Aqueous Oxidation of Sulfonamide Antibiotics: Aromatic Nucleophilic Substitution of an Aniline Radical Cation

Peter R. Tentscher,[a] Soren N. Eustis,[b] Kristopher McNeill,[b] and J. Samuel Arey*[a, c]

Abstract: Sulfonamide antibiotics are an important class of organic micropol- lutants 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 lower 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 SO₂-extruded oxidation product that was previously observed in the aquatic environment and characterized by NMR spectroscopy. We report a detailed reaction mechanism for this intramolecular aromatic nucleophilic substitution, and we discuss the possibility of this reaction pathway for other sulfonamide drugs.

Introduction

The contamination of freshwater bodies by organic micropol- lutants poses risks to these ecosystems, as well as to the human population depending on them as drinking water sources.[1] Sulfonamides and their degradation products constitute an important class of organic micropolutants.[2] Many of these compounds are (formally) derived from sulfamic acid (SA) chloride: the sulfonamide group (R₁–SO₂–NH–R₂) is substituted with R¹ = aniline, placing the –NH₂ group in para position. Several of these compounds are used as antibiotics, for example, sulfadiazine, sulfamethoxazole, or sulfamethazine.[2–4]

These sulfonamide drugs are reported to be chemically oxidized by different environmental and technical oxidants. Some transformation products have been identified, includ-

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[a] P. R. Tentscher, Prof. J. S. Arey
Environmental Chemistry Modeling Laboratory
Swiss Federal Institute of Technology Lausanne
1015 Lausanne (Switzerland)
[b] Prof. S. N. Eustis, Prof. K. McNeill
Institute of Biogeochemistry and Pollutant Dynamics
ETH Zürich, 8092 Zürich (Switzerland)
[c] Prof. J. S. Arey
Department of Environmental Chemistry
Swiss Federal Institute of Aquatic Science and Technology
8600 Dübendorf (Switzerland)
E-mail: samuel.arey@ep.ch

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The resulting radical is a p-substituted aniline radical cation. Previous work has shown that in the gas phase and in organic solvents, aromatic nucleophilic substitutions occur at aromatic rings that are activated by single-electron oxidation. For oxidized dimethylaniline, substitution in the para position can occur with various nucleophiles in acetonitrile (Scheme 1b). However, we are unaware of reports of similar reactions in aqueous solution, or of similar reactions involving anilines which are not N-substituted. We hypothesize that for the aqueous transformation of some sulfonamide drugs (R1,2 = H and R2 = SO2-NH-R’ in Scheme 1b) derived from SA chloride, oxidation of the aniline ring enables a nucleophilic attack at the C5 position in a way analogous to dimethylaniline.

In the present work, we employ sulfadiazine as a model system to answer the following questions:

- What is the intermediate formed by single-electron oxidation of sulfonamide drugs in aqueous solution?
- Which protonation states of the resulting intermediate can exist at typical pH values?
- Among these protonation state species, which ones can feasibly undergo a rearrangement reaction that can eventually lead to the observed rearranged product structure?
- What is the detailed reaction mechanism of this rearrangement reaction?

We utilized laser flash photolysis and a triplet sensitizer to mimic oxidation of sulfadiazine under environmental conditions, which allowed us to detect the intermediate formed upon oxidation. With density functional theory (DFT), we identified the reactive channel which leads to a rearranged structure in agreement with the previously identified product structure. Based on the DFT electronic structures, natural bond orbital (NBO) analysis, and natural localized molecular orbital (NLMO) analysis, we propose a detailed reaction mechanism for the rearrangement prior to the departure of SO2, including a Lewis structure representation of the different steps of the reaction.

Results and Discussion

Overview of the proposed reaction path: We investigated the 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 N13 on C6. 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 SDZH+, which can undergo the rearrangement reaction rapidly. Alternatively, SDZH can be oxidized to SDZH+, lose an acidic proton to become SDZ+, and then undergo rearrangement. In the following sections, we provide computational and experimental data to support the different proposed steps of the reaction.

