

TRANS-1,4,5,8-TETRAAZODECALIN CRYSTALS OCCURRING IN ETHYLENEDIAMINE Structural elucidation and evolved gas analyses

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Abstract

Composition and structure of crystals of unknown origin, crystallizing spontaneously from ethylenediamine on standing, has been determined by elemental analysis, FTIR, ¹H and ¹³C NMR spectroscopy and X-ray diffraction. The crystal with molecular formula C₆H₁₄N₄ has been found to be a highly symmetric saturated imino compound with double-ring structure, and unambiguously identified as *trans*-1,4,5,8-tetraazodecalin by ¹H NMR and powder X-ray diffraction based on both its specific AA'BB' spin coupling system and simulated XRD pattern calculated from available data of previous single crystal structure determination, respectively.

Simultaneous TG/DTA measurement shows one-step degradation of this compound. The volatile decomposition products have been followed by both TG/DTA-MS and TG-FTIR. Group of the largest fragments (*m/z*=80, 81 and 82) observed by TG/DTA-MS corresponds to an aromatic 1,4-diazine (pyrazine). In the EGA-FTIR spectrum of released gaseous species measured at the highest evolution rate by TG-FTIR, ethylenediamine can be identified as another decomposition product.

Keywords: aminophylline, 1,4-diazine, ethylenediamine, TG/DTA-EGA-MS, TG-EGA-FTIR, *trans*-1,4,5,8-tetraazodecalin

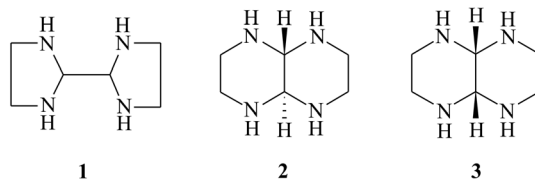
Introduction

Ethylenediamine is a solubilizer of theophylline in aminophylline which is a drug for treatment of acute asthma [1–3]. Ethylenediamine with carbon dioxide of air forms two polymorphs of ethylenediamine carbamate at room temperature [4]. Nevertheless, we have observed from time to time a spontaneous crystallization of translucent prisms of crystals from ethylenediamine stored in closed vessel at room temperature, which have been different from the carbamate polymorphs and may cause a contamination of

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aminophylline later. Our preliminary investigation on the filtered crystals indicates that it is a saturated imino compound, $C_6H_{14}N_4$ with a highly symmetric double-ring structure. Some of the candidate compounds are shown in Scheme 1.



Scheme 1 Highly symmetric double-ring isomers with $C_6H_{14}N_4$ composition: (1) 2,2'-bisimidazolidine, (2) *trans*-1,4,5,8-tetraazodecalin, (3) *cis*-1,4,5,8-tetraazodecalin

Our literature search shows that each of these compounds could be formed from ethylenediamine with some simple or sophisticated reagents. Rezende *et al.* [5, 6] prepared 2,2'-bisimidazolidine (**1**) from cooled solutions of ethylenediamine adding various reactants (e.g. carbon dioxide, hexachloroacetone, ethyl trichloroacetate, etc.), and characterized it with its MS fragments and data of 1H and ^{13}C NMR spectra measured in D_2O (Table 1). Melting point of 2,2'-bisimidazolidine (**1**) was measured to be 182–184°C.

Ring closure reactions of ethylenediamine to tetraazodecalins were also observed. Castellani-Bisi *et al.* [7] reported such a reaction of ethylenediamine with oxygen in presence of lanthanum chloride, checked by mass spectrometry. ‘Naphthpiperazin’ (1,4,5,8-tetraazodecalin) was also prepared from ethylenediamine and 1,2-dichloro-1,2-diethoxy-ethane by Baganz *et al.* [8]. After recrystallization from ethanol the melting point of the product was 195°C.

Trans-1,4,5,8-tetraazodecalin (**2**) was prepared by Fuchs and Ellenweig [9] in reaction of ethylenediamine with glyoxal. They studied in details also *cis* and *trans* isomers of various substituted 1,4,5,8-tetraazodecalins by 1H NMR and ^{13}C NMR in order to unambiguously establish their structural assignments. They calculated the theoretical 1H NMR spectrum of $N-CH_2-CH_2-N$ moiety of *trans*-1,4,5,8-tetraazodecalin (**2**) by LAOCN3 method in comparison with its experimentally measured 1H NMR spectrum at 300 MHz. The NMR data available in the special literature for compounds **1–3** are listed in Table 1.

