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A Review of Kinetic and Thermodynamic Study of Oxidation of Sulpha Drugs by Metallic and Non-Metallic Oxidants

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ABSTRACT

Sulfa drug, also called sulfonamide, any member of a group of synthetic antibiotics containing the sulfanilamide molecular structure. Sulfa drugs were the first chemical substances systematically used to treat and prevent bacterial infections in humans. Their use has diminished because of the availability of antibiotics that are more effective and safer and because of increased instances of drug resistance. Sulfonamides are still used, but largely for treating urinary tract infections and preventing infection of burns. They are also used in the treatment of certain forms of malaria. The antibacterial effects of sulfonamides were first observed in 1932, when German bacteriologist and pathologist Gerhard Domagk noted the effects of the red dye Prontosil on Streptococcus infections in mice. It was later proved by French researchers that the active agent of Prontosil was sulfanilamide, or para-aminobenzenesulfonamide, a product of the body's metabolism of Prontosil. By the 1940s sulfanilamide was a widely used drug. During World War II white sulfanilamide powders became standard in first-aid kits for the treatment of open wounds, and sulfanilamide tablets were taken to fight intestinal infections. Though the medicine was relatively safe, allergic reactions such as skin rashes, fever, nausea, vomiting, and even mental confusion were common. With the introduction of less-toxic derivatives and especially with the mass production of penicillin, its use declined.

Many other sulfa drugs were derived from sulfanilamide in the 1940s, including sulfathiazole (systemic bacterial infections), sulfadiazine (urinary tract and intestinal tract infections), and sulfamethazine (urinary tract infections). However, all sulfa drugs induced some of the side effects listed above, and bacteria developed resistant strains after exposure to the drugs. Within a few decades many of the sulfa drugs had lost favour to more-effective and less-toxic antibiotics.

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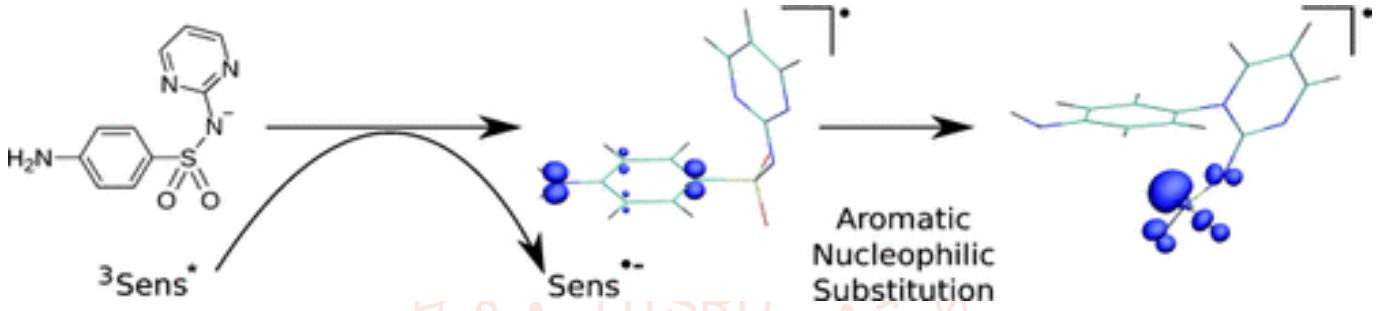
INTRODUCTION

