X-ray diffraction analysis.

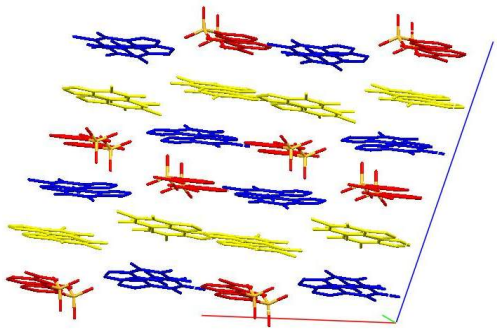


Figure 2. Structure of theophylline – theophylinium – 3-carboxy-benzolsulfonate's crystals: ionic and neutral layers in the same unit cell
(red: 3-carboxy-benzolsulfonate anion, blue: theophyllinium cation, yellow: neutral theophylline molecule)

4.7. On the basis of my experiments it has been established that the form of amphoteric theophylline in its molecular compounds does not depend unambiguously on the characteristics of solubilizers. The acidic or basic character of the solubilizers is necessary but not sufficient condition to form a new lattice compound.

It has been established that the more possibility exist to build H-bonds the more likely is the crystallization of a new molecular compound.

It has been determined that the quality and quantity of the possible H-bonds is the main condition for forming of the rare theophyllinium cations.

5. Application of the new scientific results

The most of experiments in my Ph.D. thesis belong to basic research, but results could be used in the real life, in the pharmaceutical industry to preparation new molecular compounds containing theophylline and to examine that of structures and thermal behaviour.

Decomposition of solid aminophylline has been investigated by gaseous species developing during heating. Description of aminophylline's thermal degradation processes could give more information in connection with transport and storage of solid medicament in extreme conditions.

The finding and the identification of *trans*-1,4,5,8-tetraazadecaline as a potential contamination in process of preparation of aminophylline confirm the necessity of storage of diamines excepting carbon-dioxide.

Description of thermal degradation processes of α,ω-alkanediamines facilitates their recognition and identification, and gives information in connection with thermal behaviour of other compounds containing carbamate.

Structural and analytical characterization of new molecular compounds prepared by myself contributes to recognize and determined the structure and thermal behaviour of aminophylline molecule. Results of my experiments and measurements could serve ideas for syntheses of new medicaments containing theophylline against acute asthma.

The crystal structure of theophylline-theophyllinium-3-carboxy-benzol-sulfonate is very special, similar structure is not published previously in the chemical literature. This lattice compound contains ionic and neutral layers in the same unit cell which may have great significance in pharmaceutical industry, semiconductor industry or nanotechnology. To use the practical application it needs to know the physicochemical properties (*e.g.* conductivity, electrochemical features *etc.*) of this lattice compound.

6. Publications related to the present work

[1] M. Bán, J. Madarász, G. Pokol, S. Gál,
Evolved gas analysis of aminophylline and related compounds containing theophylline
Solid State Ionics, **172** (2004) 587-589.

Impact Factor: 1.862 Cited references: 1

[2] M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál,
Trans-1,4,5,8-tetraazodecalin crystals occuring in ethylenediamine
Journal of Thermal Analysis and Calorimetry, **78** (2004) 545-555.

Impact Factor: 1.478 Cited references: 2

[3] J. Madarász, P. Bombicz, K. Jármi, M. Bán, G. Pokol, S. Gál,
Thermal, FTIR and XRD study on some 1:1 molecular compounds of theophylline
Journal of Thermal Analysis and Calorimetry, **69** (2002) 281-290.

Impact Factor: 0.598 Cited references: 11

[4] M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál,
Thermal and structural study on the lattice compound 1,4-diammoniumbutane bis(theophyllinate)
Thermochimica Acta, **420** (2004) 105-109.

