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Article

Structures of Benzenesulfonylamino-3-(4-benzenesulfonyloxy-phenyl)-propionic acid and 2-(toluene-4-sulfonylamino)-3-[4-(toluene-4-sulponyl-oxy)-phenyl]-propionic acid: Variations in L-tyrosine Backbone Conformation, Intramolecular Aromatic π–π Stacking and Short C–H···O Interactions

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Abstract: The syntheses and crystal structures of benzenesulfonylamino-3-(4-benzenesulfonyloxy-phenyl)-propionic acid (**1**) and 2-(toluene-4-sulfonylamino)-3-[4-(toluene-4-sulponyloxy)-phenyl]-propionic acid (**2**) are described. The L-tyrosine cores of the molecules show significant conformational differences. In **1**, both organic molecules show intramolecular aromatic π–π stacking and in **2** a very short intermolecular C^{α}–H···O interaction is seen. The structures of **1** and **2** are compared with those of related materials. Crystal data: $\mathbf{1}_2\cdot H_2O\cdot MeOH$ [$2(C_{21}H_{19}NO7S_2)\cdot H_2O\cdot CH_4O$], M_r = 973.04, monoclinic, $P2_1$ (No. 4), a = 8.0078 (4) Å, b = 34.0704 (16) Å, c = 8.5506 (3) Å, β = 94.239 (3)°, V = 2326.47 (18) Å^3, Z = 2, T = 296 K, $R(F)$ = 0.062, $wR(F^2)$ = 0.157, $\mathbf{2}\cdot H_2O$ ($C_{23}H_{25}NO7S_2\cdot H_2O$), M_r = 507.56, monoclinic, $P2_1$ (No. 4), a = 5.7171 (7) Å, b = 24.359 (3) Å, c = 9.1043 (10) Å, β = 104.563 (6)°, V = 1227.2 (2) Å^3, Z = 2, T = 296 K, $R(F)$ = 0.055, $wR(F^2)$ = 0.092.

