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Crystalline products of tolbutamide decomposition in water after microwave treatment†

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Microwave treatment of a hot water–drug suspension has resulted in the partial decomposition of tolbutamide (form I). Two new crystalline phases were isolated from the precipitate: the *n*-butylammoniun salt of tolbutamide and the novel polymorph of *p*-toluenesulfonamide. Their crystal structures were determined by single-crystal X-ray diffraction. The *n*-butylammoniun salt of tolbutamide is unstable in air and after decomposition crystallizes in the starting form I tolbutamide. The novel polymorph (β) of *p*-toluenesulfonamide differs from the old one (α) in an unusual arrangement of layers.

Introduction

Tolbutamide, *N*-(butylcarbamoyl)-4-methylbenzenesulfonamide, is an antidiabetic drug with low solubility in water. It is used as the model substance in investigations of the increasing bioavailability. Under normal conditions, tolbutamide is known to exist in five polymorphs, I–IV,[1–5] V.[6] Polymorph transitions were investigated and new low- and high-temperature forms were discovered.[5–8] Kimura and co-authors[4] have showed that various forms of tolbutamide have differing dissolution rates and exhibit different oral bioavailability. Form I with the least dissolution rate was concluded to possess also the least oral bioavailability. At the same time, chemical ''tolbutamide'' can be purchased exactly in form I. The aim of our work was to change the properties of water suspension of tolbutamide form I with microwave treatment, in trying to obtain new polymorphs with improved properties. The microwave technique for the modification of the drug was chosen because it was reported to increase the dissolution rate of organic compounds in water.[9]

Results and discussion

Suspension of tolbutamide in distilled water was heated in a microwave reactor at 106 °C for several minutes under an applied power of 200 W. Just after the treatment, the test-tube contained transparent liquid. After shaking, the liquid became turbid and precipitated two types of crystals (Fig. 1). The first type (compound **A**) comprised rather large well-shaped transparent crystals, just after being taken out of the liquid. The second type (compound **B**) comprised flexible accrete plates. Exposed to air, crystals of compound **A** became opaque, but a soft porous mass of accrete plates of compound **B** remained unchanged after drying.

Small crystals were picked up from the precipitate and then used for the structure determination. The phase unstable under air exposure was found to be the *n*-butylammoniun salt of tolbutamide (compound **A**). Its crystal structure was determined at 100 K in a capillary. Results after the

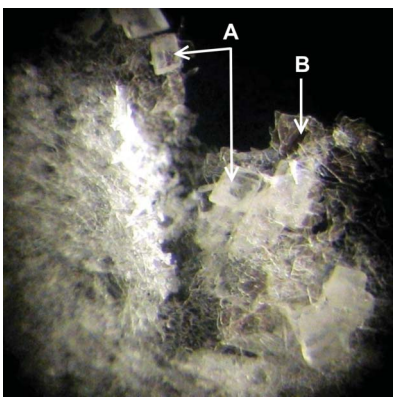

Fig. 1 Optical image of the precipitate taken out of the liquid (binocular microscope, magnification ~8), A – compound **A**, B – compound **B**.

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experiments at room temperature were not quite accurate, allowing us only to calculate the unit cell parameters. When corrected for the thermal expansion, the latter agreed with those at 100 K.

The crystal structure of compound **B** was reliably determined at room temperature and turned out to be a novel polymorph of *p*-toluenesulfonamide. The structure of the old polymorph of *p*-toluenesulfonamide was published about 20 years ago.[10] In order to distinguish the two structures, we will discuss hereafter the old one as the α-form and our new one as the β-form.

Thus, microwave treatment has caused partial decomposition of tolbutamide and the products of the decomposition interact with water. Thermal decomposition of tolbutamide was found to occur after long heating in water (dissociation).[11] We suppose that the formation of *p*-toluenesulfonamide (**3**) during the microwave heating of a water solution can be described by the reaction shown in Scheme 1. This reaction was suggested by Bottari and co-authors[11] for one of the probable ways for thermal dissociation of sulfonylureas in water, and *p*-toluenesulfonamide (**3**) was shown to form only through an intermediate phase of isocyanate (**4**). In our work, the remainder of tolbutamide (**1**) forms a salt with *n*-buthylamine (**2**).