Müller *et al.* [10] reported also a study of some known and new 1,4,5,8-tetraazodecalin derivatives including *trans*- (**2**) and *cis*-1,4,5,8-tetraazodecalin (**3**) and characterized them with their 1H , ^{13}C and ^{15}N NMR spectra (Table 1).

From ethylenediamine and glyoxal as starting materials Ferrari *et al.* [11] prepared also *trans*-1,4,5,8-tetraazodecalin (**2**). After recrystallizing from ethanol 1,4,5,8-tetraazodecalin melted with decomposition at 195–198°C. Data of ^{13}C NMR of tetraazodecalin were measured both in D_2O and $CDCl_3$ (Table 1).

Antoine *et al.* [12] applied 1,4,5,8-tetraazodecalins as initial compounds for synthesis of new cyclam-glyoxal diamides. *Trans*-1,4,5,8-tetraazodecalin (**2**) was obtained from ethylenediamine and glyoxal, and characterized by data of ^{13}C NMR measured in D_2O (Table 1).

Table 1 ^1H , ^{13}C and ^{15}N NMR chemical shift data of 2,2'-bisimidazolidine (1), *trans*-1,4,5,8-tetraazodecalin (2) and *cis*-1,4,5,8-tetraazodecalin (3) (in ppm)

| NMR (solvent) | MHz | 2,2'-bis-imidazolidine (1) | <i>Trans</i> -1,4,5,8-tetraazodecalin (2) | <i>Cis</i> -1,4,5,8-tetraazodecalin (3) | Reference |
|---|-------|----------------------------|---|---|-----------|
| ^1H NMR (D_2O) | 200.0 | 2.63, 2.77, 2.90 | | | [5, 6] |
| ^{13}C NMR (D_2O) | 200.0 | 45.9, 74.2 | | | |
| ^1H NMR (D_2O) | 300.0 | | 2.79, 2.94, 3.24 | | [9] |
| ^1H NMR (D_2O) | 360.0 | | 2.79, 2.94, 3.24 | | |
| ^{13}C NMR (D_2O) | 90.5 | | 44.6, 73.0 | 41.0, 64.9 | [10] |
| ^{15}N NMR (D_2O)* | 40.6 | | -331.5 | -339.8 | |
| ^1H NMR (D_2O) | 200.0 | | 2.75, 2.84, 2.99 | | |
| ^{13}C NMR (D_2O) | 50.3 | | 44.8, 73.0 | | [11] |
| ^{13}C NMR (CDCl_3) | 50.3 | | 46.7, 75.0 | | |
| ^{13}C NMR (D_2O) | 75.5 | | 47.2, 75.5 | | [12] |

* ^{15}N -Nitromethane ($\text{CH}_3^{15}\text{NO}_2$) was external reference for ^{15}N NMR [10]

Schnering *et al.* determined the crystal structure of *trans*-1,4,5,8-tetraazodecalin (**2**) twice by single crystal X-ray diffraction. At first they had solved the structure in space group *P1* of triclinic crystal system [13]. Later they refined in monoclinic space group *C2/m* to *R*=0.061 [14]. The molecule has full *2/m* symmetry.

As part of our ongoing research on thermal and structural study of aminophylline [15] and related compounds [16, 17] we report here the identification, structural characterization and evolved gas analysis of *trans*-1,4,5,8-tetraazodecalin (**2**) as a potential contamination of aminophylline preparations. Elemental analysis, FTIR, ¹H and ¹³C NMR spectroscopy and X-ray diffraction methods have been applied for identification of its crystals. Decomposition of *trans*-1,4,5,8-tetraazodecalin (**2**) has been studied by TG/DTA-EGA-MS and TG-EGA-FTIR methods.

Experimental

Sample preparation

Crystals occurred from time to time in ethylenediamine (Merck, 99%, Cat. No. 800.947) were filtered and dried on glass filter with vacuum at room temperature. They were uniform and stable.