Oxidation of a wide range of sulfonamide antibiotics (SAs) containing five- and six-membered heterocyclic moieties (R) in their molecular structures. Kinetics measurements of the reactions between Fe^{VI} and SAs at different pH (6.5–10.0) give species-specific second-order rate constants, k_5 and k_6 of the reactions of protonated Fe^{VI} ($HFeO_4^-$) and unprotonated Fe^{VI} ($Fe^{VI}O_4^{2-}$) with protonated SAs (HX), respectively. The values of k_5 varied from $(1.2 \pm 0.1) \times 10^3$ to $(2.2 \pm 0.2) \times 10^4$ M^{-1} s^{-1}, while the range of k_6 was from $(1.1 \pm 0.1) \times 10^2$ to $(1.0 \pm 0.1) \times 10^3$ M^{-1} s^{-1} for different SAs.[1,2] The transformation products of reaction between Fe^{VI} and sulfadiazine (SDZ, contains a six-membered R) include SO_2 extrusion oxidized products (OPs) and aniline hydroxylated products. Comparatively, oxidation of sulfisoxazole (SIZ, a five-membered R) by Fe^{VI} has OPs that have no SO_2 extrusion in their structures. Density functional theory calculations are performed to demonstrate SO_2 extrusion in oxidation of SDZ by Fe^{VI}. The detailed mechanisms of oxidation are proposed to describe the differences in the oxidation of six- and five-membered heterocyclic moieties (R) containing SAs (i.e., SDZ versus SIZ) by Fe^{V}. The photocatalytic degradation of sulfonamides in aqueous TiO_2 suspension under UV irradiation has been investigated using potassium ferrate as electron acceptors. The results showed that the stability of Fe(VI) is dependent on pH significantly, and the stability reduces obviously in the presence of UV-TiO_2. The experiments indicated that Fe(VI) could effectively scavenge the conduction band electrons from the surface of TiO_2.[3,4] The photocatalytic oxidation of sulfonamides with Fe(VI) was found to be much faster than that without Fe(VI). The SD, SM, and SMX concentration was greatly reduced by 89.2%, 83.4%, and 82.0%, respectively, after 10 min with UV-TiO_2-Fe(VI), comparing to 65.2%, 66.0%, and 71.9%, respectively, with Fe(VI) only in the dark and 71.3%, 72.7%, and 76.0%, respectively, with UV-TiO_2. The pH value of solution significantly influenced the sulfonamides degradation in UV-TiO_2-Fe(VI) system. The degradation amount of sulfonamides after 10 min was a maximum at pH 7. The intermediate products of sulfonamides oxidation by UV-TiO_2-Fe(VI) were analysed by LC-HESI-MS-MS and the results suggested that a majority of sulfonamides turned into large-molecule products without complete mineralization. Antimicrobial sulfonamides are important medications. However, their use is associated with major immune-mediated drug

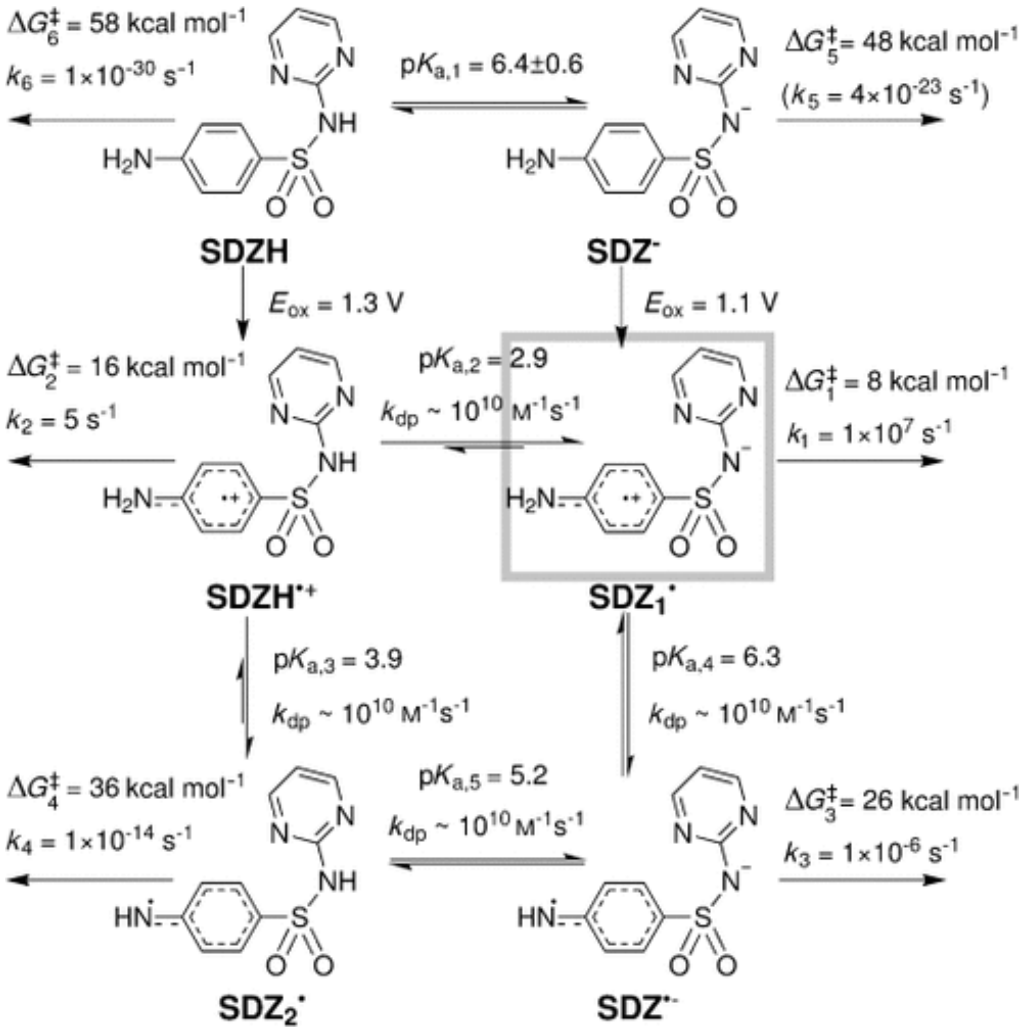
hypersensitivity reactions with a rate that ranges from 3% to 4% in the general population. The pathophysiology of sulfa-induced drug hypersensitivity reactions is not well understood, but accumulation of reactive metabolites (sulfamethoxazole [SMX] hydroxylamine [SMX-HA] and SMX N-nitrosamine [SMX-NO]) is thought to be a major factor. These reactive metabolites contribute to the formation of reactive oxygen species (ROS) known to cause cellular damage and induce cell death through apoptosis and necroptosis. ROS can also serve as "danger signals," priming immune cells to mount an immunological reaction. We recruited 26 sulfa-hypersensitive (HS) patients, 19 healthy control subjects, and 6 sulfa-tolerant patients to this study. Peripheral blood monocytes and platelets were isolated from blood samples and analyzed for in vitro cytotoxicity, ROS and carbonyl protein formation, lipid peroxidation, and GSH (glutathione) content after challenge with SMX-HA. When challenged with SMX-HA,[5,6] cells isolated from sulfa-HS patients exhibited significantly (P ≤. 05) higher cell death, ROS and carbonyl protein formation, and lipid peroxidation. In addition, there was a high correlation between cell death in PBMCs and ROS levels. There was also depletion of GSH and lower GSH/GSSG ratios in peripheral blood mononuclear cells from sulfa-HS patients. The amount of ROS formed was negatively correlated with intracellular GSH content. The data demonstrate a major role for oxidative stress in in vitro cytotoxicity of SMX reactive metabolites and indicate increased vulnerability of cells from sulfa-HS patients to the in vitro challenge.[7,8]