Besides two new phases, X-ray powder diffraction reveals that the precipitate contains the starting form I tolbutamide. Compound **A** also transforms back into form I tolbutamide which decomposes. It was proven with the X-ray powder diffraction patterns obtained from the opaque crystals exposed to air. It is still unclear whether form I tolbutamide precipitates immediately from solution or after decomposition of the salt.

Crystal structure of *n*-butylammoniun salt of tolbutamide (compound A)

Compound **A** crystallizes in the space group $P2_1/n$ (monoclinic). The asymmetric unit contains four molecules (Fig. 2), two anions of tolbutamide and two cations of *n*-butylammonium. Tolbutamide molecules are in two different conformations, which differ from one another in the disordering of their alkyl tails. The first molecule was refined well with only one conformation and does not show the disordering in the alkyl tail. The alkyl tail of the second molecule is disordered over two positions (Fig. 2), with site-occupancy factors of 0.560(6) and 0.440(6). The S–N distance in the tolbutamide anion is shortened (1.588(2) and 1.578(2) Å) as compared with that in the neutral molecule (1.637(4) Å, averaged over all found crystal structures of tolbutamide). The conformations of two symmetry-independent cations of *n*-butylammonium are similar to each other and to that typical of alkyl chains of flat conformation.

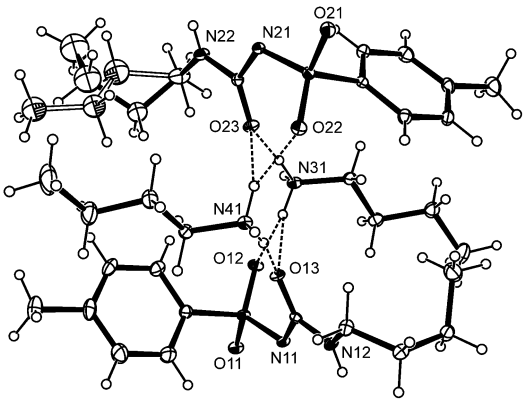


Fig. 2 The asymmetric unit of compound **A**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown with an arbitrary radius. Hydrogen bonds are shown by dashed lines.

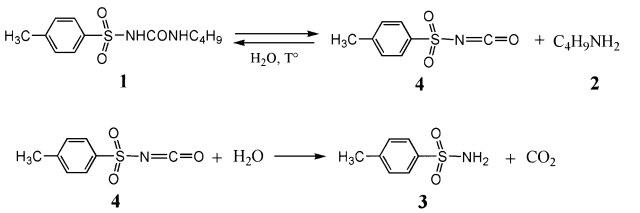
Hydrogen bonds link the molecules into infinite layers. H-bond layers are parallel to plane (001) (Fig. 3). Geometric parameters of hydrogen bonds are summarized in Table 1. The hydrogen bonds N–H···O (indicated with numbers 1 and 2 in Fig. 3b) link neighboring tolbutamide molecules into infinite chains along the crystallographic axis *b*. The hydrogen bonds N–H···N link tolbutamide anions with *n*-butylammonium cations (indicated with numbers 3 and 4 in Fig. 3b). It forms the unstable salt under ambient conditions. When compound **A** decomposes and *n*-butylamine molecules leave the sample, the product crystallizes in form I tolbutamide, which is confirmed by the XRPD patterns.

Tolbutamide molecules in compound **A** are arranged in a similar way to that in form I of pure tolbutamide. Aromatic rings of two neighboring molecules are separated with the plane of the hydrogen bonding, being on the opposite sides of the plane (Fig. 3a). The layers attract each other by means of weak van der Waals interaction.

Crystal structure of novel polymorph (β) of *p*-toluenesulfonamide (compound B)

Compound **B** crystallizes in space group *P*1 (triclinic). The asymmetric unit contains two molecules of *p*-toluenesulfonamide (Fig. 4). The crystal structure of β-polymorph as a whole does not possess the inversion centre (triclinic space group *P*1). Nevertheless, one of the two molecules in the asymmetric unit matches almost completely with the other in the inverted conformation. The molecules of *p*-toluenesulfonamide are connected with hydrogen bonds (Table 2, Fig. 5) and form infinite layers parallel to the plane (001). All aromatic rings in a layer are located on one side of the hydrogen bond plane (Fig. 6a).