![Scheme 1. a) Structure of sulfadiazine and a rearranged product structure. b) Reactivity of oxidized dialkylanilines with nucleophiles in acetonitrile.[13] Scheme 2. Speciation of sulfadiazine before and after single-electron oxidation. Redox potentials and pKₐ values from quantum chemical calculations, except pKₐd. The computed free energies of activation and corresponding rate constants (ΔG⧧, k) refer to an attack of N13 at C6. Deprotonation rates, catalyzed by HO· (kdp), are assumed to be close to the diffusion controlled limit. Box: the intermediate proposed to undergo rearrangement.](image-url)
What is the intermediate formed by abstraction of an electron from sulfadiazine? 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\(^{+}\) lone pair (SDZ\(^{+}\) only), yielding a \(\sigma\)-radical with a localized unpaired electron; or 3) the N\(^{11}\) \(\pi\)-lone pair, yielding a \(\pi\)-radical, with the unpaired electron possibly stabilized by resonance with the pyrimidine ring. By means of implicitly solvated DFT calculations employing the ROMP-W1K 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. ROMP-W1K 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\(^{11}\) \(\pi\)-radical for SDZ\(^{+}\); 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.

These results are in contrast with previous findings for sulfamethazine (SMZ) by Gao et al.[5] who used a similar computational methodology to study oxidized SMZ, using the B3LYP functional and the PCM continuum solvation model. In their results, structures of SMZ\(^{+}\) were reported in which the unpaired electron is either delocalized over the pyrimidine ring and the sulfonamide nitrogen, or delocalized over the entire molecule. We performed additional calculations on SMZ conformers in both protonation states, using several model chemistries with both the PCM and SMD implicit solvation models. The results were equivalent to what we found for SDZ when the SMD solvation model was used, that is, the spin density is localized in the aniline ring for the lowest energy structures. With the PCM solvation model, the site of ionization was less clear, but we found the spin density again localized in the aniline ring when explicit water molecules were added in a cluster-continuum approach.[17] We provide a more detailed analysis of different conformers and model chemistries in the Supporting Information. In summary, our reanalysis casts significant doubt on the species and reaction mechanism of sulfamethazine transformation proposed by Gao et al.[5]

What is the initial step during the oxidation of SDZ by \(^{3}\)DOM? In the aqueous phase, environmental oxidants can react with organic molecules by different possible mechanisms, but for the oxidation of SDZ by environmental oxidants, we expect SET to be the initial step. Other common oxidation reactions are hydrogen atom transfer (HT) and variations thereof, such as proton-coupled electron transfer (PCET). The sequence of events is often unclear, but SET is suspected to be the initial step in some cases.[18,19] This assumption is in agreement with a postulated reaction sequence of Wenk and Canonica.[19] who found that phenols inhibit the formation of oxidation products of sulfonamides and anilines. These authors postulate that an oxidized intermediate formed by SET from SDZ to triplet-excited state dissolved organic matter (\(^{3}\)DOM) is reduced back to the parent sulfonamide via SET from phenol.[19] However, H transfer may provide an alternative explanation for anti-oxidant behavior. This mechanism cannot be ruled out, since these authors did not directly observe the oxidized intermediate.

DFT calculations indicate that the oxidation potentials of SDZ species are sufficiently low to allow SET reactions with environmental oxidants. Using linear regression of DFT oxidation energies against experimental oxidation potentials[20] of \(p\)-substituted anilines (Figure S3 in the Supporting Information, \(r^2 = 0.96\)) we calculated the one-electron oxidations of SDZH, SDZ, and deprotonated sulfanilic acid (SA\(^{+}\)) to be 1.30, 1.09, and 1.10 V, respectively. The latter two have similar \(E_{\text{ox}}\) values, slightly higher than that of aniline (1.02 V).[20] These values are in a range that allows ready oxidation by common environmental oxidants, such as \(^{3}\)DOM. In laboratory studies, model triplet sensitizers are typically employed as proxies for the complex mixture of DOM found in the environment. These compounds possess reduction potentials \((E_{\text{red}})\) ranging roughly from 1.26 V (1-acetonaphthone) to 1.83 V (benzophenone-4-carboxylate).[21] That is, an SET from SDZH or SA\(^{-}\) to triplet sensitizers is thermodynamically feasible for many sensitizers, and an oxidation of SDZH may also be possible by stronger oxidants.