Elemental analysis

C, H and N analyses of the filtered crystals was carried out by a Heareus-CHN-O-Rapid analyzer in Microanalytical Laboratory of Eötvös Loránd University of Sciences (Budapest, Hungary) (Calculated for *trans*-1,4,5,8-tetraazodecaline (**2**) C₆H₁₄N₄ 50.68 C%, 9.92 H%, 39.40 N%; measured: 50.86 C%, 9.84 H%, 39.52 N%).

FTIR spectroscopy

The Fourier transform infrared spectrum of the crystals was 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 pattern of crystals was recorded on a HZG-4 diffractometer (Karl Zeiss-Freiberger Präzisions Mechanik) using Ni filtered CuK_α radiation. The simulated XRD pattern of **2** has been calculated from single crystal data of *trans*-1,4,5,8-tetraazodecalin (**2**, reference code: GAZNIE [14, 18]) by using λ(CuK_α)=1.54056 Å.

¹H and ¹³C NMR spectroscopy

¹³C NMR and ¹H NMR spectra of crystals in CDCl₃ were recorded on an Bruker Avance DRX-500 spectrometer at 500 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as internal reference. Number of scans was 20480 in

^{13}C NMR and 16 in ^1H NMR spectrum. Applied pulzus programs were: zgpg30 (^{13}C NMR) and zg30 (^1H NMR).

Simultaneous TG/DTA

Thermal behaviour of the crystals **2** was investigated up to 400°C by a simultaneous TG/DTA apparatus (STD 2960, TA Instruments). Sample sizes of about 8 mg, open Pt crucible, a heating rate of 10°C min⁻¹ and Al₂O₃ as reference material were used. The measurements were carried out in flowing nitrogen and air atmosphere at a rate of 130 mL min⁻¹.

EGA by online coupled TG-FTIR

Gases evolved from crystals **2** 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/Digilab) 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 11 mg of sample was heated up to 400°C in an open Pt crucible in flowing nitrogen and air atmosphere of 120 mL min⁻¹. The heating rate was 10°C min⁻¹. Interferograms were accumulated in every 30 s and spectra (4000–550 cm⁻¹) of gaseous mixture are obtained at a resolution of 4 cm⁻¹.

EGA by online coupled TG/DTA-MS

Gases evolved from crystals **2** heated in the furnace of a simultaneous TG/DTA apparatus (STD 2960, TA Instruments) are led to a quadruple mass spectrometer (Balzers Instruments Thermostar GSD 300 T3) through a heated quartz capillary ($l=1$ m, $d_{\text{in}}=150$ μm). Detector of mass spectrometer (Quadrupole CH-TRON) and the connecting capillary were kept at 200°C. About 8 mg of sample was heated up to 400°C in an open Pt crucible in flowing nitrogen atmosphere of 130 mL min⁻¹. The heating rate was 10°C min⁻¹.

Results and discussion

Structural elucidation of the crystal 2

Elemental analysis and FTIR spectroscopy

Results of elemental analysis (see experimental part) shows that the compound consists of C, H and N only. The smallest possible molecular formula of crystals has been unambiguously calculated as C₆H₁₄N₄. More than 40 molecules with this formula having two double bound equivalents have already been described in Beilstein database of organic compounds [19], but much more structural isomers can exist.

In the FTIR spectrum (Fig. 1) of crystals two important properties are obvious. At 3182 cm⁻¹ only one ν(NH) band occurs, so the compound contains only imino (>NH)

