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Preliminary experimental results on charge density of sulfathiazole

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Biré

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Xiaoxuan Shi, Nouha El Hassan, Nour-Eddine Ghermani, Anne Spasojevic - de Biré. Preliminary experimental results on charge density of sulfathiazole. Colloque de cristallographie, Jun 2014, Orsay, France. <hal-02298962>

HAL Id: hal-02298962

<https://hal.science/hal-02298962v1>

Submitted on 23 Sep 2020

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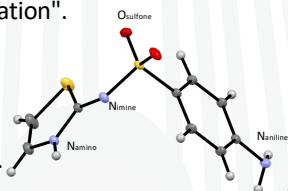


HAL Authorization

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Why sulfathiazole?

- Sulfathiazole is an antimicrobial agent discovered in 1939. It is no longer widely used among human since less toxic compounds have replaced it.
- Yet its crystallographic properties have been studied thoroughly, as the molecular structure enables it to form a large variety of hydrogen-bonded networks. The polymorphic compound has an extensive family of solvates and adducts. Sulfathiazole can be considered as a model for polymorphism study.
- Accurate polymorphism characterization belongs to a wider project "Non Photochemical Light Induced Nucleation". This compound has been obtained by spontaneous nucleation, NPLIN is in progress.



Polymorphism

- 5 polymorphs have been crystallized and identified, where 3 forms share similar crystal packing. The form considered as the most thermodynamically stable is the form IV^[1].

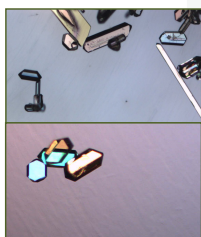
Form	Space Group	Unit Cell	Intermolecular H bonds	Remark
I	P2 ₁ /c	a=10.50, b=12.96, c=17.18, α=90, β=107.65, γ=90	dimer N _{amine} H...N _{imine} inter N _{aniline} H...O _{sulfone}	centrosymmetric α dimers
II	P2 ₁ /c	a=8.190, b=8.532, c=15.45, α=90, β=94.14, γ=90	dimer N _{amine} H...N _{aniline} dimer N _{aniline} H...O _{sulfone} inter N _{aniline} H...O _{sulfone}	β dimers
III	P2 ₁ /a	a=15.50, b=8.494, c=17.43, α=90, β=112.76, γ=90	dimer N _{amine} H...N _{aniline} dimer N _{aniline} H...O _{sulfone} inter N _{aniline} H...N _{imine}	β dimers
IV	P2 ₁ /n	a=1.77, b=8.467, c=11.37, α=90, β=91.65, γ=90	dimer N _{amine} H...N _{aniline} dimer N _{aniline} H...O _{sulfone} inter O _{sulfone} ...O _{sulfone}	β dimers
V	P2 ₁ /n	a=15.50, b=8.494, c=17.43, α=90, β=112.76, γ=90	inter N _{amine} H...O _{sulfone} inter N _{amine} H...N _{aniline} inter N _{aniline} H...O _{sulfone}	

Experiments and preliminary results

- In crystal studies, charge density $\rho(\mathbf{r})$ refers to the distribution of charge around and in the molecule. It could be determined theoretically or experimentally.
- The classical experimental method is through single crystal high resolution X-ray diffraction experiment.
- To better describe the electron density, the Hansen-Coppens aspherical-atom formalism is widely used^[2].

$$\rho_{at}(\mathbf{r}) = P_c \rho_c(\mathbf{r}) + P_v \kappa^3 \rho_v(\kappa \mathbf{r}) + \sum_{l=0}^{l_{max}} \kappa^{l^3} R_l(\kappa \mathbf{r}) \sum_{m=0}^l P_{lm\pm} d_{lm\pm}(\theta, \phi)$$

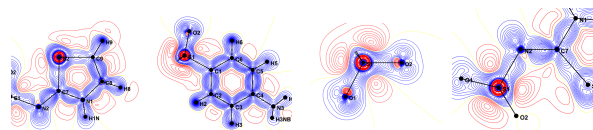
Spherical term
Aspherical term



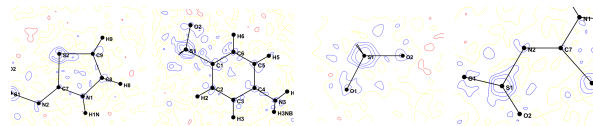
- Single crystal of sulfathiazole is prepared by slow evaporation of supersaturated 1:1 water-ethanol solution. Due to the energetic similarity, form II, III et IV are crystallized simultaneously. As proved by the following experiment, the tested sample is a form IV crystal.

- The X-ray diffraction experiment is carried out at 100 K ($\lambda = 0.71073 \text{ \AA}$), with 13641 independent reflections of 100% completeness. $R_{int} = 2.01\%$.

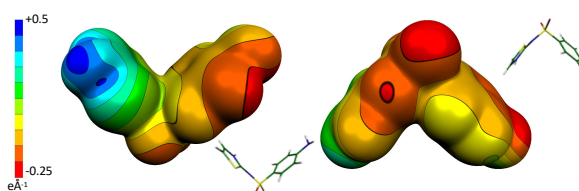
- The multipole refinement is performed using program package MoPro (Rf = 1.464, wR = 1.371, GOF = 0.690).
- Static deformation density of thiazole, phenyl, S=O bond and S-N bond.



- The refinement of sulfur parameters is still under process



- The experimental electrostatic potential is shown on the below. EP is generated on molecule surface (0.01 e\AA^{-3}).



Conclusion and perspective

- A variety of methods to improve the sulfur density have been performed: anharmonicity, relativist effect, optimized parameter for sulfur, etc.
- Possible disorder due to the vibration of S=O bond.
- Other improvement during the refinement.
- New sample from NPLIN of sulfathiazole have been prepared for high resolution X-ray diffraction experiment.