Keywords: L-tyrosine; green chemistry; torsion angles; C–H···O interactions

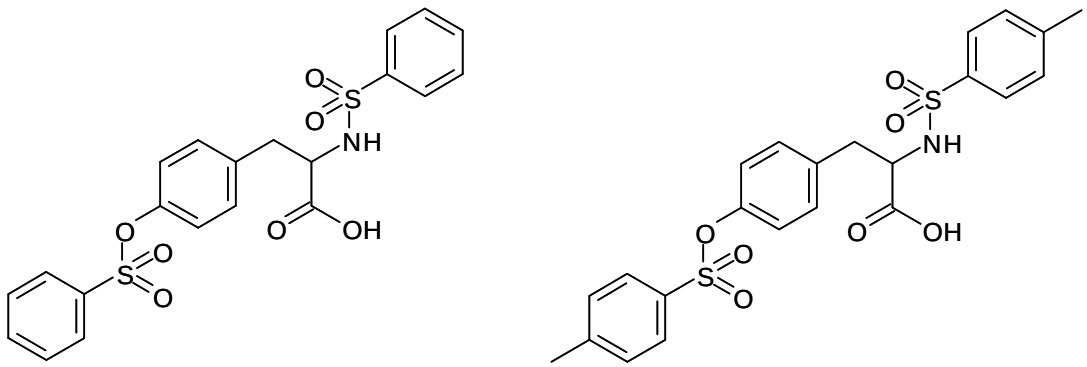
1. Introduction

Tyrosine ($C_9H_{11}NO_3$) is one of the non-essential amino acids, which has been found as a constituent of naturally occurring proteins [1,2]. The crystal structures of chiral L-tyrosine and racemic DL-tyrosine were reported nearly 40 years ago, with both found to crystallize in their zwitterionic forms. The chiral form (space group $P2_12_12_1$) [3] features intermolecular N–H···O_c and N–H···O_h (c = carboxyl, h = hydroxyl) hydrogen bonds as well as O–H···O_h links, which generate a three-dimensional network in the crystal. Although it was not identified at the time, a very short intermolecular C–H···O_c link (H···O = 2.36 Å, compared to the van der Waals' contact distance of about 2.72 Å) arising from the stereogenic (chiral) α carbon atom also occurs [3]. This is now recognized as an important general interaction in amino acids, peptides and even proteins [4,5]. There is no possibility of aromatic π–π stacking in L-tyrosine, as the minimum separation of aromatic ring centroids is greater than 4.51 Å. In the racemic DL-tyrosine crystal structure [6] (space group $Pna2_1$), the zwitterions are linked by the same types of hydrogen bond, although the N–H···O_h bond is notably longer (H···O = 2.31 Å). Again, a three-dimensional array of molecules is generated by the hydrogen bonds and an intermolecular C–H···O_c link also occurs: the equivalent α C atom is again involved, although the H···O separation of 2.54 Å is significantly longer than that in the chiral form.

The crystal structures of various acylated L-tyrosine derivatives (containing C–N–C bonds) have been reported, including N-acetyl-L-tyrosine [7], N-acetyl-L-phenylalanyl-L-tyrosine [8] and (*R*)-2-(2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetamido)-3-(4-hydroxyphenyl)-propanoic acid dimethylformamide solvate [9]. It is notable that intermolecular C–H···O interactions from the α-carbon atom occur in the first and third of these, with H···O = 2.57 and 2.30 Å, respectively.

In this paper, we report the syntheses and crystal structures of benzenesulfonylamino-3-(4-benzenesulfonyloxy-phenyl)-propionic acid (**1**) (see Figure 1 below) and 2-(toluene-4-sulfonylamino)-3-[4-(toluene-4-sulponyloxy)-phenyl]-propionic acid (**2**), in which the L-tyrosine core is substituted at both its N and O_h atoms. Their structures are compared to those of the related compounds noted above.

Figure 1. Structures of **1** and **2**



(**1**) (**2**)

2. Results and Discussion

*2.1. Structure of **1***

The asymmetric unit of $\mathbf{1}_2 \cdot H_2O \cdot MeOH$ consists of two organic molecules (**1A** containing N1 and **1B** containing N2), accompanied by one molecule of water and one molecule of methanol, which is consistent with the mixed solvent used for recrystallization (see Experimental section). **1** has arisen from the reaction of L-tyrosine with two molecules of benzene sulfonyl chloride to form new S–N and S–O bonds in the product [10]. It is notable that there are no other compounds containing L-tyrosine with an equivalent S–N bond in the Cambridge Structural Database (version 5.32 of November 2010 with two updates) [11]. The transferrable hydrogen atoms (acidic protons) are clearly located on atoms O4 and O12, *i.e.* the molecules of **1** are not zwitterions. The absolute structure of $\mathbf{1}_2 \cdot H_2O \cdot MeOH$ is well established based on the refined value of –0.03 (8) of the Flack absolute structure parameter [12] and the *S* configurations of the stereogenic atoms in **1** (C6 in molecule A and C27 in molecule B) are consistent with that of the equivalent carbon atom in L-tyrosine itself [3]. In order to simplify the comparison of **1** with related structures, we will designate atom-sets C13, C6, C5 and C4 (molecule A) and C34, C27, C26 and C25 (molecule B) as Ca, Cα, Cβ and Cγ, respectively.

Table 1. Key torsion angles (°) in **1**, **2** and related compounds.

S–N–Cα–Cβ or C–N–Cα–Cβ			
1a	140.5 (4)	**1b**	146.9 (4)
2	129.7 (3)	**3**	–176.6
4	–171.1	**5**	–68.6
N–Cα–Cβ–Cγ			
1a	–67.6 (6)	**1b**	–59.7 (6)
2	–61.1 (5)	**3**	–71.5
4	–179.8	**5**	–60.5
6	69.3	**7**	–69.7
Ca–Cα–Cβ–Cγ			
1a	170.2 (5)	**1b**	178.3 (5)
2	174.4 (4)	**3**	165.6
4	58.2	**5**	64.6
6	–53.1	**7**	52.5
N–Cα–Ca–OH			
1a	166.0 (5)	**1b**	–37.4 (6)
2	165.3 (3)	**3**	–28.7
4	–46.9	**5**	170.0

3 = N-acetyl-L-tyrosine (ref. 7). Standard uncertainty (s.u.) for angles ≈ 0.2°; **4** = N-acetyl-L-phenylalanyl-L-tyrosine (ref. 8). S.u. for angles ≈ 0.4°; **5** = (*R*)-2-(2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetamido)-3-(4-hydroxyphenyl)-propanoic acid dimethylformamide solvate (ref. 9). S.u. for angles ≈ 0.2°; **6** = L-tyrosine (ref. 3). S.u. for angles ≈ 0.5°; **7** = DL-tyrosine (ref. 6). S.u. for angles ≈ 0.5°.

