CROATICA CHEMICA ACTA CCACAA **74** (1) 103–120 (2001)

ISSN-0011-1643
CCA-2718 *Original Scientific Paper*

Chemistry of Torasemide. Molecular and Crystal Structure of New Polymorph N

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Received July 14, 2000; revised October 27, 2000; accepted October 31, 2000

It is known from literature that torasemide, generic name for N^1-isopropyl-N^3-[4-(3-methylphenylamino)-3-pyridylsulphonyl]urea, can have two polymorphic forms, denoted as **T-I** and **T-II**. A novel, third polymorph N of torasemide, **T-N** has been discovered and fully characterised. It crystallises in the centrosymmetric monoclinic space group $P2_1/c$ with two crystallographically independent molecules, which differ primarily in their different phenyl ring and N^1-isopropyl side chain orientations. Both independent molecules, *i.e.* conformations, can adopt a zwitter-ionic structure. The new polymorph of torasemide is characterised by a considerably complex three-dimensional hydrogen-bonding network that spans all over the crystal unit cell. The crystal packing of **T-N** is rather crowded, dense and compact. It is pointed out that the degree of crystal structure diversity of the existing torasemide polymorphs is considerably high, with different conformational properties of distinct torasemide molecules in its asymmetric unit.

Key words: torasemide, pyridylsulphonylurea, polymorphism, X-ray diffraction, conformation.

INTRODUCTION

Torasemide, generic name for N^1-isopropyl-N^3-[4-(3-methylphenylamino)-3-pyridylsulphonyl]urea, and many of its derivatives represent a new class

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of loop diuretics capable of inhibiting the NaCl reabsorption in the thick ascending limb of Henle's loop. Their diuretic activity may be attributed to a strong inhibition of the luminal side of the Na^+, $2Cl^-$, K^+ cotransporter rather than to inhibition of the chloride channels in the basolateral membrane of this nephron. These substances interact in their anionic form with the Na^+, $2Cl^-$, K^+ cotransporter at the chloride ion binding site. As a new clinical perspective, antihypertensive indications of torasemide have been found, utilising the reduction of arterial pressure due to an increase in the intracellular cAMP and cGMP content. Therefore, torasemide may be considered as the first-line treatment in the mild to moderate essential hypertension, as well.[1–4]

In comparison with furosemide, the generic name for 3-carboxy-6-chloro-4-(2-furylamino)-1-phenylsulphonamide, as the reference high ceiling diuretic, torasemide demonstrates some interesting advantages; its inhibitory properties may be manifested in a dose-dependent way at much lower concentrations and in a longer duration of action, it has equipotent activity after *i.v.* and *p.o.* application with almost 100% bioavailability after oral administration, and it has lower potassium excretion. These features may be promising for the clinical use of torasemide.[4]

Structurally, torasemide and its derivatives belong to the group of 4-substituted (4-alkyl, 4-cycloalkyl and 4-aryl) amino-3-pyridylsulphonyl moieties, ranging from common ureas to their bioisosters guanidines and thioureas (Figure 1). Therefore, these compounds could have a wide range of substituents on either the 4-amino or the sulphonylurea N^1 nitrogen atoms, as well as on 3-pyridylsulphonyl cores. Most of them behave as reasonably active diuretics. Fortunately, these compounds do not exhibit the hypoglycemic activity a characteristic of many sulphonylureas.[4] If the 4-anilino and its related groups, as most predominant amino-3-pyridylsulphonyl core substituents, are investigated, with regard to the substitution on the 4-arylamino moiety itself, one substituent is superior to the other two, *i.e.* R^3-substitution is superior to R^2 or R^4-substitution.[4]

It is known from literature that torasemide can have two polymorphic forms, described as CSD[5] codes TORSEM[6] (**T-I**) and TORSEM01[7] (**T-II**). Therefore, on this occasion we would like to report the discovery of a new, third polymorph N of torasemide, *i.e.* polymorph **T-N**. Polymorphism could be defined as the existence of more than one crystalline form of the same chemical substance. It is affected by the ability of a discrete molecule to change its conformation and(or) to form different intermolecular and intramolecular interactions, particularly hydrogen bonds. This is reflected in different atom arrangements in the crystal lattices of different polymorphs.[8,9]

Additionally, the intention of this paper is to confirm unambiguously the crystal structure uniqueness and existence of this new, third polymorph **T-N**