Laser flash photolysis (LFP) experiments provided further evidence that \(^{3}\)DOM oxidizes the aniline ring of SDZ via SET. We selected 4-methoxyacetophenone (\(^{3}\)MAP, \(E_{\text{red}} = 1.71\) V)[21] as a model sensitizer. The setup allows the observation of the quenching of the triplet sensitizer as well as (oxidized) intermediates by their optical absorption. Spectra taken 0.25 µs after the pump laser pulse, which excites \(^{3}\)MAP, in the presence of SA\(^{-}\) and SDZ\(^{-}\) are given in Figure 1.

For both SA\(^{-}\) and SDZ, we were able to observe a transient, which we assigned to oxidation of the aniline ring. The spectrum observed for SA\(^{-}\) (pH 4) agrees well with previously published spectra[22] taken after the oxidation of SA\(^{-}\) by azide radical, a known single-electron oxidant. The two distinct peaks \((\lambda_{\text{max}} = 425, 445\) nm) correspond to two protonation states of SA\(^{-}\), which deprotonates the aniline group once oxidized. Due to the limited solubility of the protonated form of SDZ, the pH had to be increased to 12 in order to obtain a transient signal. To provide a direct comparison between SA\(^{-}\) and SDZ, the SA\(^{-}\) experiment was repeated under these conditions. At this pH value, the oxidized SA\(^{-}\) exhibits a single broad absorption peak. In the spectrum recorded for the reaction of SDZ, no distinct peaks for the different protonation states can be distinguished; only a single
Figure 1. Transient absorption spectra of LFP experiments (pH 12) for the oxidation of SA (top) and SDZ (bottom) by 4-MAP as model triplet sensitizer (3Sens). Note the logarithmic time scale. Insets: optical absorption spectra at 0.25 \( \mu \text{s} \) after the pump pulse, with proposed transient structures.

broad absorption peak \( \lambda_{\text{max}} \approx 450 \text{ nm} \) is present. However, this peak is in the spectral region that can be expected for single-electron oxidized or H-atom abstracted aniline rings.\(^{[20,22–24]} \) Also, it is not uncommon to see only a single absorption band for an oxidized aniline, as for example, in oxidized aminobenzoic acid.\(^{[23,24]} \)

SET reactions of SDZ can be expected to be fast enough to compete with other processes in the aquatic environment. Sulfonamides can be potentially oxidized by various aquatic oxidants. The main purpose of the present work is to study the fate of the oxidized sulfadiazine intermediate, and we did not measure second order rate constants for the triplet quenching reaction. However, we believe that oxidation of SDZ and chemical analogues should be fast for many environmental oxidants. For comparison, \( \text{SA}^- \) is oxidized by azide radical \( \left( N_3, E_{\text{red}} = 1.33(\pm 0.01) \text{ V} \right) \)\(^{[25]} \) at a diffusion controlled rate \( k = 6.5 \times 10^9 \text{ m}^{-1} \text{s}^{-1} \), forming the corresponding radical cation via SET.\(^{[22]} \) Aniline undergoes the same reaction with \( N_3 \) with \( k = 4.4 \times 10^9 \text{ m}^{-1} \text{s}^{-1} \).\(^{[26]} \) Consequently, SET reactions with redox potential differences \( > 0.3 \text{ V} \) may be kinetically fast, assuming that oxidants act as outer sphere electron transfer agents, and that the reorganization energies of the specific oxidant and \( N_3 \) are similar.