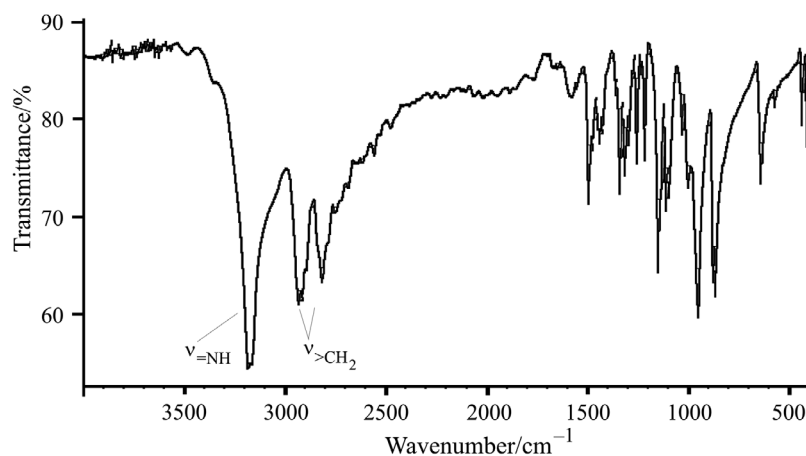


Fig. 1 FTIR spectrum of *trans*-1,4,5,8-tetraazodecalin (**2**) using KBr pellet

group(s), but not amino (NH₂) groups. Above 3000 cm⁻¹ ν(CH) bands do not appear, i.e. the compound does not contain unsaturated =CH groups (ν(CH)=2931 and 2815 cm⁻¹).

NMR spectroscopy

On ¹³C NMR spectrum of crystals only two carbon signals have appeared at 75.76 and 46.53 ppm, what also shows that our compound is a saturated imine, and does not contain any double bonds. The few ¹³C signals belonging to the compound containing at least six carbon atoms refer to a highly symmetric double-ring structure. Structural formulas of the most probable compounds are shown in Scheme 1.

¹H NMR spectrum is shown in Fig. 2. It contains a singlet signal of anellation hydrogens (2H) at 2.99 ppm and a AA'BB' multiplet spin system of -CH₂-CH₂- (8H) between 2.85 and 3.03 ppm coupled in a complex way.

¹H and ¹³C NMR spectra of crystals have been compared with published data of 2,2'-bisimidazolidine (**1**) [5, 6], *trans*- (**2**) and *cis*-1,4,5,8-tetraazodecalin (**3**) [9–12] (Table 1) and the spectra of our unknown compound has been assigned as that of *trans*-1,4,5,8-tetraazodecalin (**2**) based on the simulated and experimental ¹H NMR spectrum found in [9].

X-ray diffraction

The final proof of structure has been achieved by comparison of the experimental and simulated powder X-ray diffraction patterns (Fig. 3, bottom and top, respectively) and unit cell parameters of our crystal with those of *trans*-1,4,5,8-tetraazodecalin (**2**) calculated from available data of its single crystal's structure [14, 18]. The measured and calculated powder X-ray diffraction patterns (Fig. 3) are very similar, distances between each set of atomic planes of the crystal lattice are the same, slight differences appear only in relative intensities of the peaks. Accordingly, we can identify unambiguously the crystals occurring in ethylenediamine as *trans*-1,4,5,8-tetraazodecalin (**2**).

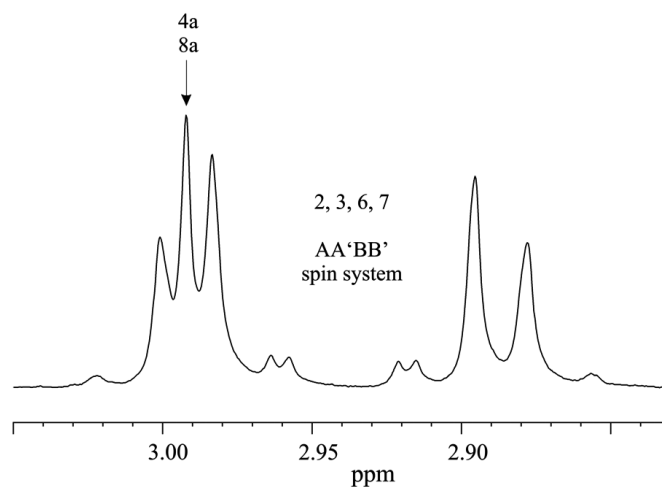


Fig. 2 ^1H NMR spectrum of *trans*-1,4,5,8-tetraazodecalin (**2**) in CDCl_3 , measured at 500 MHz. The signal of hydrogens (4a, 8a) at the anellation is singlet, while the $\text{CH}_2\text{-CH}_2$ protons (at position 2, 3, 6 and 7) give the special multiplet signal