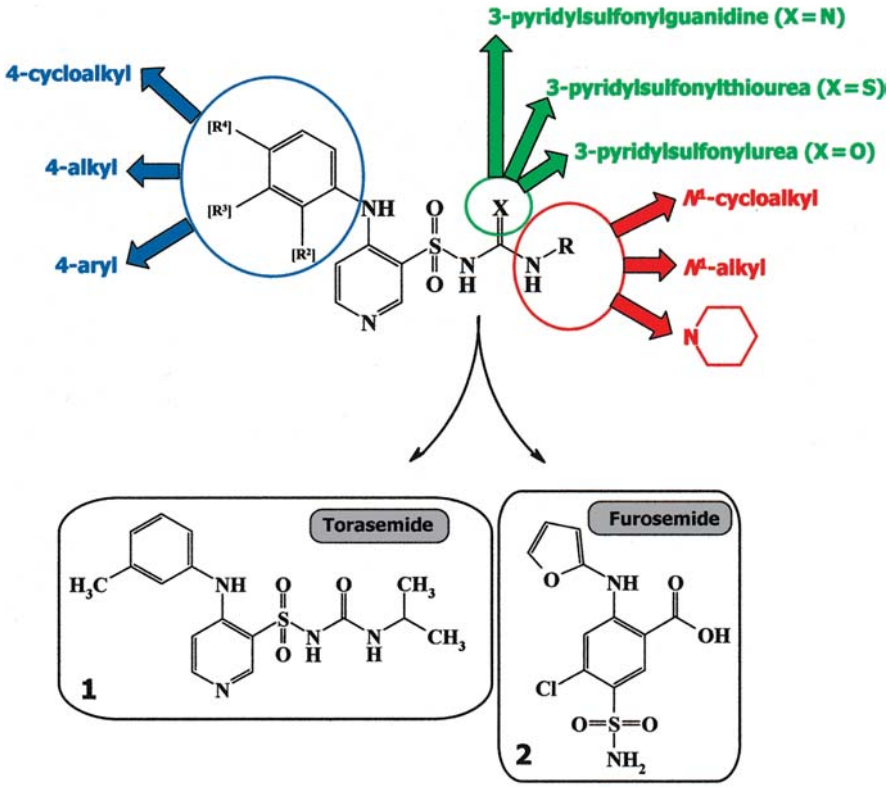

Figure 1. Possible chemical modifications on the 4-substituted amino-3-pyridylsulphonyl cores, with emphasis on structural differences between two commercial diuretics, torasemide (**1**) and furosemide (**2**).

of torasemide. Special attention is paid to indicating the crystal structure diversity among the three existing polymorphs of torasemide, as well as to point out the different conformational properties of distinct torasemide molecules in its asymmetric unit.

EXPERIMENTAL

Chemistry

Torasemide was synthesised in accordance with the procedure described in DE Pat. 2516025,[10] while the new polymorph of torasemide **T-N** was prepared in accordance with PCT/WO Pat. Appl. No. 0020395.[11]

X-Ray Structure Analysis

The single crystal of the new polymorph N of torasemide chosen for the X-ray structure determination was a colourless prism with dimensions $0.60 \times 0.45 \times 0.36$ mm^3. It was obtained by slow evaporation of methanol solution at a temperature of 4 °C.

The cell parameters and intensities were collected on a PHILIPS PW1100 automatic four-circle diffractometer (Stoe/Cie upgrade) using graphite mono-chromatised Mo-Kα radiation (λ = 0.71069 Å), at room temperature. STADI4 programme[12] was used for the control of the diffractometer. Intensities were measured by the ω-scan technique. The measured intensity data were corrected for Lorentz and polarisation effects (XRED programme),[13] but not for absorption.

The molecular and crystal structure of the title compound was solved by direct methods incorporated in the SHELXS-97 programme[14] and refined on F^2 with anisotropic displacement parameters for all non-hydrogen atoms, by the SHELXL-97 programme.[15] The pyridine hydrogen atoms were located in the difference Fourier maps, while all other hydrogen atoms were let to ride on their carrier non-hydrogen atoms, at calculated positions.

Drawings of molecular and crystal structures were prepared by the PLATON-2000 programme,[16] while crystal packings were prepared by the WebLab Viewer Pro 3.20 programme.[17] PARST-96 programme[18] was used to calculate the molecular geometries, *i.e.* hydrogen bonding, best planes, *etc.*

RESULTS AND DISCUSSION

*Description of the Molecular and Crystal Structure of the New Polymorph of Torasemide **T-N***

The new polymorph of torasemide **T-N** is crystallised in the centrosymmetric monoclinic space group $P2_1/c$ in the presence of two crystallographically independent molecules (**T-NA** and **T-NB**) per asymmetric unit. A view of the only one independent molecule (**T-NA**) with the atomic numbering scheme is shown in Figure 2. The majority of relevant details concerning the general crystal data and intensity collections are listed in Table I, while selected geometric parameters, *i.e.* selected bond lengths, bond and torsion angles are listed in Table II (data have been already deposited in CCDC, as supplementary material).[19]

The overlap diagram (Figure 3) of two independent molecules of **T-N** was prepared by fitting atoms of the 3-pyridosulphonamide moiety, *i.e.* by matching atoms N1, C2, C3, C4, C5, C6, S31 and N34. The root mean square difference (RMSD)[20] between matched atoms of 0.106 Å indicates uniqueness of these two independent molecules with their conformational diversity, mainly in different phenyl ring and N^1-isopropyl side chain orientations.

TABLE I

Crystal data and structure refinement parameters for the new polymorph **T-N** of torasemide

Parameter	**T-N**
Crystal data	
Molecular formula	$C_{16}H_{20}N_4O_3S$
M_r	348.42
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell parameters:	
a / Å	11.430(3)
b / Å	19.090(6)
c / Å	16.695(6)
β / °	93.90(2)
V / Å^3	3634(2)
Z	4 × 2
D_x / g cm^{-3}	1.274
F(000)	1472
μ (Mo-Kα) / mm^{-1}	0.199
Θ_{max} / °	27
R_{int}	0.0188
Refinement data	
Number of reflections:	
Unique	6386
Observed [a]	2852
Used in refinement	6386
Number of refined variables	433
R_F	0.0590
wR_F^2	0.1579
Goodness of fit, S	0.974
$\Delta\rho_{max}$; $\Delta\rho_{min}$ / e Å^{-3}	0.288; –0.251

[a] $I \geq 2\sigma(I)$.

