

# **pH METRIC STUDIES OF COMPLEXES OF Cu (II) WITH N- ACETYLBENZENESULPHONAMIDE AND N-ACETYL-p-TOLUENESULPHONAMIDE**

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**ABSTRACT:** The influence of pH on the complex formation of phosphoethanolamine and pyrimidine nucleosides (uridine, cytidine and thymidine) with copper(II) ions was studied. All investigations were performed in aqueous solution. The overall stability constants of the complexes and non-covalent compounds were obtained using the potentiometric method with computer calculation of the data. Moreover, equilibrium constants of the reaction were determined. The mode of coordination was obtained using spectroscopic methods. Analysis of the potentiometric and spectroscopic data confirmed the involvement and effectiveness of phosphate groups in species formation as well as the influence of pH on the mode of coordination of the investigated biomaterials. In the next step, studied complexes will be applied as potential biomaterials with biological applications.

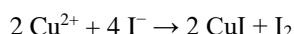
**KEYWORDS:** pH metric, complexes, Cu(II), n-acetylbzenesulphonamide, n-acetyl-p-toluenesulphonamide, spectroscopic

## **I. INTRODUCTION**

Copper forms a rich variety of compounds, usually with oxidation states +1 and +2, which are often called cuprous and cupric, respectively.<sup>[1]</sup>

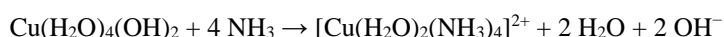
Copper compounds, whether organic complexes or organometallics, promote or catalyse numerous chemical and biological processes.<sup>[2]</sup> As with other elements, the simplest compounds of copper are binary compounds, i.e. those containing only two elements, the principal examples being oxides, sulfides, and halides. Both cuprous and cupric oxides are known. Among the numerous copper sulfides, important examples include copper(I) sulfide and copper(II) sulfide.<sup>[2]</sup>

Cuprous halides with fluorine, chlorine, bromine, and iodine are known, as are cupric halides with fluorine, chlorine, and bromine. Attempts to prepare copper(II) iodide yield only copper(I) iodide and iodine.<sup>[1]</sup>



Copper forms coordination complexes with ligands. In aqueous solution, copper(II) exists as  $[\text{Cu}(\text{H}_2\text{O})_6]^{2+}$ . This complex exhibits the fastest water exchange rate (speed of water ligands attaching and detaching) for any transition metal aquo complex. Adding aqueous sodium hydroxide causes the precipitation of light blue solid copper(II) hydroxide. A simplified equation is:  $\text{Cu}^{2+} + 2 \text{OH}^{-} \rightarrow \text{Cu}(\text{OH})_2$ <sup>[3]</sup>

Aqueous ammonia results in the same precipitate. Upon adding excess ammonia, the precipitate dissolves, forming tetraamminecopper(II):<sup>[4]</sup>



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Many other oxyanions form complexes; these include copper(II) acetate, copper(II) nitrate, and copper(II) carbonate. Copper(II) sulfate forms a blue crystalline pentahydrate, the most familiar copper compound in the laboratory. It is used in a fungicide called the Bordeaux mixture.<sup>[3]</sup> Polyols, compounds containing more than one alcohol functional group, generally interact with cupric salts. For example, copper salts are used to test for reducing sugars. Specifically, using Benedict's reagent and Fehling's solution the presence of the sugar is signaled by a color change from blue Cu(II) to reddish copper(I) oxide.<sup>[4]</sup> Schweizer's reagent and related complexes with ethylenediamine and other amines dissolve cellulose.<sup>[5]</sup> Amino acids such as cystine form very stable chelate complexes with copper(II).<sup>[6][7][8]</sup> Many wet-chemical tests for copper ions exist, one involving potassium ferrocyanide, which gives a brown precipitate with copper(II) salts. Compounds that contain a carbon-copper bond are known as organocopper compounds. They are very reactive towards oxygen to form copper(I) oxide and have many uses in chemistry. They are synthesized by treating copper(I) compounds with Grignard reagents, terminal alkynes or organolithium reagents;<sup>[9]</sup> in particular, the last reaction described produces a Gilman reagent. These can undergo substitution with alkyl halides to form coupling products; as such, they are important in the field of organic synthesis. Copper(I) acetylide is highly shock-sensitive but is an intermediate in reactions such as the Cadiot-Chodkiewicz coupling<sup>[10]</sup> and the Sonogashira coupling.<sup>[11]</sup> Conjugate <sup>5</sup> addition to enones<sup>[12]</sup> and carbocupration of alkynes<sup>[13]</sup> can also be achieved with organocopper compounds. Copper(I) forms a variety of weak complexes with alkenes and carbon monoxide, especially in the presence of amine ligands.<sup>[14]</sup> Copper(III) is most often found in oxides. A simple example is potassium cuprate,  $KCuO_2$ , a blue-black solid.<sup>[15]</sup> The most extensively studied copper(III) compounds are the cuprate superconductors. Yttrium barium copper oxide ( $YBa_2Cu_3O_7$ ) consists of both Cu(II) <sup>6</sup>and Cu(III) centres. Like oxide, fluoride is a highly basic anion<sup>[16]</sup> and is known to stabilize metal ions in high oxidation states. Both copper(III) and even copper(IV) fluorides are known,  $K_3CuF_6$  and  $Cs_2CuF_6$ , respectively.<sup>[1]</sup>