Sulfadiazine reacts with a triplet photosensitizer to form an aniline radical cation (see figure). One protonation state species of this short-lived intermediate exhibits a greatly lowered energy barrier for an intramolecular nucleophilic aromatic substitution, which differs in mechanism from analogous closed-shell reactions (Sens = sensitizer).



Sulfonamide antibiotics are an important class of organic micropollutants in the aquatic environment. For several, sulfur dioxide extrusion products have been previously reported upon photochemical or dark oxidation. Using quantum chemical modeling calculations and transient absorption spectroscopy, it is shown that single-electron oxidation from sulfadiazine produces the corresponding aniline radical cation. Density functional theory calculations indicate that this intermediate can exist in four protonation states. One species exhibits a low barrier for an intramolecular nucleophilic attack at the para position of the oxidized aniline ring, in which a pyrimidine nitrogen acts as a nucleophile. This attack can lead to a rearranged structure, which exhibits the same connectivity as the SO_2-extruded oxidation product that was previously observed in the aquatic environment and characterized by NMR spectroscopy.[9,10]

oxidative transformation of sulfadiazine as a model compound for structurally similar sulfonamide antibiotics. Our results provide evidence for a two-step reaction that can lead to a rearranged structure: the first step is a single-electron transfer from the drug to a suitable oxidant, producing an aniline radical cation. This oxidized intermediate undergoes speciation, but only one species exhibits a low barrier for a nucleophilic attack of N^{13} on C^5. This reaction can out-compete deprotonation of the oxidized aniline moiety, leading to a rearranged structure, in agreement with previous experimental results. The speciation of sulfadiazine, along with barrier heights for possible rearrangement reactions of all species, is given in Scheme 2. Based on this schematic, SDZ^- is oxidized to $^{SDZ}_{1}^{\bullet}$, which can undergo the rearrangement reaction rapidly. Alternatively, SDZH can be oxidized to $SDZH^{\cdot+}$, lose an acidic proton to become $^{SDZ}_{1}^{\bullet}$, and then undergo rearrangement. In the following sections, we provide computational and experimental data to support the different proposed steps of the reaction.[11,12]



