Crystal Structure of Sodium Guaiazulene Sulfonate Hemihydrate

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The crystal structure of sodium guaiazulene sulfonate hemihydrate was determined by X-ray diffraction analysis. The compound crystallizes in the monoclinic space group $P2_1/c$ with four molecules per unit cell. The cell parameters are $a = 23.271(4)\text{\AA}$, $b = 7.1965(12)\text{\AA}$, $c = 8.8334(15)\text{\AA}$, $\beta = 93.178(3)^\circ$, $V = 1477.0(4)\text{\AA}^3$. The structure was refined to the final $R1 = 0.092$. It reveals that the compound has the layer structure, stacked with hydrophobic interactions at one side and Coulomb interactions at the other side.

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Guaiazulene, 7-isopropyl-1,4-dimethylazulene, (GA) is an active component of the plant, “*Matricaria chamomilla* L.”, which has been used as self-medication for gastritis or canker sores for many years. Sodium guaiazulene sulfonate (GASO_3Na) is a hydrophilic derivative of GA, and has excellent anti-inflammatory and wound-healing properties. Thus, GASO_3Na has been widely used as an essential component of

pharmaceuticals and cosmetics. However, it is comparatively unstable and gradually decomposes in the solid state, even at room temperature. Some ways to combat this unwanted behavior have been tried. Antioxidants and weak basic metallic salts or alkaline-earth metals were employed as stabilizing agents by Kohlstaedt *et al.*,¹ while an amino acid was added by Kohara *et al.*² Kawamata *et al.*^{3,4} proposed stabilized amorphous GASO_3Na prepared by spray-drying or freeze-drying aqueous solutions of GASO_3Na containing a polymeric excipient, such as polyvinyl pyrrolidone. In order to discuss the stabilization methods, it is useful to know the crystal structure of GASO_3Na . It has, however, not been known up to now. We report here on the crystal structure of the title compound, which is one of the GASO_3Na forms usually used for pharmaceuticals and

Table 1 Crystal and experimental data

Formula: $\text{C}_{15}\text{H}_{17}\text{SO}_3\text{Na} \cdot 1/2\text{H}_2\text{O}$
Formula weight = 309.36
Temperature = 193(2)K
Wavelength = 0.71073 Å
Crystal system: monoclinic
Crystal color, habit: blue, plate
Crystal size: $0.36 \times 0.35 \times 0.02\text{ mm}^3$
Space group, Z: $P2_1/c$, 4
Unit cell dimensions:
$a = 23.271(4)\text{\AA}$ $b = 7.1965(12)\text{\AA}$
$c = 8.8334(15)\text{\AA}$
$\beta = 93.178(3)^\circ$ $V = 1477.0(4)\text{\AA}^3$
Density _{calc.} = 1.387 g/cm ³
No. of reflections used = 7832
$\theta_{\text{max}} = 27.38^\circ$
$R1 [2436\text{ refs. } I > 2\sigma(I)] = 0.092$
$wR2 (\text{all data}) = 0.250$
$(\Delta/\sigma)_{\text{max}} = 0.000$
$(\Delta\rho)_{\text{max}} = 0.616\text{ e\AA}^{-3}$
$(\Delta\rho)_{\text{min}} = -0.769\text{ e\AA}^{-3}$
Measurement: Bruker smart 1000
Program system: SHELX
Structure determination: direct method
Refinements: full-matrix least-squares on F^2

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free from charge, by quoting the publication citation and deposition number: CCDC290058.

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Fig. 1 Chemical structure of the title compound.

Fig. 2 Perspective view of the molecular structure of the title compound. The thermal ellipsoids are drawn at the 50% probability level. The spheres present the hydrogen atoms. (See text for the hydrogen atoms of the hydration water (O1w) and the two Na^+ cation sites.)