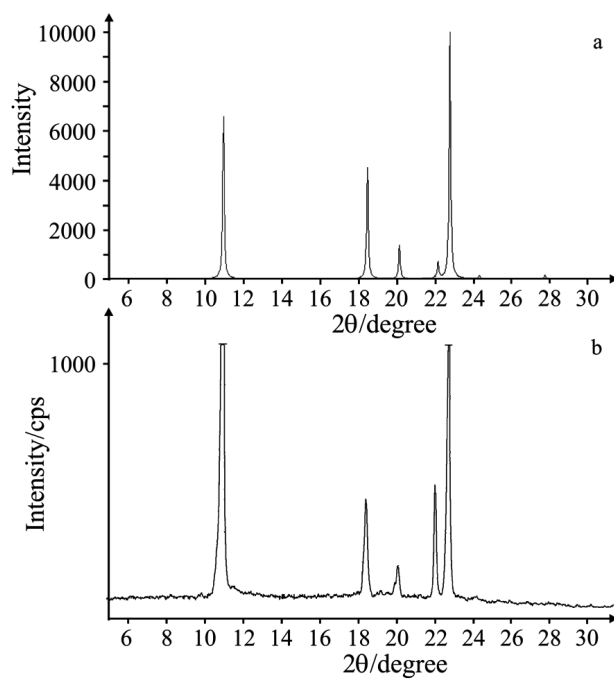


Fig. 3 Powder X-ray diffraction patterns of *trans*-1,4,5,8-tetraazodecalin (**2**). a – simulated according to Refs. [14, 18]; b – measured ($\text{CuK}\alpha$ radiation, $\lambda=1.54056 \text{ \AA}$)

Thermal studies on trans-1,4,5,8-tetraazodecalin (2)

Simultaneous TG/DTA

Figure 4 shows the crystal's TG and DTA curves measured simultaneously in flowing nitrogen atmosphere. The compound is quite stable, it degrades without melting only above 150°C. Its degradation takes place in one step, and leaves a coked final residue of 11.6% at 400°C. The degradation process is accompanied by an endothermic heat effect shown by the endothermic peak on the DTA curve at 233°C.

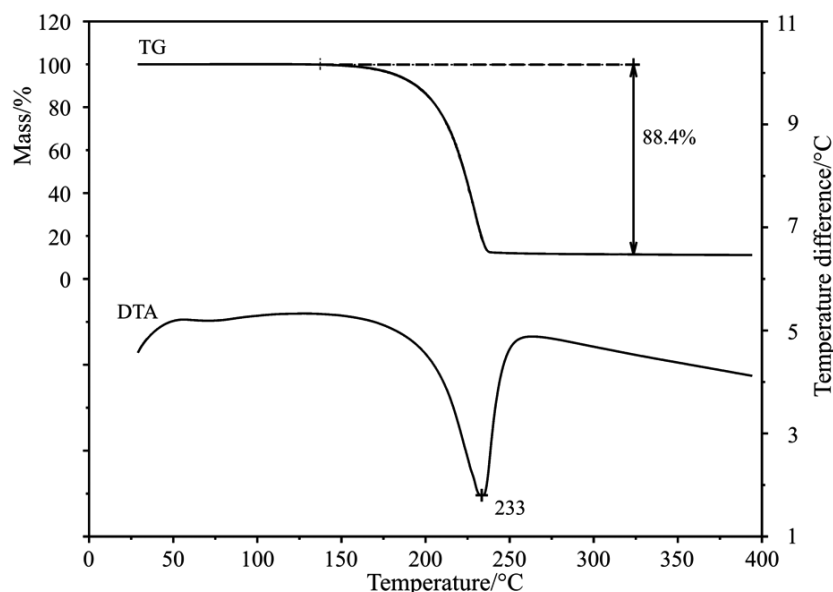


Fig. 4 Simultaneously measured TG and DTA curves of *trans*-1,4,5,8-tetraazodecalin (**2**) in nitrogen (initial mass: 7.99 mg, heating rate: 10°C min⁻¹, gas flow of 130 mL min⁻¹, open Pt crucible, reference material: α -Al₂O₃)