DFT calculations indicate that the preferential site of electron abstraction of SDZ is the aniline ring. Three moieties in SDZH or SDZ^- are potentially susceptible to electron transfer/single-electron oxidation: 1) the aniline group, resulting in an aniline radical cation; 2) the N^{11} σ-lone pair (SDZ^- only), yielding a σ-radical with a localized unpaired electron; or 3) the N^{11} π-lone pair, yielding a π-radical, with the unpaired electron possibly stabilized by resonance with the pyrimidine ring. By means of implicitly solvated DFT calculations employing the ROMPW1K functional, we searched different structural conformers of the oxidized species in both protonation states. On resulting minimum energy structures, wavefunction stability analysis was performed with UB3LYP in order to verify that the electronic structure found corresponded to the electronic ground state. ROMPW1K and UB3LYP results were compared by visual inspection of the location of the unpaired electron/the spin density. Whenever aqueous solvent effects (SMD) were included, the minimum energy structures were found to be aniline radical cations with both model chemistries. However, in gas-phase calculations, both model chemistries predict the formation of the N^{11} π-radical for $SDZ_1^{\bullet}$. Based on these calculations, we concluded that an aniline radical cation would be the predominant intermediate formed when SDZ reacts with a single-electron oxidant in aqueous solution.[13,14]

Discussion

The oxidized SDZ species can exist in different protonation states. By a thermodynamic cycle employing the computed oxidation potentials of SDZH and SDZ^-, we estimate the experimental $pK_{a,1}$=6.4±0.6 of SDZH to be lowered by approximately four units to $pK_{a,2}$=2.9 for $SDZH^{\cdot+}$. For the estimation of $pK_{a,3/4}$ we used linear regression of DFT calculated pK_a values with experimental valuesfor p-substituted aniline radical cations (Figure S3 in the Supporting Information, r^2=0.96). The regression formula of the results omitting vibrational effects (Figure S3) was chosen because of its better r^2 value. We estimate the error in the predicted $pK_{a,3/4}$ values to be <1.0; $pK_{a,5}$ was calculated directly from $pK_{a,2/3/4}$. Based on these results, several species may exist under equilibrium conditions, of which SDZ^- should be the most prominent species.