3-Pyridylsulphonylureas, guanidines and(or) thioureas are suitable for achieving various resonance forms (see Figure 4). Depending on the specific reaction conditions applied for their synthesis, they can exist in a simple neutral or in more complex ionic forms, manifested as counter-ions or zwitter-ions. Among the different possibilities, resonance forms (I) and (II) are the most predominant ones and are attributed to neutral or counter-ionic, and zwitter-ionic structures, respectively. Bond length analysis of **T-N** and its comparison with standard bond length values for organic compounds, ac-

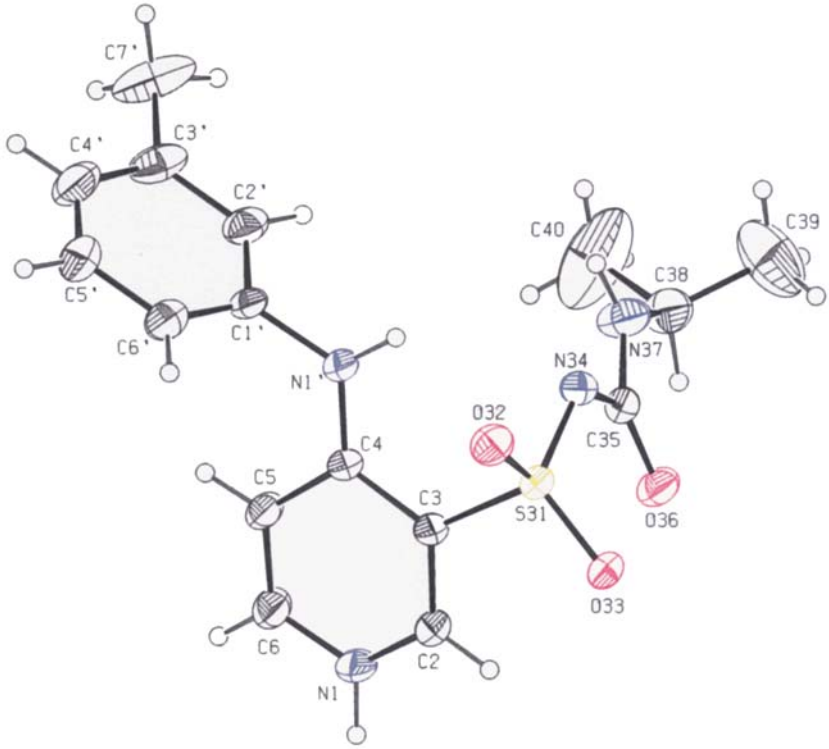

Figure 2. Molecular structure of one crystallographically independent molecule **T-NA** of the new polymorph **T-N** of torasemide, showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level, while hydrogen atoms are drawn as spheres of arbitrary radii.

cording to F. H. Allen *et al.*,[21] suggests that both crystallographically independent molecules adopt zwitter-ionic structure with the prevalent resonance form (II). Even though bonds S31–O32, S31–O33 and C35–O36 have an explicit double bond character characteristic of the resonance form (II), a relative shortening of the S31–N34 single bond followed by the N34–C35 single bond lengthening are noticed. Besides, the location of hydrogen atom, in the difference Fourier map, in the vicinity of pyridine nitrogen atom, enabled N1–H1 bond formation and led to the hypothesis of the presence of a pyridinium cation moiety assigned to the resonance form (II). The pyridinium cation is formed due to the deprotonation of sulphonamide nitrogen atom yielding N34 nitrenium anion. As a consequence, the side chain is in an anionic form, which favours interaction with the Na^+, $2Cl^-$, K^+ cotransporter at the chloride ion binding site.[22]

TABLE II

Selected bond lengths, angles and torsion angles with their standard uncertainties (s.u.) for both independent molecules of the new polymorph **T-N** of torasemide

Parameter	**T-NA**	**T-NB**
	Bond Lengths / Å	
C3–S31	1.779(4)	1.788(4)
S31–O32	1.444(3)	1.442(3)
S31–O33	1.453(2)	1.445(2)
S31–N34	1.559(3)	1.565(3)
N34–C35	1.388(5)	1.377(5)
C35–O36	1.234(4)	1.243(4)
C35–N37	1.341(5)	1.337(5)
	Bond Angles / °	
C3–S31–N34	104.5(2)	106.1(2)
S31–N34–C35	118.4(3)	119.7(3)
N34–C35–N37	111.6(3)	112.9(4)
C35–N37–C38	124.4(4)	123.9(4)
N37–C38–C39	110.5(5)	110.0(5)
N37–C38–C40	111.1(4)	110.2(4)
C4–N1'–C1'	123.7(3)	126.7(4)
	Torsion Angles / °	
C4–C3–S31–N34	–57.4(4)	–48.8(4)
C3–S31–N34–C35	–65.3(3)	–69.0(3)
S31–N34–C35–N37	159.6(3)	166.7(3)
N34–C35–N37–C38	177.7(4)	178.3(4)
C4–N1'–C1'–C2'	–109.9(5)	–131.2(5)
C4–N1'–C1'–C6'	72.1(6)	57.0(6)