The α-form of *p*-toluenesulfonamide (space group $P2_1/n$) is also formed with the infinite layers of the molecules, but in another way.[10,12] Aromatic rings of neighboring molecules are



Scheme 1

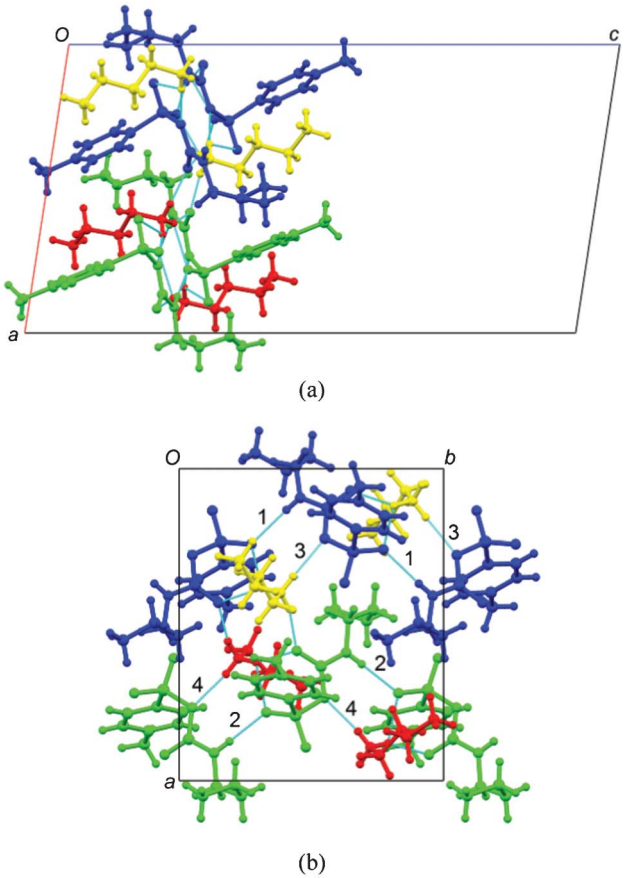


Fig. 3 One layer of molecules in the crystal structure of compound **A**, viewed along (a) the *b* axis and (b) the *c* axis. Hydrogen bonds are shown in blue lines. Symmetry-independent molecules are coloured differently: green and dark-blue for molecules of tolbutamide; red and yellow for molecules of *n*-butylammonium. Hydrogen bonds N–H···O between tolbutamide molecules are indicated with numbers 1 and 2, those N–H···N between tolbutamide and *n*-butylammonium with 3 and 4.

located on the opposite sides of the plane of hydrogen bonding, thus the molecules are arranged antiparallel (Fig. 6b). Crystal structures of two related compounds (4-chloro-benzenesulfonamide and 4-bromo-benzenesulfonamide), isostructural with the α-form of *p*-toluenesulfonamide, were also published.[12] They all have the centre of symmetry. Polymorphs similar to the β-form of *p*-toluenesulfonamide were not so far found.

Molecules of *p*-toluenesulfonamide in α- and β-polymorphs differ significantly from one another in the rotation of the aromatic ring against the rest of the molecule (Fig. 7).

Table 1 Geometric parameters of the hydrogen bonds for compound **A**[a]

D–H···A	*d*(D–H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	∠(DHA)/°
N12–H12N···O12^{i}	0.84(3)	2.06(3)	2.908(3)	176(3)
N22–H22N···O22^{ii}	0.80(3)	2.14(3)	2.936(3)	174(3)
N31–H31A···O23	0.93(4)	1.88(4)	2.792(3)	164(3)
N31–H31B···N11^{iii}	0.87(3)	2.05(4)	2.908(4)	168(3)
N31–H31C···O12	0.94(4)	2.29(4)	2.873(3)	120(3)
N31–H31C···O13	0.94(4)	1.97(4)	2.830(4)	152(3)
N41–H41A···N21^{iv}	0.89(4)	2.11(4)	2.993(4)	178(3)
N41–H41B···O13	0.91(4)	1.88(4)	2.738(3)	157(3)
N41–H41C···O22	0.95(4)	2.20(4)	2.861(3)	126(3)
N41–H41C···O23	0.95(4)	2.04(4)	2.881(4)	147(3)

[a] Symmetry codes: (i) $3/2 - x, 1/2 + y, 1/2 - z$; (ii) $1/2 - x, -1/2 + y, 1/2 - z$; (iii) $3/2 - x, -1/2 + y, 1/2 - z$; (iv) $1/2 - x, 1/2 + y, 1/2 - z$.