Some copper proteins form oxo complexes, which also feature copper(III).<sup>[17]</sup> With tetrapeptides, purple-colored copper(III) complexes are stabilized by the deprotonated amide ligands.<sup>[18]</sup>

Complexes of copper(III) are also found as intermediates in reactions of organocopper compounds.<sup>[19]</sup> For example, in the Kharasch-Sosnovsky reaction<sup>7</sup>

## II. DISCUSSION

In organic chemistry, the sulfonamide functional group (also spelled sulphonamide) is an organosulfur group with the structure  $R-S(=O)_2-NR_2$ . It consists of a sulfonyl group ( $O=S=O$ ) connected to an amine group ( $-NH_2$ ). Relatively speaking this group is unreactive. Because of the rigidity of the functional group, sulfonamides are typically crystalline; for this reason, the formation of a sulfonamide is a classic method to convert an amine into a crystalline derivative which can be identified by its melting point.<sup>8</sup> Many important drugs contain the sulfonamide group.<sup>[1]</sup> A sulfonamide (compound) is a chemical compound that contains this group. The general formula is  $R-SO_2NR'R''$  or  $R-S(=O)_2-NR'R''$ , where each R is some organic group; for example, "methanesulfonamide" (where R = methane, R' = R'' = hydrogen) is  $CH_3SO_2NH_2$ . Any sulfonamide can be considered as derived from a sulfonic acid by replacing a hydroxyl group ( $-OH$ ) with an amine group. In medicine, the term "sulfonamide" is sometimes used as a synonym for sulfa drug, a derivative or variation of sulfanilamide. The first sulfonamide was discovered in Germany in 1932.<sup>[2]</sup> Sulfonamides can be prepared in the laboratory in many ways. The classic approach entails the reaction of sulfonyl chlorides amine<sup>9</sup>

A base such as pyridine is typically added to absorb the HCl that is generated. Illustrative is the synthesis of sulfonylmethylamide.<sup>[3]</sup> A readily available sulfonyl chloride source is tosyl chloride.<sup>[4]</sup> The reaction of primary and secondary amines with benzenesulfonyl chloride is the basis of the Hinsberg reaction, a method for detecting primary and secondary amines. Sultams are cyclic sulfonamides. Bioactive sultams include the anti-inflammatory amproxicam 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.<sup>[5]</sup> An alternative synthesis of sultams involves initial preparation of a linear

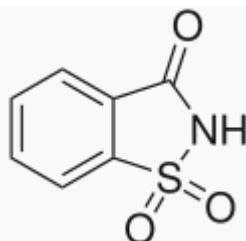
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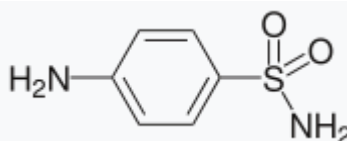
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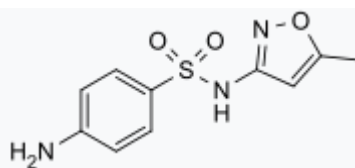
sulfonamide<sup>10</sup>, followed by intramolecular C-C bond formation (i.e. cyclization), a strategy that was used in the synthesis of a sultam-based deep-blue emitter for organic electronics.<sup>[6]</sup>



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.