Table 2 Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

Atom	x	y	z	U_{eq}
C1	0.2615(2)	0.4510(7)	-0.2202(6)	0.0243(11)
C2	0.3212(2)	0.4489(7)	-0.2120(6)	0.0253(11)
C3	0.3424(2)	0.4844(7)	-0.0623(5)	0.0208(10)
C4	0.2936(2)	0.5450(7)	0.1873(5)	0.0234(10)
C5	0.2433(2)	0.5817(8)	0.2648(6)	0.0309(12)
C6	0.1862(2)	0.5854(9)	0.2226(6)	0.0364(13)
C7	0.1562(2)	0.5466(9)	0.0819(6)	0.0328(12)
C8	0.1847(2)	0.5054(8)	-0.0487(6)	0.0309(12)
C9	0.2948(2)	0.5113(7)	0.0313(6)	0.0222(10)
C10	0.2422(2)	0.4898(7)	-0.0765(6)	0.0257(11)
C11	0.2240(2)	0.4210(9)	-0.3613(6)	0.0346(13)
C12	0.3479(3)	0.5440(9)	0.2882(6)	0.0349(13)
C13	0.0913(3)	0.5500(12)	0.0749(8)	0.0508(18)
C14	0.0676(3)	0.7405(16)	0.1135(11)	0.085(3)
C15	0.0666(4)	0.3941(19)	0.1705(11)	0.091(4)
S1	0.41724(5)	0.49518(16)	-0.02159(13)	0.0196(3)
O1	0.43304(16)	0.3361(5)	0.0730(5)	0.0338(9)
O2	0.43029(16)	0.6696(5)	0.0545(5)	0.0341(9)
O3	0.44208(16)	0.4876(6)	-0.1693(4)	0.0382(11)
Na1*	0.51163(17)	0.1979(6)	0.1961(4)	0.0263(9)
Na2*	0.50648(17)	0.8033(6)	0.1926(4)	0.0266(9)
O1w	0.5	0.0	0.0	0.070(3)

*0.50 occupancy for Na1 and Na2.

Fig. 3 Ball-and-stick views of the crystal structure of the title compound along the b -axis. The broken line represents the plane on which the Na^+ cations are roughly located.cosmetics.⁵

Single crystals of the title compound were prepared by recrystallization from a methanol solution of GASO_3Na . Blue crystals were obtained from the solution at room temperature by slow evaporation for a few days. Diffraction data were collected by a Bruker smart 1000 CCD diffractometer at 193 K with graphite-monochromated $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct methods.⁶ The non-hydrogen atoms were refined anisotropically by a full-matrix least-squares method.⁷ The hydrogen atoms of the hydration water, located on a center of symmetry, were not used in the present refinement. The positions of other hydrogen atoms were calculated geometrically. SHELX programs were used for these calculations.

Table 3 Selected bond distances and angles

Distances ($\text{\AA}$)		Angles ($^\circ$)	
S1-O1	1.453(4)	O1-S1-O2	112.1(2)
S1-O2	1.448(4)	O1-S1-O3	112.7(3)
S1-O3	1.458(4)	O2-S1-O3	111.4(3)

The crystal and experimental data are given in Table 1. This compound crystallizes in the monoclinic $P2_1/c$ space group. The chemical structure, the molecular structure, and the final atomic parameters of non-hydrogen atoms are shown in Figs. 1 and 2, and Table 2 respectively. The crystal structure reveals that GASO_3^- anions stack themselves up, forming lamellar layers with a one-molecule width (Fig. 3). In the layers the aromatic rings are almost parallel to each other, but staggered so as not to completely overlap. Thus, the methyl group at the 1-position is located just over the adjacent seven-membered rings. Hydrophobic isopropyl and hydrophilic sulfo groups are placed separately, so that isopropyl groups are projecting at one side of the layer, while the sulfo groups are at the other side. Then, the layers are stacked with hydrophobic interactions among isopropyl groups at one side and Coulomb interactions between sulfo groups and Na^+ cations at the other side, alternating upside down and rightside up, along the a -axis. A couple of stacked layers correspond to the repetition sequence of the crystal. The Na^+ cation is disordered at two sites with a half occupancy. Thus, the Na^+ cations at the two sites are drawn just as a dumbbell in Fig. 3. The Na^+ cation is formally coordinated to six oxygen atoms (four from two adjacent sulfo groups and two from two adjacent hydration water molecules). The hydration water molecule is located almost on the Na plane (see Fig. 3) and coordinates to four adjacent Na^+ cations. The sulfo groups from the upper and lower layers face each other at the interface of the two layers, and are related by a pseudo-rotation-reflection axis, S_6 . All of the S-O bond distances and all of the O-S-O bond angles are *ca.* 1.45 $\text{\AA}$ and *ca.* 112 $^\circ$, respectively (Table 3). Thus, the three oxygen atoms of the sulfo group are described as being almost equivalent.

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