As another conformational discrepancy between the two crystallographically independent molecules **T-NA** and **T-NB**, a different relative orientation of pyridine and phenyl rings is found. The best planes through these rings could be defined as follows; atoms N1, C2, C3, C4, C5 and C6 outline the best pyridine ring plane, while atoms C1', C2', C3', C4', C5' and C6' outline the phenyl ring. The dihedral angles between these best planes are 80.3(2)° and 62.8(3)° in molecules **T-NA** and **T-NB**, respectively.

The new polymorph of torasemide **T-N** is characterised by a considerably complex three-dimensional hydrogen-bonding network. Figure 5 depicts all possible hydrogen bonds between two independent molecules in the crystal

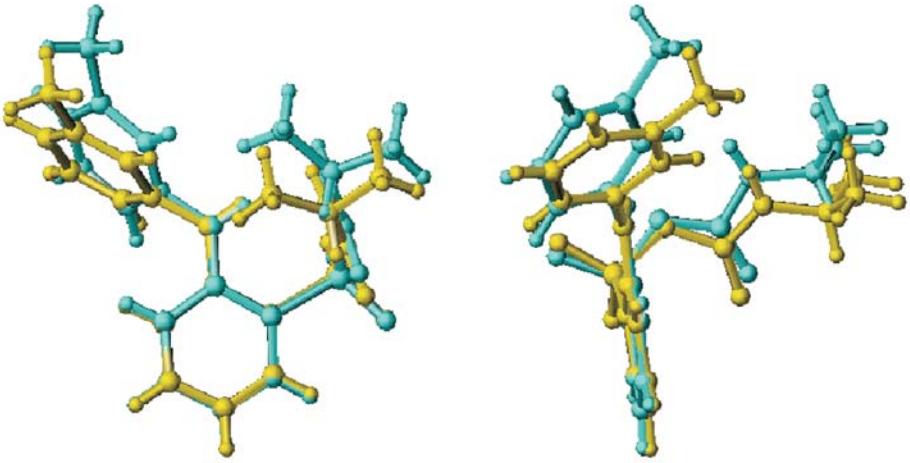

Figure 3. Overlap diagram of two crystallographically independent molecules of the new polymorph **T-N** of torasemide, in orthogonal projection. Molecule **T-NA** is depicted in cyan, while molecule **T-NB** in yellow colour. Hydrogen atoms are omitted for clarity.

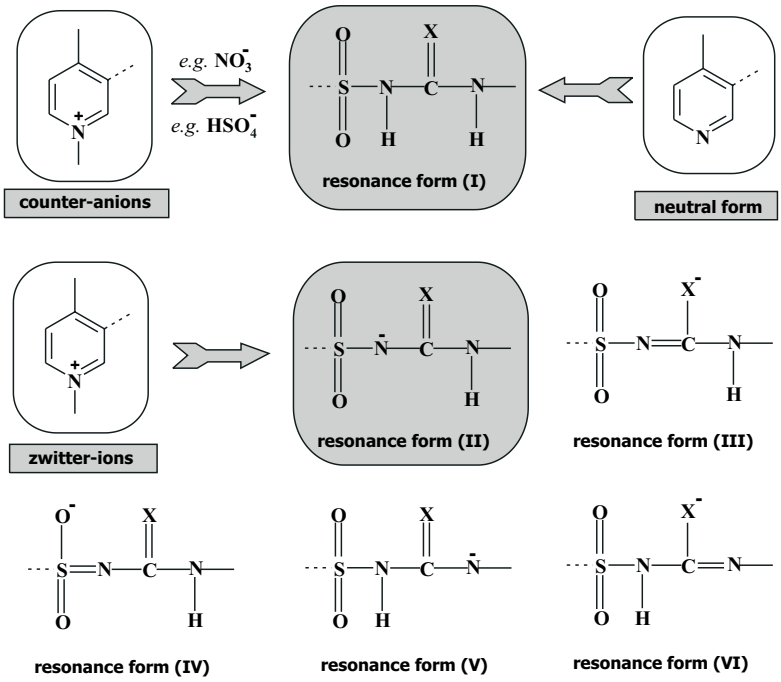

Figure 4. Plausible resonance forms of 3-pyridylsulphonyl moiety (X = O, S, N), *i.e.* 3-pyridylsulphonylureas, guanidines and/or thioureas. The most abundant forms (I) and (II) are highlighted as grey boxes.