### III. RESULTS

Sulfonamide is a functional group (a part of a molecule) that is the basis of several groups of drugs, which are called sulphonamides, sulfa drugs or sulpha drugs<sup>11</sup>. The original antibacterial sulfonamides are synthetic (nonantibiotic) antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based upon the antibacterial sulfonamides.<sup>[1][2]</sup>

Allergies to sulfonamides are common. The overall incidence of adverse drug reactions to sulfa antibiotics is approximately 3%, close to penicillin,<sup>[3]</sup> hence medications containing sulfonamides are prescribed carefully.<sup>12</sup>

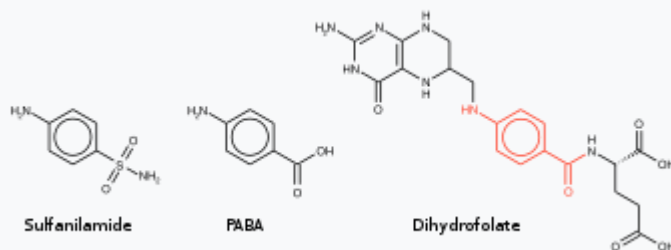
Sulfonamide drugs were the first broadly effective antibacterials to be used systemically, and paved the way for the antibiotic revolution in medicine. In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthase (DHPS), an enzyme involved in folate synthesis.<sup>13</sup> Sulfonamides are therefore bacteriostatic and inhibit growth and multiplication of bacteria, but do not kill them. Humans, in contrast to bacteria, acquire folate (vitamin B<sub>9</sub>) through the diet.<sup>[4]</sup>

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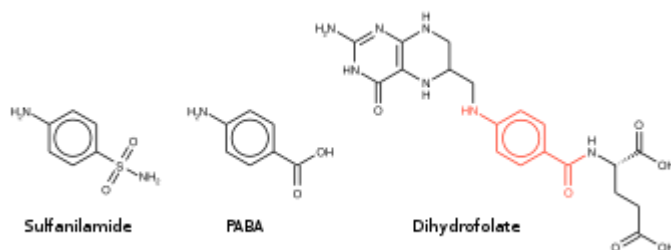
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Structural similarity between sulfanilamide (left) and PABA (center) is the basis for the inhibitory activity of sulfa drugs on tetrahydrofolate (right) biosynthesis.

Sulfonamides are used to treat allergies and coughs, as well as having antifungal and antimalarial functions. The moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide, and torsemide), acetazolamide, sulfonylureas (including glipizide, glyburide, among others), and some COX-2 inhibitors (e.g., celecoxib).<sup>14</sup>

Sulfasalazine, in addition to its use as an antibiotic, is also used in the treatment of inflammatory bowel disease.<sup>15</sup>



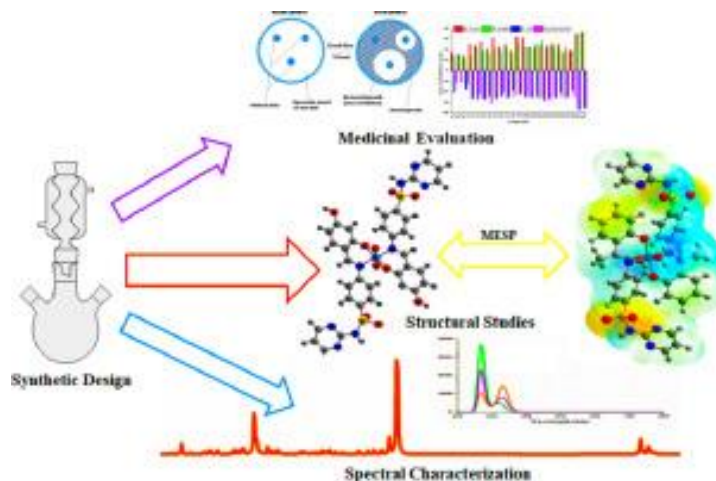
Sulfonamide drugs were the first broadly effective antibacterials to be used systemically, and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade-named Prontosil, was a prodrug.<sup>15</sup> Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes which are able to bind preferentially to bacteria and parasites might be used to attack harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk<sup>16</sup> (working under the general direction of IG Farben executive Heinrich Hörlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice.<sup>17</sup>