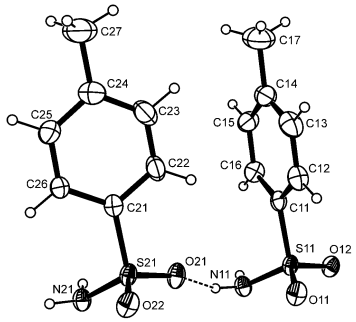


Fig. 4 The asymmetric unit of compound **B**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown with an arbitrary radius. Hydrogen bonds are shown by dashed lines.

Table 2 Geometric parameters of the hydrogen bonds for compound **B**[a]

D–H···A	*d*(D–H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	∠(DHA)/°
N11–H11···O21	0.87(3)	2.32(3)	3.064(4)	144(3)
N11–H11···O11^{i}	0.87(3)	2.63(3)	3.293(3)	134(2)
N11–H12···O22^{ii}	0.83(3)	2.31(3)	3.056(4)	149(3)
N21–H22···O11^{i}	0.85(4)	2.24(4)	2.973(4)	145(3)
N21–H21···O12^{iii}	0.90(3)	2.21(4)	3.025(4)	151(3)
N21–H21···O22^{i}	0.90(3)	2.67(3)	3.320(3)	130(3)

[a] Symmetry codes: (i) $-1 + x, y, z$; (ii) $x, 1 + y, z$; (iii) $-1 + x, -1 + y, z$.

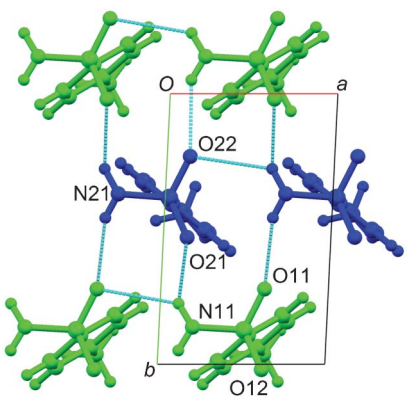


Fig. 5 Hydrogen bonds within one layer of compound **B** (blue line). Different molecules in the asymmetric unit are shown in different colors.

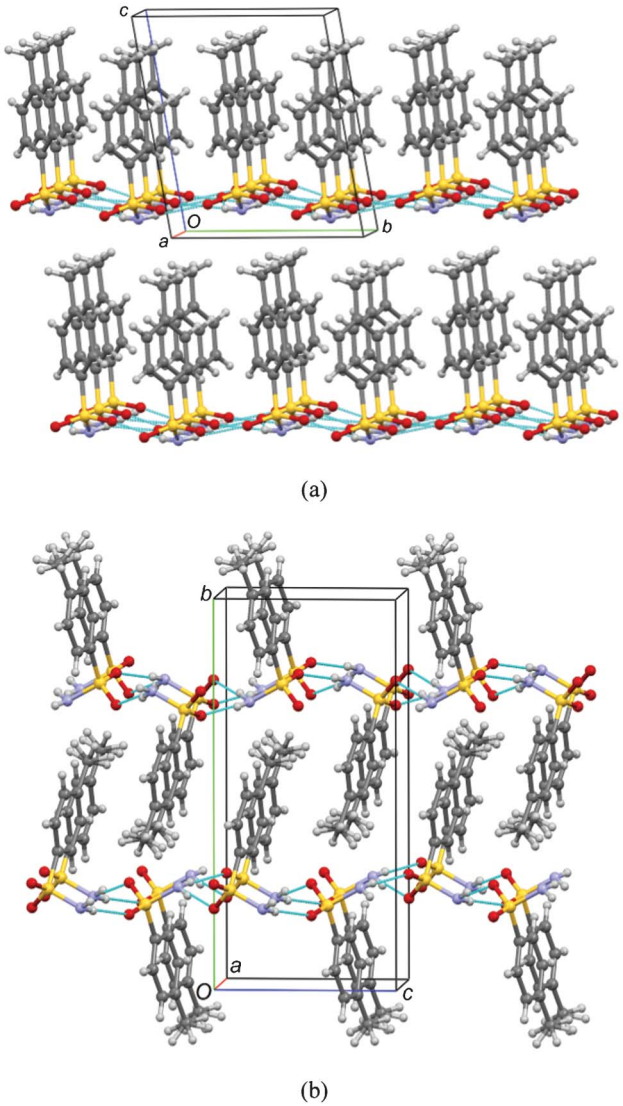


Fig. 6 Fragment of the crystal structure (a) of β-polymorph of *p*-toluenesulfonamide (compound **B**) and (b) of α-polymorph.[12] Hydrogen bonds are shown by blue lines.