EGA of *trans*-1,4,5,8-tetraazodecalin (**2**) by TG/DTA-MS

Volatile degradation products of the crystals **2** have been measured by TG/DTA-MS (Fig. 5). The largest observed fragments ($m/z=80$, 81 and 82) indicate aromatic pyrazine which have been evolved most probably from tetraazodecalin ring system. Using reference mass spectra of pyrazine (1,4-diazine) [20, 21] we could see that the level of most intense fragments from it ($m/z=80$, 53 and 26) has increased during the main evolution step several magnitudes, and the $m/z=12-13$, 24-27, 37-41, 50-55 groups of ion fragments of pyrazine occurred also with similar dynamics (Fig. 5a). A release and occurrence of ethylenediamine [20, 21] seems to be also possible, judged on the presence of $m/z=15-18$, 27-31, 40-45, 59-61 ion fragment groups (Fig. 5b). Nevertheless presence of simple reduced gas species, as H₂O, NH₃, CH₄ and C₂H₆

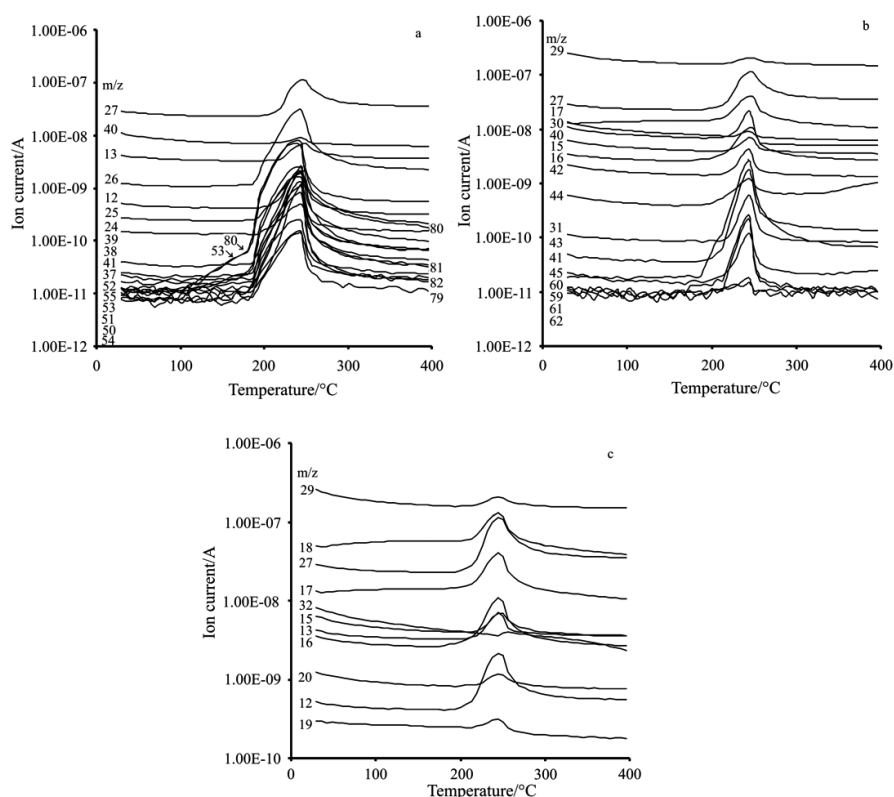


Fig. 5 Ion current vs. temperature curves of ion fragments of volatile degradation products from decomposition of *trans*-1,4,5,8-tetraazodecalin (**2**) in nitrogen measured by online coupled TG/DTA-MS system (initial mass: 7.99 mg, heating rate: 10°C min⁻¹, gas flow of 130 mL min⁻¹). Characteristic fragments of a – pyrazine, b – ethylenediamine, c – water, ammonia, ethane and methane

cannot be excluded based on their characteristic group of ion fragments 16–20, 15–17, 12–16 and 24–30, respectively (Fig. 5c). Thermal fragmentation and dehydroaromatization of **2** into pyrazine results also in hydrogen formation changing the gaseous environment above the sample into reductive one as it has been observed in the air decomposition, as well. A slight decrease of oxygen ($m/z=32$, Fig. 5c) has been also explained by water formation. One of the possible ways of degradation is formulated in Scheme 2.