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The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. Prontosil, as Bayer named the new drug, was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body. It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci.<sup>[16]</sup> However, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later, it was discovered by Daniel Bovet,<sup>[8]</sup> Federico Nitti, and Jacques and Thérèse Tréfouël, a French research team led by Ernest Fourneau at the Pasteur Institute, that the drug was metabolized into two parts inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulfanilamide.<sup>[9]</sup> The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone.<sup>[10]</sup>

The result was a sulfa craze.<sup>[11]</sup> For several years in the late 1930s, hundreds of manufacturers produced myriad forms of sulfa. This and the lack of testing requirements led to the elixir sulfanilamide disaster in the fall of 1937, during which at least 100 people were poisoned with diethylene glycol. This led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938 in the United States. As the first and only effective broad-spectrum antibiotic available in the years before penicillin, heavy use of sulfa drugs continued into the early years of World War II.<sup>[12]</sup> They are credited with saving the lives of tens of thousands of patients, including Franklin Delano Roosevelt Jr. (son of US President Franklin Delano Roosevelt) and Winston Churchill.<sup>[13][14]</sup> Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulfa pills and powder and were told to sprinkle it on any open wound.<sup>[15]</sup>

The sulfanilamide compound is more active in the protonated form. The drug has very low solubility and sometimes can crystallize in the kidneys, due to its first  $pK_a$  of around 10. This is a very painful experience, so patients are told to take the medication with copious amounts of water. Newer analogous compounds prevent this complication because they have a lower  $pK_a$ , around 5–6, making them more likely to remain in a soluble form.<sup>[18]</sup>

Sulfonamides have the potential to cause a variety of adverse effects, including urinary tract disorders, haemopoietic disorders, porphyria and hypersensitivity reactions. When used in large doses, they may cause a strong allergic reaction. The most serious of these are classified as severe cutaneous adverse reactions (i.e. SCARs) and include the Stevens–Johnson syndrome, toxic epidermal necrolysis (also known as Lyell syndrome), the DRESS syndrome, and a not quite as serious SCARs reaction, acute generalized exanthematous pustulosis. Any one of these SCARs may be triggered by certain sulfonamides.<sup>[3]</sup>

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Approximately 3% of the general population have adverse reactions when treated with sulfonamide antimicrobials. Of note is the observation that patients with HIV have a much higher prevalence, at about 60%.<sup>[17]</sup>

## IV. CONCLUSIONS

Hypersensitivity reactions are less common in nonantibiotic sulfonamides, and, though controversial, the available evidence suggests those with hypersensitivity to sulfonamide antibiotics do not have an increased risk of hypersensitivity reaction to the nonantibiotic agents.<sup>[18]</sup> A key component to the allergic response to sulfonamide antibiotics is the arylamine group at N4, found in sulfamethoxazole, sulfasalazine, sulfadiazine, and the anti-retrovirals amprenavir and fosamprenavir.<sup>19</sup> Other sulfonamide drugs do not contain this arylamine group; available evidence suggests that patients who are allergic to arylamine sulfonamides do not cross-react to sulfonamides that lack the arylamine group, and may therefore safely take non-arylamine sulfonamides.<sup>[19]</sup> It has therefore been argued that the terms "sulfonamide allergy" or "sulfa allergy" are misleading and should be replaced by a reference to a specific drug (e.g., "cotrimoxazole allergy").<sup>[20]</sup>

Two regions of the sulfonamide antibiotic chemical structure are implicated in the hypersensitivity reactions associated with the class.

- The first is the N1 heterocyclic ring, which causes a type I hypersensitivity reaction.
- The second is the N4 amino nitrogen that, in a stereospecific process, forms reactive metabolites that cause either direct cytotoxicity or immunologic response.<sup>20</sup>

The nonantibiotic sulfonamides lack both of these structures.<sup>[21]</sup>

The most common manifestations of a hypersensitivity reaction to sulfa drugs are rash and hives. However, there are several life-threatening manifestations of hypersensitivity to sulfa drugs, including Stevens–Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, hemolytic anemia, thrombocytopenia, fulminant hepatic necrosis, and acute pancreatitis, among others.<sup>[22]</sup>

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