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The crystal structure of sulfamethoxazole, interaction with DNA, DFT calculation, and molecular docking studies

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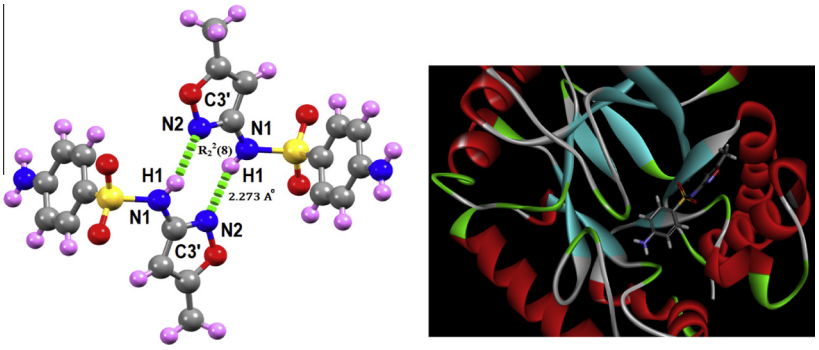
HIGHLIGHTS

- X-ray structure of Sulfamethoxazole (SMX).
- DFT calculation of SMX and the spectral properties.
- The DNA interaction with SMX, $K_b = 4.37 \times 10^4\ M^{-1}$.
- Molecular docking study of SMX with DHPS from *E. coli* and *S. pneumoniae*.

GRAPHICAL ABSTRACT



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ABSTRACT

Sulfamethoxazole (SMX) [4-amino-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide] is structurally established by single crystal X-ray diffraction measurement. The crystal packing shows H-bonded 2D polymer through N(7)—H(7A)—O(2), N(7)—H(7B)—O(3), N(1)—H(1)—N(2), C(5)—H(5)—O(3)—S(1) and N(7)—(H7A)—O(2)—S(1). Density Functional Theory (DFT) and Time Dependent-DFT (TD-DFT) computations of optimized structure of SMX determine the electronic structure and has explained the electronic spectral transitions. The interaction of SMX with CT-DNA has been studied by absorption spectroscopy and the binding constant (K_b) is $4.37 \times 10^4\ M^{-1}$. The *in silico* test of SMX with DHPS from *Escherichia coli* and *Streptococcus pneumoniae* helps to understand drug metabolism and accounts the drug–molecule interactions. The molecular docking of SMX–DNA also helps to predict the interaction feature.

Introduction

Sulfonamides, the antibacterial and antifungal drugs [1], have inhibited the enzyme that incorporates *para*-aminobenzoic acid (PABA) into folic acid [2–5]. Sulfamethoxazole (SMX), a known sulfonamide, is most often used as part of a synergistic combination with trimethoprim in a 5:1 ratio in co-trimoxazole [6] since its approval by FDA in 1961. SMX resists bacterial proliferation by inhibition of synthesis of dihydrofolic acid (a dihydrofolate reductase inhibitor) [7] which is an important intermediate in folate synthesis. It also inhibits the enzyme activity of DHPS (dihydropteroate synthase) (Scheme 1). SMX has shown antitumor, anti-viral, anti-fungal, anti-carbonic anhydrase, diuretic, antithyroid, hypoglycemic and protease inhibitor activity [8–12].

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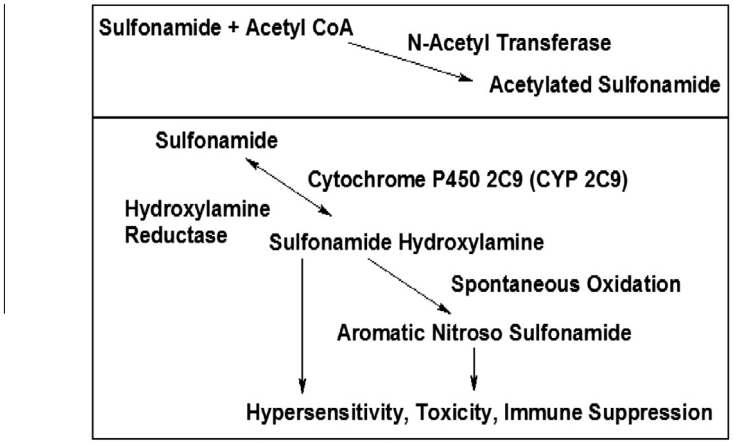

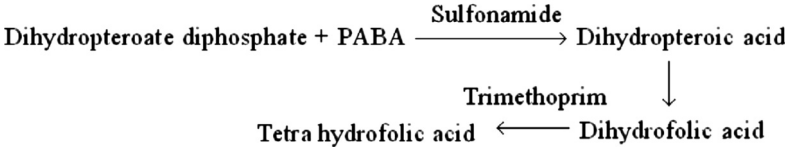

Scheme 1. Synthesis of folic acid and participation of sulfonamide in metabolic process.