Key torsion angles for the amino-acid cores of the molecules are as follows: in **1A**, the conformation of the S–N–Cα–Cβ bond is substantially twisted from nominal *gauche* [torsion angle =

140.5 (4)°] whilst the N–Cα–Cβ–Cγ [–67.6 (6)°] series is closer to being *gauche*. The Ca–Cα–Cβ–Cγ torsion angle is close to *anti* [170.2 (5)°] as is the N–Cα–Ca–O(H) torsion angle of 166.0 (5)°. In **1B**, the conformation of the S–N–Cα–Cβ bond is even more twisted from *gauche* [torsion angle = 146.9 (4)°] whilst N–Cα–Cβ–Cγ [–59.7 (6)°] is almost ideally *gauche*. The Ca–Cα–Cβ–Cγ torsion angle is close to *anti* [178.3 (5)°], and compares well to the equivalent value for molecule A. However, the N–Cα–Ca–O(H) torsion angle of –37.4 (6)° indicates a completely different conformation, as compared to molecule A. This is backed up by the dihedral angles of 80.4 (5)° between C34/O11/12 and C26/C27/N2 in molecule B and 65.2 (5)° for the equivalent atoms in molecule A. The torsion angles in **1A** are similar to those in **2** (*vide infra*) but quite different to those in related N-acylated L-tyrosine derivatives (Table 1) and in L-tyrosine and DL-tyrosine.

The dihedral angles between the mean planes of the central C1/C2/C3/C4/C14/C15 aromatic ring and the terminal C7–C12 and C16–C21 rings in **1A** are 7.9 (2)° and 60.1 (2)°, respectively. The dihedral angle between the terminal rings is 66.9 (2)°. Equivalent values for **1B** for the C22/C23/C24/C25/C35/C36, C28–C33 and C37–C42 rings are 6.1 (2)°, 53.5 (2)° and 58.33 (19)°, respectively. The molecular conformation of **1A** (Figure 2) leads to a striking intramolecular aromatic π–π stacking interaction between the C1/C2/C3/C4/C14/C15 and C7–C12 rings, with a centroid–centroid separation of 3.807 (3) Å. In **1B**, which has a broadly similar overall shape (Figure 3), the separation between the equivalent rings is significantly longer at 4.067 (3) Å, which must indicate a much weaker interaction. A similar situation has been seen in a series of isostructural 5-phenyl-2-(benzalhydrazonyl)-1,3,4-thiadiazoles [13], in which some compounds show much shorter centroid–centroid separations than others.

Figure 2. The molecular structure of molecule **1A** showing 40% displacement ellipsoids. The intramolecular π–π stacking interaction is indicated by a double-dashed line.