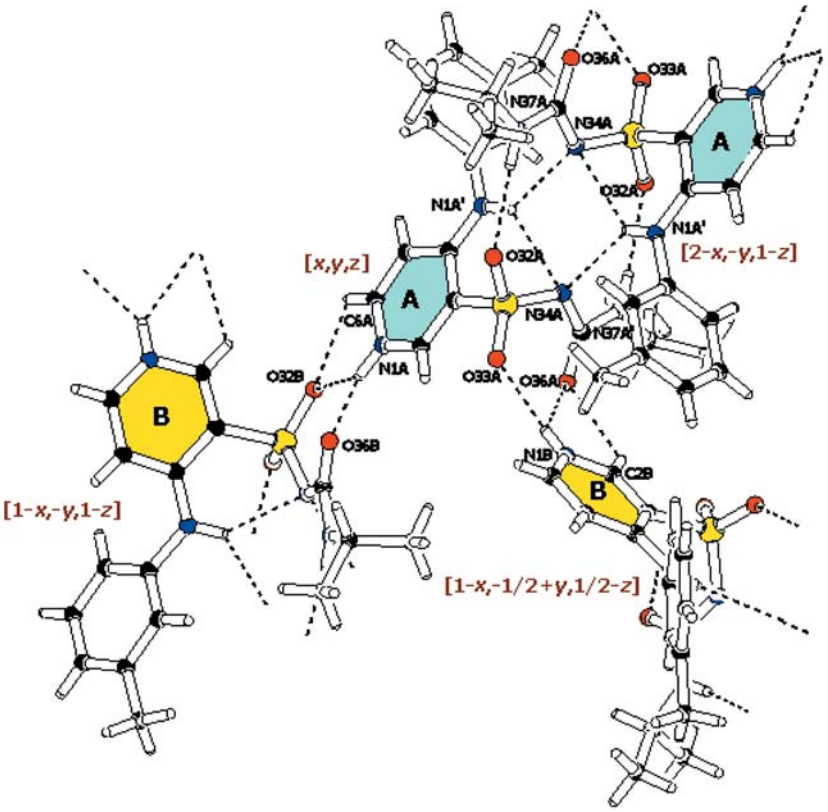

Figure 5. Hydrogen-bonding network of the new polymorph **T-N** of torasemide. Crystallographically independent molecule **T-NA** is depicted in cyan, while molecule **T-NB** in yellow colour, with the underlying symmetry codes in brackets. Hydrogen bonds are shown as dashed lines.

unit cell. According to the achieved patterns, they could be classified in three major groups, *i.e.* the first group (i) is made up of intramolecular hydrogen bonds only, the second (ii) of intermolecular hydrogen bonds that interlink independent molecules of the same origin (*e.g.* **A**–**A** or **B**–**B)**, and the third (iii) of intermolecular bonds that bring together different independent molecules (*e.g.* **A**–**B**). Hydrogen bonds are designated according to the graph-set notation introduced by Bernstein *et al.*[23] (Table III).

The core building elements of this complex hydrogen-bonding network are dimeric **A**–**A** and **B**–**B** units that are formed through N1A(B)'–H1A(B)'···N34A(B) and N37A(B)–H37A(B)···O32A(33B) hydrogen bonds, resulting in two nearly perpendicular binary ring patterns, *i.e.* 8- and 12-membered

TABLE III

Hydrogen-bonding pattern for the new polymorph **T-N** of torasemide. Geometric parameters, notation and classification

Hydrogen bond (No.)[a]	d(H···A)/ Å	d(D···A)/ Å	∠(D···A)/ °	Symmetry code	Notation[b]		Group
					$N_1(a)$	$N_2(a,b)$	
(1) N1A'–H1A'···N34A	2.45	3.081(5)	131	intramolecular	$S(6)$	$N_2(1,5) = R_2^2(8)$	i (**A**)
(2) N1B'–H1B'···N34B	2.24	2.949(5)	140	intramolecular	$S(6)$	$N_2(2,6) = R_2^2(8)$	i (**B**)
(3) N37A–H37A···O32A	2.23	3.086(4)	177	[2–x,–y,1–z]	D	$N_2(3,3) = R_2^4(12)$	ii (**A–A**)
(4) N37B–H37B···O33B	2.07	2.930(4)	173	[1–x,–y,–z]	D	$N_2(4,4) = R_2^4(12)$	ii (**B–B**)
(5) N1A'–H1A'···N34A	2.31	2.977(5)	134	[2–x,–y,1–z]	D	$N_2(5,3) = R_2^2(10)$	ii (**A–A**)
(6) N1B'–H1B'···N34B	2.50	3.135(5)	131	[1–x,–y,–z]	D	$N_2(6,4) = R_2^2(10)$	ii (**B–B**)
(7) N1A–H1A···O32B	2.34	2.926(5)	121	[1–x,–1/2+y,1/2–z]	D	$N_2(7,8) = C_2^2(12)$ $N_2(7,9) = R_1^3(7)$ $N_2(7,11) = R_2^1(5)$	iii (**A–B**)
(8) N1B–H1B···O33A	2.11	2.847(4)	142	[1–x,–y,1–z]	D	$N_2(8,10) = R_1^3(7)$ $N_2(8,12) = R_2^1(5)$	iii (**B–A**)
(9) N1A–H1A···O36B	1.81	2.652(4)	150	[1–x,–1/2+y,1/2–z]	D	$N_2(9,8) = C_2^3(14)$ $N_2(9,11) = R_2^3(9)$	iii (**A–B**)
(10) N1B–H1B···O36A	2.36	2.987(4)	129	[1–x,–y,1–z]	D	$N_2(10,12) = R_2^3(9)$	iii (**B–A**)
(11) C6A–H6A···O32B	2.43	2.970(5)	117	[1–x,–1/2+y,1/2–z]	D	$N_2(11,12) = C_3^2(14)$	iii (**A–B**)
(12) C2B–H2B···O36A	2.44	3.020(5)	120	[1–x,–y,1–z]	D		iii (**B–A**)

[a] Hydrogen bond number.