The administration of SMX for a longer period has identified large number of side effects and toxicity to human health [13–15]. The hypersensitivity [16] is due to oxidative metabolite of SMX such as SMX-hydroxylamine (SMX-NHOH) and SMX-nitroso (SMX-NO). To generate an antigenic signal, cytochrome P450 enzymes in the liver metabolize SMX to SMX-NHOH, SMX-NO [17]. Herein, we use single crystal X-ray diffraction technique to confirm the structure of SMX and the electronic properties have been computed from Density Functional Theory (DFT) and Time Dependent-DFT (TD-DFT) data of optimized geometry. The docking approach is used recently in the drug-design science where docking allows screening of large molecular databases [18] on resolved or modeled proteins. In this work we have used docking studies with SMX and DHPS protein to define the zone of interaction. The drug–DNA interaction is also examined experimentally and by docking studies.

Experimental section

Materials and physical measurement

Sulfamethoxazole (SMX) was purchased from Sigma–Aldrich and used without further purification. The solvents were dried and purified by standard methods [19]. The acetonitrile used for electrochemical studies was dried with CaH_2 and distilled prior to use. Dinitrogen was purified by bubbling through an alkaline pyrogallol solution. All other chemicals and solvents were of reagent grade and were used without further purification. Tris–HCl buffer solution and CT-DNA were purchased from Bangalore-Genie, India and used without further purification. Spectroscopic data were obtained using the following instrument: UV–Vis spectra by Perkin Elmer UV–Vis spectrophotometer model Lambda 25. Electrochemical measurements were performed using computer-controlled CH-Instruments, Electrochemical workstation, Model No CHI 600D (SPL) with Pt-disk electrodes. All measurements were carried out under nitrogen environment at 298 K with reference to *vs* Ag/AgCl at 50 mV s^{-1} scan rate using Pt-bead working electrode in acetonitrile and $[nBu_4N]ClO_4$ as supporting electrolyte. The reported potentials are uncorrected for junction potential.

X-ray crystal structure analysis

Sulfamethoxazole was crystallized by slow diffusion of CH_2Cl_2 solution to hexane (size – 0.35 × 0.34 × 0.19 mm). Data were collected (Table 1) by Bruker Smart Apex II CCD Area Detector at 293(2) K. Diffraction was recorded in the range $3.74 \leqslant 2\theta \leqslant 67.28°$. Fine-focus sealed tube was used as the radiation source of graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). Data were corrected for Lorentz and polarization effects and an empirical absorption correction in the $h\,k\,l$ range: $-38 \leqslant h \leqslant 38$; $-9 \leqslant k \leqslant 11$; $-22 \leqslant l \leqslant 21$. Multi-scan absorption corrections were applied [20]. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2 using the SHELXL-97 [21] program with anisotropic displacement parameters for all non-hydrogen atoms. Crystallographic refinement data and selected geometric parameters are summarized in Table 1. Programs SHELXL-97 [22] and ORTEP-3 [23] were used within

Table 1
Crystal data and structure refinement for Sulfamethoxazole (SMX).

Empirical formula	$C_{10}H_{11}N_3O_3S$
Formula weight	253.28
Temperature, K	100(2)
Wavelength, Å	0.71073
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	
a, Å	*a* = 24.7195(9)
b, Å	*b* = 7.2040(3)
c, Å	*c* = 14.6631(6)
β, °	118.217(2)
Volume, Å^3	2300.89 (16)
Z	8
Density (calculated), mg/m^3	1.462
Absorption coefficient	0.282 mm−1
F (000)	1056
Reflections collected	21,304
Independent reflections	4513 [*R* (int) = 0.0260]
R_1^a	0.0377
WR_2^b	0.1080
Goodness-of-fit on F^2	1.070

$R_1^a = \Sigma|F_0 - F_c|/\Sigma F_0$. $WR_2^b = [\Sigma w(F_0^2 - F_c^2)/\Sigma w F_0^4]^{1/2}$ are general but *w* are different, $w = 1/[\Sigma^2 (F_o^2) + (0.0681P)^2 + 1.3327P]$ for SMX.