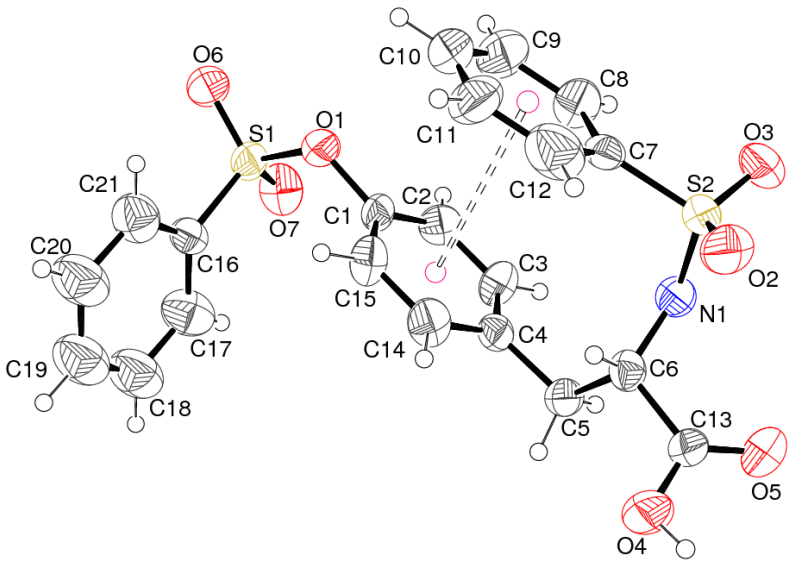
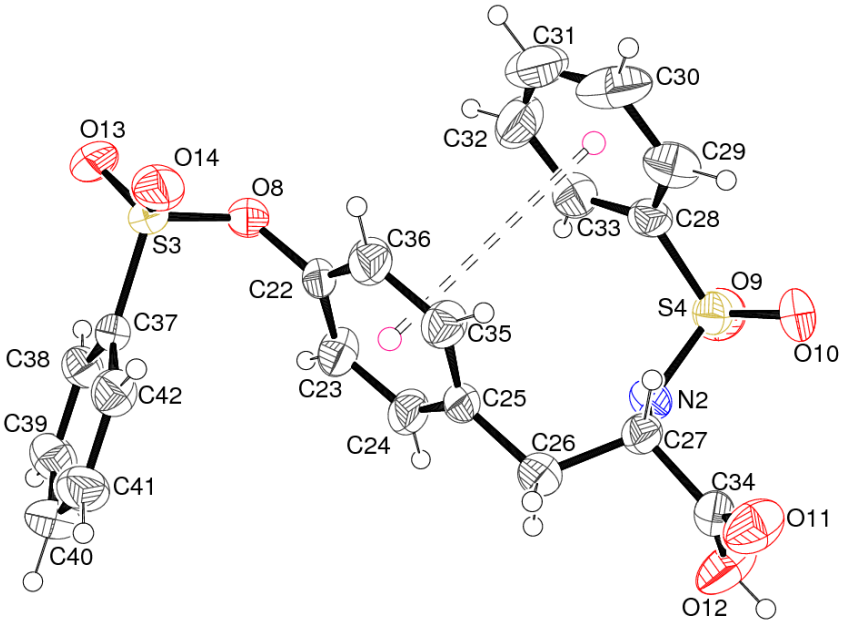


Figure 3. The molecular structure of molecule **1B** showing 50% displacement ellipsoids. The intramolecular π–π stacking interaction is indicated by a double-dashed line.



In the crystal of **1**, the components are linked by N–H···O and O–H···O hydrogen bonds (Table 2). One of the N–H···O links is to a C=O (carboxylic acid) acceptor oxygen atom and the other is to a sulfonyl O atom. Both –OH groups of the carboxylic acids form hydrogen bonds to the solvent molecules (one to a water O atom and one to a methanol O atom). In terms of the C6–H6 and C27–H27 groupings (*i.e.*, the α carbon atoms), the first of these has a distant H···O contact to a sulfonyl O atom (2.63 Å) whereas the second does not have any possible acceptor atoms within 3.5 Å.

Finally, the solvent molecules form further O–H···O links and overall a two-dimensional network lying parallel to (010) arises. With this diversity of hydrogen-bond types observed in the structure, it is hard to draw conclusions as to the preferred hydrogen bonding modes of the organic molecule in **1**, although the very short C^{α}–H···O link noted in the introduction is not present. Any intermolecular aromatic π–π stacking must be very weak, with a minimum centroid–centroid separation of greater than 4.06 Å.

Table 2. Hydrogen bonds in **1**.