Impact Factor: 1.161 Cited references: 2

[5] M. Bán, J. Madarász, G. Pokol, S. Gál
Combined analytical characterization and evolved gas analysis of new inclusion compounds containing theophylline
Journal of Analytical and Applied Pyrolysis (submitted) Reference number: 8902

[6] M. Bán, P. Bombicz, J. Madarász
Thermal stability and structure of a new co-crystal of theophylline formed with phthalic acid.
Evolved gas analytical (TG/DTA and TG-FTIR) studies.
Journal of Thermal Analysis and Calorimetry (submitted)

[7] M. Bán, P. Bombicz, J. Madarász
Molecular condensator: neutral and ionic alternating molecular layers of theophylline and its organic salt.
Chemical Communications (in preparation)

7. Oral and poster presentations on the subject of the dissertation

Oral presentations:

M. Bán, J. Madarász, P. Bombicz, R. Dorogi, G. Pokol, S. Gál
Thermal and structural elucidation of crystals occurring in ethylenediamine
Conference of Analytical Chemistry, 2004, Hungarian Chemical Society, June 30- July 2, 2004, Balatonföldvár, Hungary

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural study on lattice compounds of theophylline
Analytical Days of Hungarian Chemical Society, January 29-30, 2003, Budapest, Hungary

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural study on lattice compounds of theophylline
VIII. International Conference of Chemists, November 15-17, 2002, Cluj Napoca, Romania

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural study on lattice compounds of theophylline with ethylenediamine analogues
XXV. Chemical Discussion Days; October 28-30, 2002, Szeged, Hungary

Poster presentations:

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Structural and evolved gas analytical (TG/DTA-MS and TG-FTIR) study of a new inclusion compound, theophylline – phthalic acid
Calorimetry and Thermal Analysis Conference (CALCAT ’06)
July 9-12, 2006, Santiago de Compostela, Spain

M. Bán, J. Madarász, G. Pokol, S. Gál
Analytical characterization and evolved gas analysis of new inclusion compounds containing theophylline
17th International Symposium on Analytical and Applied Pyrolysis (Pyrolysis 2006)
May 21-26, 2006, Budapest, Hungary

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural elucidation of crystals occurring in ethylenediamine. Evolved gas analyses on trans-1,4,5,8- tetraazodecalin.
The 13th International Congress on Thermal Analyses and Calorimetry (ICTAC 13),
September 12-19, 2004, Chia Laguna, Sardinia, Italy

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural elucidation of crystals occurring in ethylenediamine. Evolved gas analyses on trans-1,4,5,8- tetraazodecalin.
3rd International Conference on Global Research and Education in Intelligent Systems (Inter-Academia 2004), September 6-9, 2004, Budapest, Hungary

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural study on lattice compounds of theophylline with ethylenediamine analogues
2nd International Conference on Global Research and Education, Inter-Academia 2003,
September 8-12, 2003, Warsaw, Poland

M. Bán, J. Madarász, P. Bombicz, G. Pokol, S. Gál
Thermal and structural study on lattice compounds of theophylline with ethylenediamine analogues
6th Mediterranean Conference on Calorimetry and Thermal Analysis, MEDICTA 2003,
July 27-30, 2003, Porto, Portugal

8. Publications not relevant to the thesis

Articles:

[8] Ana Brăileanu, Susana Mihaiu, Margit Bán, J. Madarász and G. Pokol
Thermoanalytical investigation of tin and cerium salt mixtures
Journal of Thermal Analysis and Calorimetry, **80** (2005) 613-618.

Impact Factor: 1.478 Cited references: 0

[9] S. Mihaiu, A. Brăileanu, M. Bán, J. Madarász, G. Pokol
Sn-Ce-O advanced materials obtained by thermal decomposition of some precursors.
Journal of Optoelectronics and Advanced Materials, **8** (2006) 572-575

Impact Factor: 1.138 Cited references: 0

Poster presentations:

M. Bán, J. Madarász, G. Pokol, S. Gál
Thermal degradation and analytical characterization of nystatin
9th European Symposium on Thermal Analysis and Calorimetry (ESTAC 9)
August 27-31, 2006, Krakow, Poland

A. Brăileanu, S. Mihaiu, M. Bán, J. Madarász, G. Pokol
Phase evolution in Sn-Ce-O materials obtained by the thermal decomposition of some precursors
The 13th International Congress on Thermal Analyses and Calorimetry (ICTAC 13),
September 12-19, 2004, Chia Laguna, Sardinia, Italy

A. Brăileanu, S. Mihaiu, M. Bán, J. Madarász, G. Pokol
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