**Speciation of oxidized SDZ:** The oxidized SDZ species can exist in different protonation states (Scheme 2). By a thermodynamic cycle employing the computed oxidation potentials of SDZH and SDZ\(^+ \), we estimate the experimental \( pK_{a,1} = 6.4 \pm 0.6 \)\(^{[3]} \) of SDZH to be lowered by approximately four units to \( pK_{a,2} = 2.9 \) for SDZH\(^+ \). For the estimation of \( pK_{a,3/4} \) we used linear regression of DFT calculated \( pK_a \) values with experimental values\(^{[20]} \) for \( p \)-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 depopronation, 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 depopronation of \( \text{–NH}_2 \) by \( \text{OH}^- \), we can compare to experimental rates of analogous compounds: \( \text{SA}^+ \) and \( \text{AN}^+ \) react with \( \text{OH}^- \) with rates of \( k_{\text{SA}^-} = 8.8 \times 10^{-5} \text{ m}^{-1} \text{s}^{-1} \) and \( k_{\text{AN}^-} = 2.2 \times 10^{-9} \text{ m}^{-1} \text{s}^{-1} \). We assume that the depopronation at aniline-H moiety will occur close to diffusion limitation \( (\approx 1 \times 10^{10} \text{ m}^{-1} \text{s}^{-1}) \), in agreement with a barrierless process found with a DFT cluster/continuum model for SDZH\(^+ \)/SDZ\(^–\). Direct protonation of water is likely insignificant at ambient pH for most of the species encountered here, but may further contribute to the depopronation rate associated with \( pK_{a,5} \). In the absence of the necessary experimental data,\(^{[27]} \) we do not attempt to estimate these rate constants.

**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 (Scheme 1 a), it is necessary to form a bond between \( C_3 \) and \( N^{3/4} \). Calculating charges\(^{[28]} \) of SDZ\(^–\) and SDZ\(^{1–}\) using natural population analysis (NPA), the charge on \( C_3 \) is increased from \(-0.37\) to \(-0.16\) upon oxidation. Thus, \( C_3 \) 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 (Scheme 2). 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 (Scheme 2). Details on the procedure, as well as an estimation of uncertainties of barrier heights and reaction energetics are given in the Supporting Information (Sections S1.2, S2.6).

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 \( k_{\text{dp}} = 1 \times 10^{10} \text{m}^{-1}\text{s}^{-1} \). First-order rate constants range from \( k'_{\text{dp}} = 1 \times 10^4 \text{s}^{-1} \) (pH 5) to \( k'_{\text{dp}} = 1 \times 10^9 \text{s}^{-1} \) (pH 10). Despite the uncertainty in these estimated rate constants, it is evident that SDZ\(^{+}\) is the only oxidized intermediate for which rearrangement can clearly out-compete deprotonation at \( \sim \text{NH}_2 \). For SDZH\(^{+}\), 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 (\( t_{\text{obs}} > 1 \) 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\(^{+}\), SDZ\(^{+}\)). For SDZ\(^{+}\) and SDZ\(^{-}\), dimerization can be expected. Products resulting from radical coupling at the aniline-N position have been reported for the oxidation of sulfamethazine.\(^5\)

**Detailed reaction mechanism of the open-shell rearrangement:** DFT calculations indicated that for SDZ\(^{+}\), an aromatic nucleophilic substitution at the oxidized aniline ring is kinetically possible (\( \Delta G^* = 8 \text{ kcalmol}^{-1} \)). We propose a detailed reaction mechanism of the rearrangement of SDZ\(^{+}\). Barrier heights, structures, and spin densities are shown in Figure 2a.