N1–H1N···O11	0.87 (4)	2.06 (4)	2.922 (6)	168 (5)
N2–H2N···O14^{i}	0.87 (4)	2.10 (4)	2.925 (6)	160 (4)
O4–H4O···O15^{ii}	0.82	1.95	2.702 (6)	153
O12–H12O···O1W	0.82	1.75	2.547 (7)	164
O15–H15A···O10	0.82	2.07	2.817 (6)	151
O1W–H1WA···O5^{i}	0.88 (5)	2.08 (6)	2.847 (7)	146 (6)
O1W–H1WB···O15^{iii}	0.87 (5)	2.14 (5)	2.998 (7)	172 (7)

The four values refer to the *D*–H, H···*A*, *D*···*A* separations (Å) and the D–H···A angle (°), respectively (also in Table 3). Symmetry codes: (i) *x*, *y*, *z*–1; (ii) *x*, *y*, *z*+1; (iii) *x*+1, *y*, *z*.

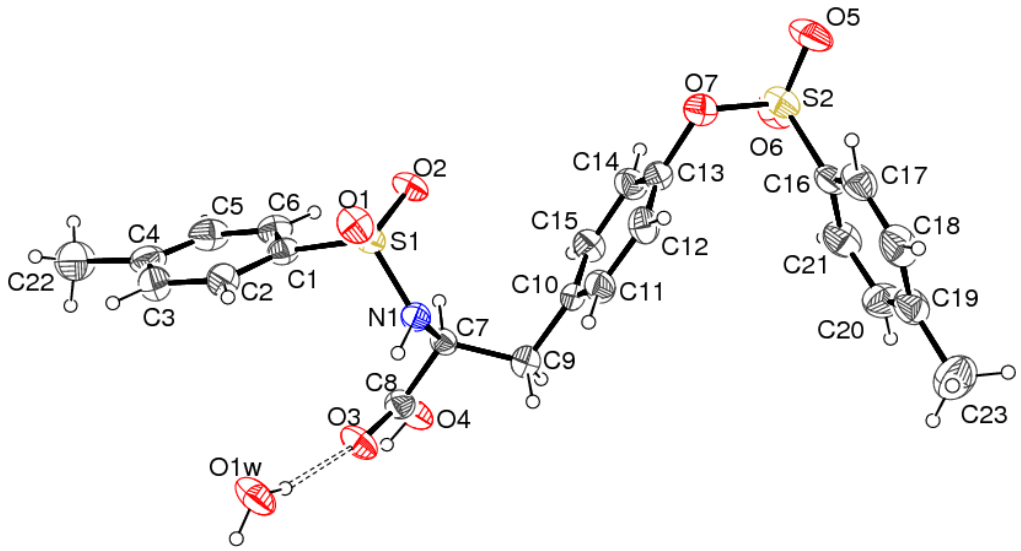
*2.2. Structure of **2***

The crystal structure of **2**·H_2O (Figure 4) shows that L-tyrosine has reacted with two equivalents of 4-toluenesulfonyl chloride to form the S1–N1 and S2–O7 bonds in the product and that a water molecule of crystallization is present. The S-configuration of the C7 stereogenic center [refined value of the Flack absolute structure parameter = –0.01 (7)] is consistent with that of the L-tyrosine starting material and the bond lengths and angles in **2** may be regarded as normal. The molecule of **2** is non-zwitterionic, *i.e.* the proton is clearly attached to O4 and not to N1, as also seen for related molecules [5-7]. In order to simplify the comparison with related structures, atoms C8, C7 C9 and C10 in **2** are referred to as Ca, Cα, Cβ and Cγ, respectively.

The conformation of the S1–N1–Cα–Cβ bond in **2** is close to *gauche* [torsion angle = 129.7 (3)°] as is N1–Cα–Cβ–Cγ [–61.1 (5)°] whereas that of Ca–Cα–Cβ–Cγ is close to anti [174.4 (4)°]. The N1–Cα–Ca–O4 torsion angle of 165.3 (3)° indicates that the –OH group of the carboxylic acid is close to *anti* with respect to the NH group. These torsion angles are broadly similar to the situation in molecule **1A** but different to those of other L-tyrosine derivatives (Table 1).

The dihedral angles between the mean planes of the central C10–C15 aromatic ring and the terminal C1–C6 and C16–C21 rings are 44.8 (2)° and 56.1 (2)°, respectively. The dihedral angle between the terminal rings is 81.4 (2)°. Their relative orientations, which are completely different to the conformations of molecules **1A** and **1B** in **1** indicate that no intramolecular aromatic π–π stacking interactions can occur in **2**.