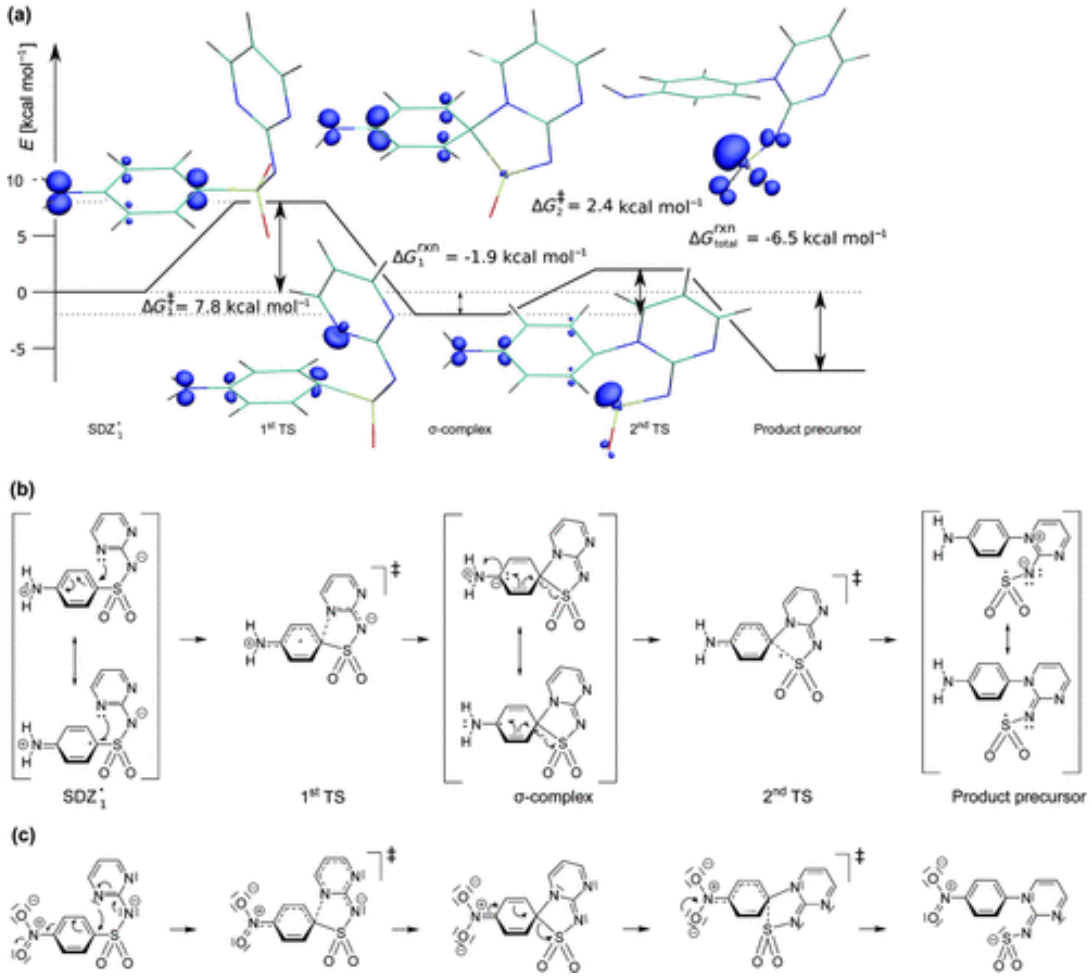
To judge whether equilibrium conditions should be assumed, we estimate the timescale of deprotonation, which we later compare to the timescale of rearrangement reactions. Deprotonation of any of the oxidized species can, in a simplified picture, proceed in two ways: either by direct protonation of a water molecule, or through protonation of a hydroxyl anion. For the deprotonation at NH_2 by OH^-, we can compare to experimental rates of analogous compounds: $SA^{\cdot}$ and $AN^{\cdot+}$ react with OH^- with rates of $k_{SA^{\cdot}}$=8.8×10^9 M^{-1} s^{-1} and $k_{AN^{\cdot+}}$=2.2×10^10 M^{-1} s^{-1}. We assume that the deprotonation at either amine-H moiety will occur close to diffusion limitation (≈1×10^10 M^{-1} s^{-1}), in agreement with a barrierless process found with a DFT cluster/continuum model for $SDZH^{\cdot+}$/$SDZ_1^{\bullet}$. Direct protonation of water is likely insignificant at ambient pH for most of the species encountered here, but may further contribute to the deprotonation rate associated with $pK_{a,2}$. In the absence of the necessary experimental data, we do not attempt to estimate these rate constants.[15,16]

Rearrangement competes with deprotonation: In order to rearrange the sulfadiazine structure in a way so that the resulting connectivity is that of the observed product it is necessary to form a bond between C^5 and $N^{13/14}$. Calculating charges of SDZ^- and $^{SDZ}_{1}{}^{\bullet}$ using natural population analysis (NPA), the charge on C^5 is increased from −0.37 to −0.16 upon oxidation. Thus, C^5 is more prone to a nucleophilic attack in the oxidized state. For all four oxidized species, we calculated barrier heights for such a nucleophilic aromatic substitution reaction. The results indicate that the attack is far less favorable if the aniline ring is deprotonated. For comparison, we give barriers of the reduced, closed-shell species, which are found to be too high to contribute to the observed reactivity. For each barrier, we estimated first-order rate constants using transition state theory. Details on the procedure, as well as an estimation of uncertainties of barrier heights and reaction energetics are given in the Supporting Information.

To compare these rates of nucleophilic attack to the rates of deprotonation, we calculated first-order rate constants for the pH-dependent equilibration reactions from an estimated second order rate constant of $k_{dp}=1\times10^{10}\ M^{-1}\ s^{-1}$. First-order rate constants range from $k'_{dp}=1\times10^{1}\ s^{-1}$ (pH 5) to $k'_{dp}=1\times10^{6}\ s^{-1}$ (pH 10). Despite the uncertainty in these estimated rate constants, it is evident that $^{SDZ}_{1}{}^{\bullet}$ is the only oxidized intermediate for which rearrangement can clearly out-compete deprotonation at NH_2. For $SDZH^{\cdot+}$, deprotonation of both possible protons is likely out-competing the rearrangement. For the structures with a deprotonated anilino group, rearrangement cannot happen on the timescale of experiment ($t_{1/2}$>1 year).