[b] According to the graph-set notation introduced by Bernstein *et al.*[23] Unitary notation codes ($N_1(a)$) refer to a single discrete hydrogen bond, while binary codes ($N_2(a,b)$) describe a combination of two unitary hydrogen bonds. Ternary ($N_3(a,b,c)$) and higher codes ($N_{n>3}(a,b,c,d,...,n)$) are omitted because of their complexity.

rings $R_2^2(8)$ and $R_2^4(12)$. Through pyridine N1A(B) and aromatic C6A(2B), as donor atoms, and *via* sulphonic O33A(32B) and carbonyl O36A(B), as acceptor atoms, dimeric units **A–A** and **B–B** are linked with each other, outlining various binary patterns ranging from chains, $C_2^2(12)$, $C_2^2(14)$ and $C_3^2(14)$ to rings, $R_1^3(7)$, $R_2^1(5)$ and $R_2^3(9)$. By combining these patterns, three distinct 4-membered infinite chains with repetition model **A–A–B–B–A, A–B–B–A–A** and **A–B–A–B–A** throughout directions [1 1 0], [–1 –1 0] and [0 0 –1], respectively, are created, giving a well-defined three-dimensional network. Two 12-membered and eight 14-membered circuits spanning all over the unit cell are an additional feature of this unique crystal packing (Figure 6).

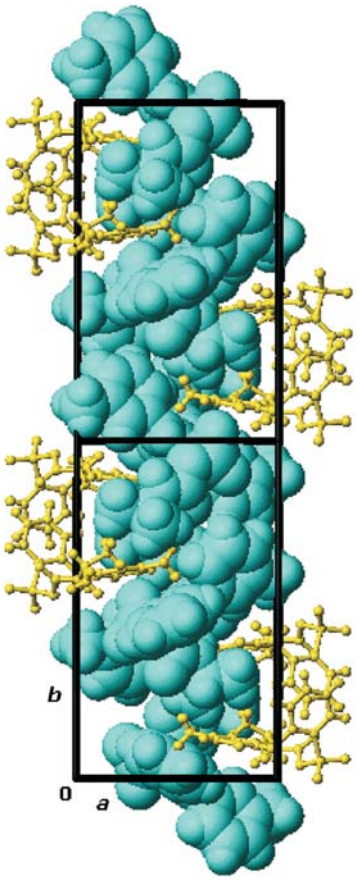

Figure 6. Packing diagram representing 121 crystal planes of the new polymorph **T-N** of torasemide viewed down the *c* [001] axes. Crystallographically independent molecule **T-NA** is depicted in cyan as a »space-filling« model, while molecule **T-NB** in yellow as a »ball and stick« model.

Search for and analysis of solvent accessible voids in the crystal packing revealed a potential solvent accessible volume of approximately 150 Å^3 (around 4% of the total unit cell volume). Having in mind that a simple water molecule has a volume of about 40 Å^3 and that the new polymorph **T-N** has 8 discrete molecules (4 × 2) in its unit cell, it may be concluded that not even a monohydrate (needed voids volume of *cca.* 320 Å^3) is possible. Therefore, the crystal packing of the new polymorph **T-N** is solvent free, dense and compact, as can be clearly seen in Figure 6. In addition, by comparing the crystal packings of all three torasemide polymorphs, it can be seen that polymorph **T-I** is the most condensed one (D_x = 1.33 g cm^{-3}), with no substantial solvent accessible voids, polymorph **T-II** should be considered as the least dense one (D_x = 1.18 g cm^{-3}) with *cca.* 550 Å^3 of solvent accessible volume (around 15% of the total unit cell volume), while the new polymorph **T-N** represents an intermediate case (D_x = 1.274 g cm^{-3}).

Three Polymorphs of Torasemide. Similarity vs. *Diversity*

Up to now, it was known that torasemide can exist in two polymorphic forms, **T-I** and **T-II**. Comparison of their unit cell parameters with the here reported new polymorph **T-N** have unquestionably confirmed the novelty of our polymorph (Table IV). From Table IV one can conclude that all three

TABLE IV

Comparison of unit cell parameters for all known polymorphs of torasemide

Parameter	**T-I**[a]	**T-II**[b]	**T-N**
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2/n$	$P2_1/c$
Unit cell parameters:			
a / Å	13.308	20.446(4)	11.430(3)
b / Å	8.223	11.615(3)	19.090(6)
c / Å	31.970	16.877(4)	16.695(6)
β / °	107.01	108.9	93.90(2)
V / Å^3	3345.5	3791.9	3634(2)
Z	4 × 2	4 × 2	4 × 2
D_x / g cm^{-3}	1.33	1.18	1.274
R_F	0.074	0.089	0.059

[a] CSD code: TORSEM.[22] The unit cell parameters could be reduced to another monoclinic unit cell: a = 13.308 Å, b = 8.223 Å, c = 30.826 Å and β = 97.37°.
[b] CSD code: TORSEM01.[23]

polymorphs belong to the same monoclinic crystal system but with considerably different and therefore unique unit cell parameters. All three polymorphs have two crystallographically independent molecules in their asymmetric unit, giving a total of six possible conformations.