Figure 4. The molecular structure of **2**·H_2O showing 40% displacement ellipsoids. The O–H···O hydrogen bond is indicated by a double-dashed line.



In the crystal, the molecules are linked by N–H···O and O–H···O hydrogen bonds. The N–H···O (see Table 3 for atom labels and symmetry codes) hydrogen bond links the organic molecules into C(5) chains propagating in the [100] direction. The carboxylic acid forms an O–H···O bond to the water molecule and the water molecule forms two further O–H···O links; one of the acceptors is the C=O bond of the carboxylic acid, the other is part of a sulfonyl group. Together, these bonds generate a three-dimensional network. An extremely short intermolecular C–H···O bond (2.34 Å) from the α-

carbon atom occurs in **2**, as does a longer C–H···O interaction from C9 (the β carbon atom). There are no aromatic π–π stacking interactions in the crystal of **2**, the shortest centroid–centroid separation being longer than 4.5 Å.

Table 3. Hydrogen bonds in **2**.

N1–H1N···O11	0.87 (4)	2.06 (4)	2.922 (6)	168 (5)
N1–H1N···O4^{i}	0.89 (4)	2.41 (4)	3.241 (5)	156 (3)
O4–H4O···O1W^{ii}	0.82 (5)	1.80 (5)	2.557 (4)	153 (6)
O1W–H1WA···O2^{iii}	0.818 (18)	2.04 (2)	2.842 (3)	166 (5)
O1W–H1WB···O3	0.82 (4)	2.06 (5)	2.864 (4)	165 (5)
C7–H7···O1^{ii}	0.98	2.34	3.260 (5)	156
C9–H9A···O6^{iii}	0.97	2.59	3.468 (5)	150

Symmetry codes: (i) *x*–1, *y*, *z*; (ii) *x*+1, *y*, *z*; (iii) *x*, *y*, *z*+1.

3. Experimental Section

3.1. Syntheses

All reagents were purchased from commercial sources and used without further purification and compound **1** was synthesized following the "green" literature method [10]. L-Tyrosine (0.50 g, 5.52 mmol) was dissolved in 15 mL of 1 M Na_2CO_3 solution. Benzene sulfonyl chloride (1.41 mL, 11.04 mmol) was suspended in the solution with stirring at room temperature. The pH was maintained at 8–9 until a clear solution resulted. Then, the pH was adjusted to 1–2, using 1 M HCl solution. The white precipitate obtained was filtered, washed with distilled water, dried and recrystallized from methanol and water (98:2 v/v) to yield colorless blocks. Calc. (obs.) analysis (%) for **1** ($C_{21}H_{19}NO_7S_2$): C 54.65 (54.65), H 4.15 (4.15), N 3.04 (3.03), S 13.90 (13.90).

To prepare compound **2**, L-tyrosine (0.50 g, 5.52 mmol) was dissolved in 15 ml of 1 M Na_2CO_3 solution and 4-toluenesulfonyl chloride (2.1 g, 11.03 mmol) was suspended in the solution with stirring at room temperature. The pH was maintained at 8–9 until the consumption of suspended 4-toluenesulfonyl chloride, to yield a clear solution and the pH was adjusted to 1–2, using 1 M HCl solution. The white precipitate obtained was filtered, washed with distilled water, dried and recrystallized from methanol and water (98:2 v/v) to yield colorless blocks. Calc. (obs.) analysis (%) for **2** ($C_{23}H_{25}NO_7S_2$): C 56.20 (56.43), H 5.13 (4.75), N 2.85 (2.86), S 13.05 (13.10).