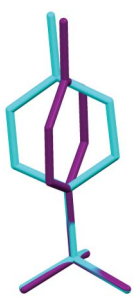


Fig. 7 Overlay of the molecular structures of *p*-toluenesulfonamide molecules in two polymorphs: dark violet for α, light blue for β.

Conclusions

Microwave heating does not result in a new polymorph of tolbutamide. Partial decomposition of tolbutamide takes place instead. The remaining tolbutamide crystallizes together with *n*-butylamine, a fragment after decomposition, as a salt. The salt is unstable in air and decomposes into the gas phase and crystalline form I of pure tolbutamide. What is more interesting is that the other fraction of thermal decomposition of the tolbutamide molecule, *p*-toluenesulfonamide, crystallizes in a new polymorph with an unusual arrangement of layers. The repetition of the experiments with microwave treatment of water–tolbutamide (form I) suspension always produces these two new crystalline phases.

Experimental

The experiments of water–tolbutamide suspension were carried out using microwave synthesis system (reactor) DiscoverTM System S-Class (CEM corp., USA) equipped with the controller of temperature, pressure, applied power, and with the function of stirring treated suspension. Starting reagent tolbutamide was purchased from SIGMA and, according to the X-ray powder diffraction pattern, it was pure tolbutamide form I. Suspension of poorly wettable tolbutamide (182 mg) in water (2 mL) in a special closed test-tube was placed into the microwave reactor, stirred for 30 s without irradiation, and then heated for 1 min at 106 °C with a power of 200 W. The test-tube was dismounted from the reactor when cooled down to 60 °C. The content of the tube was a uniform suspension. Then, 1 mL more of water was added and heated for 2 min under the same conditions (106 °C, excess pressure of 0.3 bar, 200 W). Taken off the reactor immediately (without

Table 3 Crystallographic data and structure refinement details

Compound	**A**	**B**
Formula	$C_4H_{12}N^+ \cdot C_{12}H_{17}N_2O_3S^-$	$C_7H_9NO_2S$
Formula weight	343.48	171.21
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	$P1$
T/K	100	295
a/Å	13.5031(6)	5.1562(2)
b/Å	11.2985(5)	8.3250(4)
c/Å	25.4543(12)	9.8583(7)
α/°	90	100.801(5)
β/°	98.694(4)	102.284(4)
γ/°	90	90.371(3)
V/Å^3	3838.8(3)	405.68(4)
Z	8	2
D_c/g cm^{-3}	1.189	1.402
μ (Mo Kα)/mm^{-1}	0.186	0.346
θ range/°	3.02–26.37	3.60–26.37
Measured reflections	18 001	5004
Independent reflections	7821	3302
Reflections with $I > 2\sigma(I)$	5534	2790
R_{int}	0.049	0.027
$R[F^2 > 2\sigma(F^2)]$	0.068	0.042
w$R(F^2)$	0.151	0.097

cooling), the content was pure liquid. Being shaken, the content formed the precipitation that was then analyzed with powder and single-crystal X-ray diffraction.

X-ray powder diffraction was carried out using a diffractometer Bruker D8 GADDS (Cu Kα radiation, graphite monochromator, two-dimensional Hi-Star detector). A variable-temperature single-crystal X-ray diffraction study was carried out using an Oxford Diffraction KM-4 diffractometer with a two-dimensional detector Ruby CCD (graphite monochromator, Mo Kα radiation) with a low-temperature Oxford Instruments Cryojet device. CrysAlisPro software[13] was used for cell refinement, data collection and processing. All the crystal structures were solved by direct methods using SHELXS,[14] and refined by full matrix least-squares on F^2 with all data using SHELXL[15] with anisotropic thermal parameters for all non hydrogen atoms. H atoms were located in the difference maps (in NH- and NH_3-groups) or were positioned geometrically and refined with a riding model. Crystal data collection and refinement parameters are listed in Table 3. The programs WinGX,[16] ORTEP3 for Windows,[17] Mercury[18] were used for visualization and analysis.

Acknowledgements

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