The overlap diagram (Figure 7) of these six independent molecules is made analogous to Figure 3, *i.e.* by fitting atoms of the 3-pyridosulphonamide moiety. As with two independent molecules of the new **T-N** polymorph, it is apparent from Figure 7 that all six conformations are diversified by different phenyl ring and N^1-isopropyl side chain orientations.

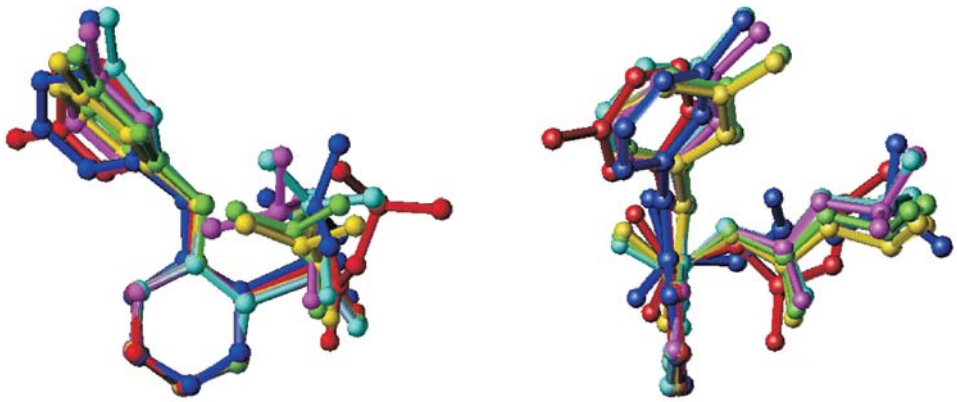

Figure 7. Overlap diagrams of all six crystallographically independent molecules found in three torasemide polymorphs, in orthogonal projections. Polymorph **T-I** is depicted in blue (molecule **T-IA**) and in red (molecule **T-IB**), **T-II** in green (molecule **T-IIA**) and in magenta (molecule **T-IIB**), while polymorph **T-N** in cyan (molecule **T-NA**) and in yellow colour (molecule **T-NB**). Hydrogen atoms are omitted for clarity.

Conformational properties of these six 3-pyridylsulphonylurea moieties correspond in general to case II of the conjugation in sulphone [$\varphi(1) = -90°$; $\varphi(2) = \pm 90°$].[24] In order to understand this historical pyridylsulphonylurea classification, we need to define the following conventional torsion angles designed as $\varphi(1)$, $\varphi(2)$, $\varphi(3)$ and $\varphi(4)$, representing C4–C3–S31–N34, C3–S31–N34–C35, S31–N34–C35–N37 and N34–C35–N37–C38, respectively. According to that, Dupont *et al.*[25] proposed the following description of the pyridylsulphonylureas by three distinct conformational classes, α [$\varphi(1) = -90°$; $\varphi(2) = 90°$; $\varphi(3) = 180°$; $\varphi(4) = 180°$], β [$\varphi(1) = -90°$; $\varphi(2) = -90°$; $\varphi(3) = 180°$; $\varphi(4) = 0°$] and γ [$\varphi(1) = -90°$; $\varphi(2) = -90°$; $\varphi(3) = 180°$; $\varphi(4) = 180°$]. As already mentioned, torasemide crystallises in three different unit cells while adopt-

TABLE V

Conformational classification of six possible crystallographically independent molecules of torasemide, according to Dupont *et al.*[25]

	T-I		**T-II**		**T-N**	
	T-IA	**T-IB**	**T-IIA**	**T-IIB**	**T-NA**	**T-NB**
	Torsion angle / °					
$\varphi(1)_{exp}$[a]	105.7	77.5	51.3	47.8	48.9	57.5
$\varphi(2)_{exp}$	–65.5	71.7	62.2	60.7	69.0	65.3
$\varphi(3)_{exp}$	–179.7	172.0	–163.0	–162.7	–166.7	–159.7
$\varphi(4)_{exp}$	–177.3	–14.4	–178.2	170.1	–178.3	–177.7
$\varphi(1)_{class}$[b]	90	90	90	90	90	90
$\varphi(2)_{class}$	–90	90	90	90	90	90
$\varphi(3)_{class}$	180	180	180	180	180	180
$\varphi(4)_{class}$	180	0	180	180	180	180
	Conformation class					
	α	β	γ	γ	γ	γ

[a] All torsion angles are enlisted with the same relative orientation of the sulphonylurea moiety to the **T-I** target molecule**.** Therefore, the torsion angle values for **T-N** are inverted, as compared to the ones given in Table II.