EGA of *trans*-1,4,5,8-tetraazodecalin (**2**) by TG-FTIR

The degradation products of crystals **2** have been analyzed and followed by TG-FTIR spectroscopy, too. In this case evolution of ethylenediamine and in addition some unidentified bands (at 3023–3008 m, 2947 st, 2911 sh, 2860 sh and 929 m, sh cm⁻¹) have been observed (Fig. 6) both in nitrogen and air. Unfortunately, neither pyrazine nor

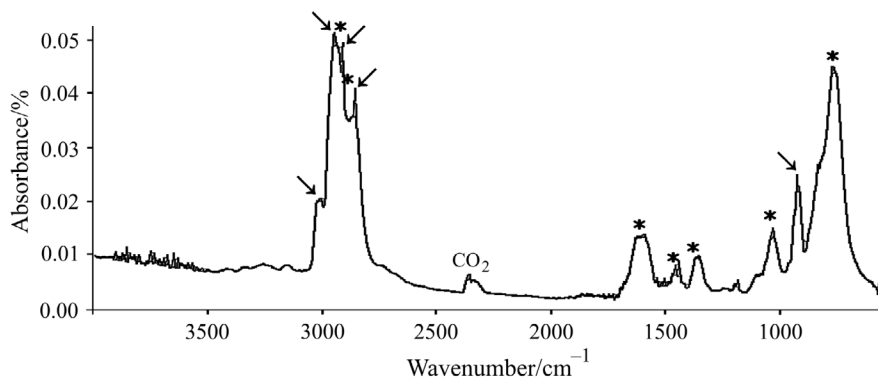
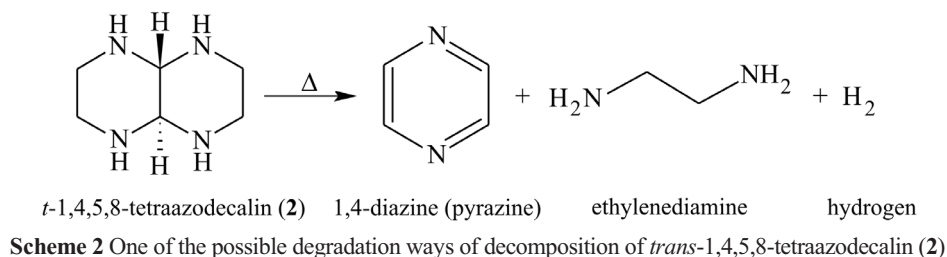


Fig. 6 FTIR spectrum of evolved gaseous species at highest evolution rate measured at 250°C by online coupled TG-FTIR in nitrogen (initial mass: 10.70 mg, heating rate: 10°C min⁻¹, gas flow of 120 mL min⁻¹, open Pt crucible). Absorption bands of ethylenediamine [20] and the unidentified bands are marked with asterisks and arrows, respectively

ammonia has been detected. (Ammonia and pyrazine has occurred during decomposition of samples contaminated with some ethylenediamine carbamate.) Causes of the different mechanism of degradation in the two measuring systems (TG/DTA-MS and TG-FTIR) may be due to the different initial masses, geometries of furnaces and dissimilarity in gas interfacing, which are still under investigation.

Measurements of both evolved gas analyses have also been carried out in air atmosphere, while other conditions are kept constant, and very similar results have been observed.

Conclusions

Thermal and structural properties of crystal occurring in ethylenediamine have been explored. Its molecular formula have been determined as C₆H₁₄N₄ by elemental analysis, and crystals have been identified as *trans*-1,4,5,8-tetraazodecalin (**2**) by FTIR, ¹H and ¹³C NMR and X-ray powder diffraction. Thermal degradation of *trans*-1,4,5,8-tetraazodecalin (**2**), being otherwise quite stable, has been followed by simultaneous TG/DTA and online coupled evolved gas analytical methods (TG/DTA-MS and

TG-FTIR). According to the evaluation of mass spectra, ethylenediamine and pyrazine have been evolved (Scheme 2). Some other degradation ways may also exist as indicated by the black coked residue which is more than 10% of original mass even at 400°C. Evolution of ethylenediamine in gaseous mixture of the decomposition has also been detected by EGA-FTIR.

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