A possible side reaction is the dimerization of radicals. For electrostatic reasons, we do not expect this reaction for species with a positively charged aniline ring ($SDZH^{\cdot+}$, $^{SDZ}_{1}{}^{\bullet}$). For $^{SDZ}_{2}{}^{\bullet}$ and $SDZ^{\cdot-}$, dimerization can be expected. Products resulting from radical coupling at the aniline-N position have been reported for the oxidation of sulfamethazine.

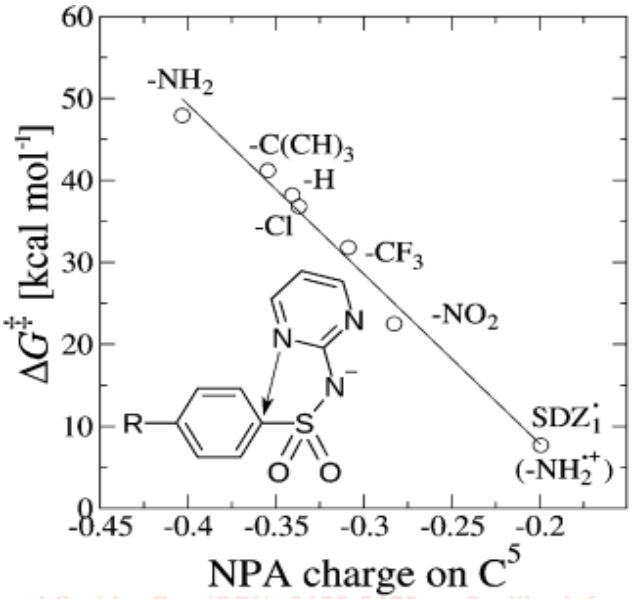
Detailed reaction mechanism of the open-shell rearrangement: DFT calculations indicated that for $^{SDZ}_{1}{}^{\bullet}$, an aromatic nucleophilic substitution at the oxidized aniline ring is kinetically possible ($\Delta G^{\neq}$=8 kcal mol^{-1}). We propose a detailed reaction mechanism of the rearrangement of $^{SDZ}_{1}{}^{\bullet}$. Barrier heights, structures, and spin densities are shown. [17,18]



In $^{SDZ}_{1}{}^{\bullet}$, the spin density is mostly localized on N^1 and C^5, regardless of the orientation of the two six-membered rings relative to each other (conformers not shown). The nucleophilic attack of N^{13} on C^5 proceeds through a transition structure in which the unpaired electron is shared between N^1, C^2, C^5, and the attacking N^{13}. By NBO analysis, this was identified as a hemibonded structure (see the Supporting Information). This transition structure connects $^{SDZ}_{1}{}^{\bullet}$ to a σ-complex, which is only slightly lower (1.9 kcal mol^{-1}) in energy than $^{SDZ}_{1}{}^{\bullet}$. In the σ-complex, the spin density is again localized in the aniline ring, where N^1 and C^2, and to a lesser extent C^4 and C^6, bear spin density. This intermediate is connected by the second transition structure to a rearranged product precursor. In the second transition structure, which exhibits a lower barrier height (2.4 kcal mol^{-1}), the spin density shifts from the aniline ring to the sulfur center. In the product precursor, the spin

density is entirely transferred to the S center and the surrounding O and N centers. We calculated the total free energy of reaction between $^{SDZ}_{1}^{\bullet}$ and the product precursor to be a favorable −6.5 kcal mol^{-1}.[19,20] The reaction mechanism presented above resembles that of the (closed-shell) Smiles-rearrangement, or, more generally, the mechanism of an aromatic nucleophilic substitution. The latter proceeds via a metastable σ-complex before breaking the C-S bond; this intermediate has been characterized spectroscopically for closed-shell reactions

By comparing charges of the C^5 position with computed barrier heights for several hypothetical analogous closed-shell reactions, we show more clearly that the attack is nucleophilic in both the open-shell and closed-shell cases. For a hypothetical rearrangement of a closed-shell species, analogous to the reaction undergone by $^{SDZ}_{1}^{\bullet}$, we propose Lewis structures, based on natural localized molecular orbital (NLMO) analysis. An electron-withdrawing group (e.g., $-NO_2$) in para position to the sulfa moiety enables the rearrangement. The transition state and the resulting intermediate are stabilized by a mesomeric effect. To explore the similarity of closed-shell aromatic nucleophilic substitutions and the rearrangement at the oxidized (open-shell) aniline ring, we calculated barrier heights for different homologues of SDZ^- by replacing $-NH_2$ by other substituents. The barrier heights are shown as a function of the NPA charge on C^5 in Figure. The oxidized sulfadiazine zwitterion fits well on the linear relationship found for closed-shell rearrangements, suggesting that the nucleophilic attack is of similar nature in both cases. By this argument, the $-NH_2^{\bullet+}$ substituent is more electron-withdrawing than $-NO_2$.