[b] Torsion angle values are rounded up to the closest number with the step size of 90° for $\varphi(1)$ and $\varphi(2)$, while with the step size of 180° for $\varphi(3)$ and $\varphi(4)$, respectively.

ing all three possible conformational classes (Table V). Consequently, both independent molecules, *i.e.* conformations of polymorphs **T-II** and **T-N**, belong to the same conformational class γ, while **T-I** adopts both α and β classes. Because this conformational classification is based on a rather high torsion angle step size, *e.g.* of 90° and 180°, used for rounding up the torsion angle values, it would be more appropriate and reliable to cluster these conformations in accordance with their root mean square difference (RMSD) between the matched 3-pyridylsulphonyl core atoms (Table VI). As a RMSD cluster criterion, the fairly rigorous cut-off value of 0.100 Å is applied, meaning that conformations with RMSD ≤ 0.100 Å belong to the same cluster, and *vice versa*, the ones with RMSD > 0.100 Å outlining different conformational clusters. Clustering analysis confirmed the results of the previously mentioned conformational classification, but with a significantly higher impact on fine conformational details. Thus, for example, one can see that conformations **T-IIA**, **T-IIB** and **T-NA** are much more closely related to each other than to the **T-NB** conformation, which just barely belong to the

TABLE VI

Conformational clustering of all six possible crystallographically independent molecules of torasemide, applying the RMSD cut-off value of 0.100 Å

	RMSD[a] / Å					
	T-IA	**T-IB**	**T-IIA**	**T-IIB**	**T-NA**	**T-NB**
T-IA (α conform.)		0.206	0.391	0.415	0.428	0.340
T-IB (β conform.)			0.209	0.241	0.252	0.156
T-IIA (γ conform.)				**0.043**	**0.058**	**0.056**
T-IIB (γ conform.)					**0.028**	**0.089**
T-NA (γ conform.)						**0.106**
T-NB (γ conform.)						

[a] Conformations belonging to the same cluster according to the applied RMSD cut-off criteria are highlighted as bold-underlined.

same cluster. This approach becomes more advantageous when trying to compare all the crystallised 4-substituted 3-pyridylsulphonyl analogues, such as various ureas, guanidines and thioureas, with which the old classification protocol would have serious problems due to its already revealed bottlenecks.[26]

Analysis of bond lengths for all six crystallographically independent molecules, (Table VII), reveals the expected predominance of the zwitter-ionic resonance form (II). The only exception is the **T-IA** molecule that possesses a neutral resonance form (I). Nevertheless, it should be stressed that due to the rather poor quality of experimental data (data from 1978) and overall refinement accuracy for known polymorphs **T-I** ($R_F = 0.074$) and **T-II** ($R_F = 0.089$), their published hydrogen positions are somewhat unreliable and could influence the relative distribution of the relevant resonance forms.

TABLE VII

Bond length analysis for all six crystallographically independent molecules found in three different polymorphs of torasemide. Determination of the resonance form predominance

	T-I[a]		**T-II**[a]		**T-N**	
	T-IA	**T-IB**	**T-IIA**	**T-IIB**	**T-NA**	**T-NB**
	Bond length / Å					
C3–S31	1.764	1.792	1.783	1.773	1.779(4)	1.788(4)
S31–O32	1.424	1.444	1.444	1.444	1.444(3)	1.442(3)
S31–O33	1.431	1.437	1.450	1.437	1.453(2)	1.445(3)
S31–N34	1.640	1.574	1.562	1.567	1.559(3)	1.565(3)
N34–C35	1.344	1.385	1.381	1.371	1.388(5)	1.377(5)
N37–C35	1.344	1.349	1.343	1.345	1.341(5)	1.337(5)
C35–O36	1.230	1.273	1.244	1.250	1.234(4)	1.243(4)
	Resonance form					
	neutral (I)	zwitter (II)	zwitter (II)		zwitter (II)	

[a] Bond length values for the known polymorphs **T-I** and **T-II** are described without their standard uncertainties[6,7] and they are given with three decimal figures for comparison with the new polymorph **T-N**. Nevertheless, these last digits should be taken as rough estimates due to the rather poor quality of experimental data and overall refinement accuracy.

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SAŽETAK

Kemija torasemida. Molekulska i kristalna struktura novog polimorfa N

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Iz literature je poznato kako se torasemid, generičko ime za N^1-izopropil-N^3-[4-(3-metilfenilamino)-3-piridilsulfonil]ureu, može pojavljivati u dva polimorfna oblika **T-I** i **T-II**. Međutim, otkriven je, potpuno okarakteriziran i nedvojbeno dokazan novi polimorf torasemida, odnosno **T-N**. Novi polimorf **T-N** kristalizira u centrosimetričnoj monoklinskoj prostornoj grupi $P2_1/c$ s dvije kristalografski neovisne molekule koje se međusobno razlikuju u prostornim rasporedima svojih fenilnih prstenova i

N^1-izopropilnih pobočnih lanaca. Obje kristalografski neovisne molekule nalaze se u obliku dvojnog iona. Osnovna značajka novog polimorfa torasemida jest složena trodimenzijska mreža vodikovih veza koja se proteže kroz cijelu kristalnu rešetku rezultirajući prilično zgusnutim i kompaktnim pakiranjem molekula polimorfa **T-N** u njegovoj kristalnoj rešetki. U konačnici, istaknut je visok stupanj strukturne raznolikosti, odnosno unikatnosti, kristalnih struktura sva tri polimorfa torasemida, kao i različitost konformacijskih značajki njihovih molekula u asimetričnoj jedinici.