3.2. Data collections and refinements

Intensity data for the solvated crystals of **1** and **2** were collected at 296 K using a Bruker Kappa APEXII CCD diffractometer. The unit-cell refinements and data reductions were carried out with SAINT [14]. The structures were solved by direct methods with SHELXS-97 and the atomic models refined against $|F|^2$ with SHELXL-97 [15]. The "observed data" criterion for calculating the $R(F)$ residuals was set as $I > 2\sigma(I)$. The carbon-bound H atoms were geometrically placed and refined as riding atoms with $U_{iso}(H) = 1.2–1.5U_{eq}(C)$. The methyl groups were allowed to rotate, but not to tip, to best fit the electron density. The O- and N-bond H atoms were located in difference maps and refined as riding atoms in their as-found relative positions with $U_{iso}(H) = 1.2U_{eq}(carrier)$. Because of the poor

data to parameter ratio for **1**, some of the benzene rings were modeled as rigid hexagons. The molecular graphics were generated with ORTEP-3 for Windows [16] and the molecular geometries were analyzed with the aid of PLATON [17].

Crystal data for $\mathbf{1}_2 \cdot H_2O \cdot MeOH$ [$2(C_{21}H_{19}NO_7S_2) \cdot H_2O \cdot CH_4O$]: colorless block, 0.47 × 0.28 × 0.21 mm, M_r = 973.04, monoclinic, $P2_1$ (No. 4), a = 8.0078 (4) Å, b = 34.0704 (16) Å, c = 8.5506 (3) Å, β = 94.239 (3)°, V = 2326.47 (18) Å^3, Z = 2, T = 296 K, ρ_{calc} = 1.389 g cm^{-3}, μ = 0.276 mm^{-1}, T_{min} = 0.881, T_{max} = 0.944, 22507 reflections measured ($-10 \le h \le 9$, $-45 \le k \le 27$, $-8 \le l \le 11$; 5.98° ≤ 2θ ≤ 57.00°), R_{Int} = 0.048, 8822 merged reflections, 5884 with $I > 2\sigma(I)$, 536 parameters, $R(F)$ = 0.062, $wR(F^2)$ = 0.157, S (goodness of fit) = 1.031, Flack parameter = –0.03 (8), $w = 1/[\sigma^2(F_o^2) + 0.0669P^2 + 0.9056P]$, where $P = (F_o^2 + 2\,F_c^2)/3$, min./max. Δρ = –0.29, +0.57 e Å^{-3}, Cambridge Database deposition number: CCDC-822154.

Crystal data for $\mathbf{2} \cdot H_2O$ ($C_{23}H_{25}NO7S_2 \cdot H_2O$): colorless block, 0.19 × 0.18 × 0.09 mm, M_r = 507.56, monoclinic, $P2_1$ (No. 4), a = 5.7171 (7) Å, b = 24.359 (3) Å, c = 9.1043 (10) Å, β = 104.563 (6)°, V = 1227.2 (2) Å^3, Z = 2, T = 296 K, ρ_{calc} = 1.374 g cm^{-3}, μ = 0.265 mm^{-1}, T_{min} = 0.00, T_{max} = 0.00, 13467 reflections measured ($-7 \le h \le 7$, $-32 \le k \le 32$, $-12 \le l \le 12$; 4.62° ≤ 2θ ≤ 56.68°), R_{Int} = 0.062, 5594 merged reflections, 2508 with $I > 2\sigma(I)$, 323 parameters, $R(F)$ = 0.055, $wR(F^2)$ = 0.092), S (goodness of fit) = 0.953, Flack parameter = –0.01 (7), $w = 1/[\sigma^2(F_o^2) + 0.0218P^2]$, where $P = (F_o^2 + 2\,F_c^2)/3$, min./max. Δρ = –0.17, +0.18 e Å^{-3}, Cambridge Database deposition number: CCDC-822155.

4. Conclusions

We have structurally characterized two doubly-substituted L-tyrosine derivatives, prepared by a "green" synthesis. The change from benzene-sulfonyl to toluene-sulfonyl substituents leads to totally different molecular conformations in the respective crystals: the benzene compound (**1**) displays a folded conformation stabilized by intramolecular π–π stacking in both asymmetric molecules, whereas the toluene-sulfonyl compound adopts an "extended" conformation. The toluene sulfonyl (**2**) derivative displays a very short intermolecular C^{α}–H···O interaction in its crystal structure, in common with L-tyrosine and DL-tyrosine, whereas the benzene derivative does not. Both crystal structures contain N–H···O and O–H···O hydrogen bonds linking the tyrosine and the solvent molecules.

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