In SDZ\(^{+}\), 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\(10\) on C\(5\) proceeds through a transition structure in which the unpaired electron is shared between N\(1\), C\(5\), C\(6\), and the attacking N\(13\). By NBO analysis, this was identified as a hemibonded structure (see the Supporting Information). This transition structure connects SDZ\(^{+}\) to a \( \sigma\)-complex, which is only slightly lower (1.9 kcal mol\(^{-1}\)) in energy than SDZ\(^{+}\). In the \( \sigma\)-complex, the spin density is again localized in the aniline ring, where N\(1\) and C\(5\), 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 kcalmol\(^{-1}\)), 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\(^{+}\) and the product precursor to be a favorable \(-6.5\) kcal mol\(^{-1}\).

A Lewis structure representation of the open-shell mechanism is given in Figure 2b. The Lewis structures were chosen to accommodate the observed spin densities. An alternative representation uses spin-separated Lewis-like structures, directly derived from NLMO analysis. We report these in the Supporting Information (Section S2.3, Figure S2).

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 \( \sigma\)-complex before breaking the C–S bond; this intermediate has been characterized spectroscopically for closed-shell reactions.\(^{29}\)

By comparing charges of the C\(\alpha\) 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\(^{+}\), we propose Lewis structures, based on natural localized molecular orbital (NLMO) analysis (Figure 2c). An electron-withdrawing group (e.g., \(-\text{NO}_2\)) in \( \sigma\)-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 \(-\text{NH}_2\) by other substituents. The barrier heights are shown as a function of the NPA charge on C\(5\) in Figure 3. 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 \(-\text{NH}_2^{+}\) substituent is more electron- withdrawing than \(-\text{NO}_2\).

Our proposed mechanism (Figure 2a and b) differs from the mechanism suggested by Gao et al.,\(^{29}\) these authors propose an electrophilic attack of a pyrimidine-N centered radical on the aniline ring, which exhibits reversed polarity compared to the mechanism reported here. We think the Gao et al. mechanism is physically unreasonable and we discuss this in more detail in the Supporting Information.

**Fate of the product precursor:** In order to arrive at the experimentally observed rearrangement product (Scheme 1), the SO\(_2\) moiety must detach from the product precursor. Additional DFT calculations show that the binding energy of SO\(_2\) is low (\( \approx -2 \) to 3 kcal mol\(^{-1}\)) if the product precursor is protonated at the N\(11\) position, and we speculate that this may be a possible reaction pathway. More details are given in the Supporting Information. However, we do not attempt to estimate the \( pK_a \) values associated with protonation of N\(11\) in the product precursor in different possible oxidation states, as the a priori estimate of this property within an implicitly solvated DFT framework may not yield reliable results.
Conclusion

The present study provides an estimate of the single-electron oxidation potential of sulfadiazine, which we calculate to be 1.09 V. Hence, sulfadiazine and congeners can be oxidized by common environmental oxidants, such as DOM or CO$_3$C/CO$_3$. 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) 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 $\sigma$-complex, in agreement with a nucleophilic aromatic substitution. However, the electronic structure of this open-shell reaction differs from analogous closed-shell reactions.
The presented mechanism may be possible for structurally similar sulfonamides. In exploratory calculations (see the Supporting Information), DFT results indicate that aniline–SO₂–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 SO₂ 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 SO₂ extrusion process observed during direct photolysis of sulfonamide antibiotics. The feasibility of formation of SO₂ extrusion by the present mechanism can be tested with DFT, leading to implications about the environmental (and possibly in vivo) fate of novel drugs.

### Experimental Section

**Chemicals and solutions:** 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 sulfamic acid solution (10.0 mM) was prepared in ammonium acetate buffer (10 mM; pH 4.0). A 4-methoxyacetophenone (4-MAP) stock (0.100 mM) 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.

**Laser flash photolysis:** 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 supercontinuum broadband laser (365–1700 nm; Leuкоs). 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 (OriginLab).