Results

Hence, sulfadiazine and congeners can be oxidized by common environmental oxidants, such as ^{3}DOM or $CO_3^{\bullet-}$. Both DFT calculations and LFP experiments indicated the formation of an aniline-centered radical upon oxidation of sulfadiazine. It is also imaginable that such single-electron oxidations occur in vivo in subjects administered sulfonamide drugs, if suitable oxidants are present. By DFT calculations, we found that the oxidized aniline ring is susceptible to a nucleophilic attack in the para position as long as the amino group remains protonated. The barriers found for nucleophilic attack are drastically lowered compared to the corresponding closed-shell compound, and this may provoke further studies of the electrophilicity of single-electron oxidized aromatics in aqueous solution. H-atom abstraction of the $-NH_2$ moiety by an oxidant may be considered as an alternative reaction mechanism. However, the predicted reactivities indicate that the corresponding product ($^{SDZ}_{2}^{\bullet}$) could not undergo the rearrangement.

To assess the fate of the oxidized species, it is necessary to investigate the timescales of deprotonation and nucleophilic attack, both of which are fast reactions. The reaction mechanism of the nucleophilic attack is found to proceed through a σ-complex, in agreement with a nucleophilic aromatic substitution. However, the electronic structure of this open-shell reaction differs from analogous closed-shell reactions.[18,19]

The presented mechanism may be possible for structurally similar sulfonamides. In exploratory calculations (see the Supporting Information), DFT results indicate that aniline$-SO_2-NH-$R compounds can undergo this mechanism if R is a 6-membered ring that contains a suitable nucleophile. For R=5-membered rings, DFT predicts either higher barriers, or an ionization of the 5-membered ring en lieu of the aniline moiety. These considerations could be included in the development and study of novel sulfonamide antibiotics: the feasibility of formation of SO_2 extrusion by the present mechanism can be tested with DFT, leading to implications about the environmental (and possibly in vivo) fate of novel drugs.

The proposed reaction mechanism does not account for the additional SO_2 extrusion process observed during direct photolysis of sulfonamide antibiotics. The excited state equivalent of the reported reaction would be an aniline→pyrimidine CT state, but exploratory DFT calculations indicated that such CT states do not correspond to S_1 or T_1 (data not shown). Hence, we expect possible excited-state transformation mechanisms to be of a different nature.

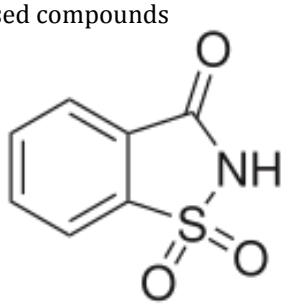
A list of chemicals, suppliers and purities is given in the Supporting Information. Unbuffered solutions (20.1 mM) of sulfanilic acid (SA) and sulfadiazine (SDZ) were prepared in NaOH (35.8 mM; ultrapure water, final pH 12.2). Additionally, a sulfanilic acid solution (10.0 mM)

was prepared in ammonium acetate buffer (10 mM; pH 4.0). A 4-methoxyacetophenone (4-MAP) stock (0.100 M) was prepared in methanol/water (60:40). 4-MAP was spiked in the working solutions immediately prior to the experiments, yielding concentrations of 1–2 mM. Spectra of the sensitizers and the radical intermediates were collected by using a pump-probe transient absorption spectrometer. The pump pulse was generated by a femtosecond laser (795 nm, 3.2 W, 80 fs FWHM; Solstice, Spectra-Physics) and was modified by an optical parametric oscillator (TOPAS, Light Conversion) to obtain the desired pump wavelength (315 nm). The modified pump pulse (<10 mW) was directed into an EOS transient absorption spectrometer (Ultrafast Systems) and focused on a 1×0.2 cm quartz cell holding the liquid sample. The probe source consisted of a super continuum broadband laser (365–1700 nm; Leukos). The probe beam travels slightly off-axis to the pump beam and yields an effective path-length of approximately 5 mm. The probe is split into a sample and reference beam and is monitored by separate array detectors. Samples were stirred and purged with nitrogen to limit competitive quenching by oxygen. Transient spectra and contour plots were generated by using SurfaceXplorer (Ultrafast Systems) and OriginPro 8.5.

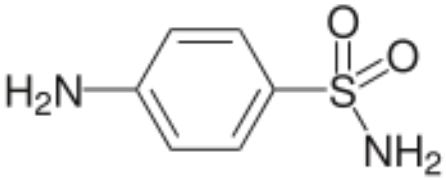
The p-substituted anilines and aniline cations used for the regression contain diverse substituents; however, we cannot rule out that the sulfonamide substituent may lead to additional effects not represented in the regression set. Nevertheless, we judge that the regression will give more accurate estimates of oxidation potentials and pK_a values compared to currently available schemes for the a priori computation of these properties.

Sultams are cyclic sulfonamides. Bioactive sultams include the antiinflammatory ampiroxicam and the anticonvulsant sulthiame. Sultams are prepared analogously to other sulfonamides, allowing for the fact that sulfonic acids are deprotonated by amines. They are often prepared by one-pot oxidation of disulfides or thiols linked to amines. An alternative synthesis of sultams involves initial preparation of a linear sulfonamide, followed by intramolecular C-C bond formation (i.e. cyclization), a strategy that was used in the synthesis of a sultam-based deep-blue emitter for organic electronics. [16,17]

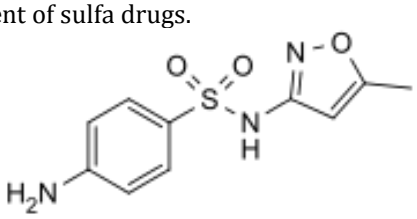
Sulfonamide-based compounds



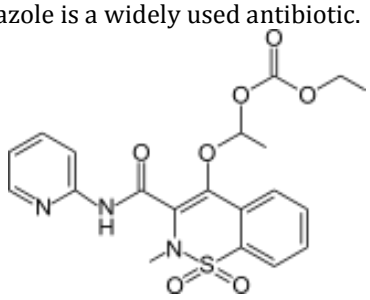
Saccharin, a cyclic sulfonamide that was one of the first artificial sweeteners discovered.



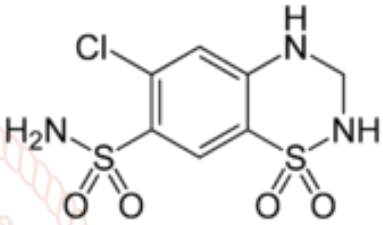
Sulfanilamide, a compound that foreshadowed the development of sulfa drugs.



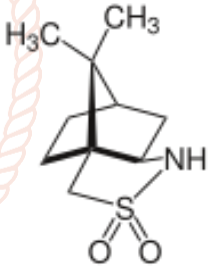
Sulfamethoxazole is a widely used antibiotic.



Ampiroxicam is a sultam used as an antiinflammatory drug.



Hydrochlorothiazide is a drug that features both acyclic and cyclic sulfonamide groups.



Camphorsultam is a sultam used as a chiral auxiliary in organic synthesis.

Conclusions

New spectrophotometric and titrimetric methods for the determination of sulphonamides with N-chlorosuccinimide (NCS) were developed. The spectrophotometric measurements can be made at 324–395 nm at pH 7.4 at room temperature, the stoichiometry being 1: 2, ($p\text{-}H_2N\text{-}C_6H_4\text{-}SO_2NHR$): (NCS) forming a dibromination product in presence of acidified potassium bromide. Potentiometrically or visually using methyl red as indicator, sulphonamides are titrated in pharmaceutical preparations by NCS always in presence of acidified potassium bromide. Ascorbic acid is determined alone and also in combinations, by first titrating it using potassium iodide and starch or 2,6-dichlorophenolindophenol as indicator. Acylation or diazotization of the aromatic amino groups that prevents substitution at the two ortho positions, is used as additional prereaction to analyze various binary and ternary mixtures of certain sulphonamides. These methods are accurate, simple, rapid, reproducible, useful at higher concentrations, do not involve any preseparation, and can tolerate several compounds that cause interference in other methods.[20]

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