**Computational methods:** Calculations employing density functional theory (DFT) were carried out with the Gaussian09[31] electronic structure code. All calculations employed the MPW1K[32] functional with a pruned (99, 590) integration grid and “very tight” energy and geometry convergence criteria. We chose this functional based on its good performance for barrier heights[32,33] and radical–nonradical interactions,[34,35] including 2-center-3-electron interactions, and problems involving the self-interaction error (SIE).[36,37] as species exhibiting such situations were encountered in the present study. The restricted open-shell (RO) formalism[38] was chosen because of the significant spin contamination that we encountered with all hybrid functionals tested. All thermodynamic data reported refer to Gibbs free energies (including implicit aqueous solvation) calculated by the (RO)MPW1K/aug-cc-pVTZ/(RO)MPW1K/6-31+G(d,p) model chemistry, employing the rigid rotor and harmonic oscillator approximation,[39] unless otherwise noted. The SMD[40] aqueous solvation model was used throughout. All free energies are given for T = 298 K. Thermodynamic cycles using gas-phase single-point calculations were not used, because the electronic structures of some compounds in the gas phase are different from those in the solution phase; that is, the pyrimidine ring is ionized en lieu of the aniline ring. The nature of all structures was confirmed with normal mode analysis.[41] For all stationary points of open-shell species, minimum energy structures were confirmed to be electronic minima by wavefunction stability analysis,[42,43] as implemented in Gaussian09, with the UB3LYP/6-31+G(d,p) model chemistry.[44] Guess structures for transition structures were searched for by “relaxed scans” by using an interatomic distance as a reaction coordinate (see the Supporting Information, Section S1.2). Transition structures were verified by normal mode analysis and rate constants were calculated by using canonical transition state theory (see the Supporting Information for details). Computed free energies for a restricted-open-shell (RO) formalism[45] analysis was carried out at stationary points with the NBO[44,45] analysis employed the (RO)MPW1K/6-31+G(d,p) electron density. Lewis structures were assigned based on visual inspection of the NLMOs by using the Chemcraft[46] software. In some cases, the NBO set found by NBO 5.0 was manually altered in order to avoid non-intuitive delocalizations. In such cases, the NBO set chosen always exhibited <0.2% less Lewis-character than the NBO set proposed by NBO 5.0.

All aqueous oxidation potentials used are with respect to the standard hydrogen electrode (SHE). Oxidation potentials were estimated as follows. Using DFT, we calculated free energies of oxidation (ΔGₐq = Gₓ       = Gₓ       = Gₓ       ) of a set of 10 p-substituted anilines for which accurate experimental oxidation potentials from pulse radiolysis are available.[39] Linear regression between computed and experimental values was performed, and oxidation potentials of sulfonamide drugs, sulfanilic acid, and –SO₂ extrusion products were estimated by using the resulting regression formula. The pKₐ values of the aniline protons in aniline radical cations were estimated similarly: using DFT, we calculated aqueous deprotonation energies (ΔGₓ       = Gₓ       + Gₓ       – Gₓ       ) for a set of eight p-substituted aniline radical cations for which experimental pKₐ values are available.[46] For the free energy of hydration of the proton, we used a value of −1100.9 kJ mol⁻¹, together with an absolute value of the SHE potential of 4.251 V.[40] We performed linear regression between the calculated and experimental pKₐ values, both with and without vibrational contributions to the free energy of reaction. The pKₐ values of oxidized aniline rings were estimated employing the resulting regression formula.
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.

Supporting information: A list of chemicals used, details on computational protocols, discussion of the mechanistic interpretation, linear regression of $pK_a$ values and linear regression of $E_{ox}$ values, binding of $\text{SO}_2$ to the product precursor, extension to structurally similar sulfonamides, and molecular structures of stationary points of $SDZ$ along the reaction path.

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[28] Charges reported are per atomic center and do not implicitly include other centers.


[38] The wavefunction stability analysis in the Gaussian09 software package is only compatible with unrestricted wavefunctions. Because of its lower spin contamination, we chose UB3LYP instead of UMPW1K for this purpose.


[45] As we do not attempt the calculation of absolute oxidation potentials or $pK_a$ values, the choices of reference values for the SHE potential and $\Delta G^\ominus_{HE}(\text{H})$ do not affect the predicted values.

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