Earthline Journal of Chemical Sciences
ISSN (Online): 2581-9003
Volume 6, Number 2, 2021, Pages 209-214
https://doi.org/10.34198/ejcs.6221.209214

On the Mechanism of the Caro Synthesis of Methylene Blue

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Abstract

The recent interest for new applications of methylene blue as a promising drug for several important ailments prompted us to fill unknown aspects related to this compound. Since there is no mechanism on the Caro synthesis of methylene blue, we provide the electron flow, step by step, from the starting N,N-dimethylphenylenediamine to the dibenzothiazine derivative. It is a free radical generation system due to the oxidizing properties of ferric chloride. We pointed out the alternative reactions that take place with hydrogen sulphide, the reducer from which the thiazine ring is formed.

1. Introduction

Paul Ehrlich noticed in 1886 that methylene blue turned live neurons blue and had the same effect on plasmodium. Thus, he tested methylene blue as a remedy to treat swamp fever, with success. Several years ago Dr. O. Müller found out that methylene blue is superior to all known antimalarial agents, [1].

Methylene blue is used to treat urinary tract infections and as a remedy for cyanide poisoning, and offers many more potential health benefits, [2].

The first synthesis of this important dyestuff and drug is due to H. Caro. However, its reaction mechanism has not been advanced. In this communication we provide the reaction route and the electron flow, step by step.

This paper is a follow up of our studies on reaction mechanism, [3-7].

Received: August 22, 2021; Accepted: September 1, 2021

Keywords and phrases: p-benzoquinone diimine, dibenzothiazine, imino intermediates, radical ions, sulfhydryl radical, thioxo group.

2. Antecedents

The first synthesis of methylene blue, Figure 1, was achieved by Heinrich Caro (1834-1910). He was working at the Badische Anilin und Soda Fabrik, in Ludvigshafen, Rhineland. The synthesis was not published, but patented a year later to BASF. It consists in the oxidation of p-dimethylaminoaniline and hydrogen sulphide with ferric chloride, [8].

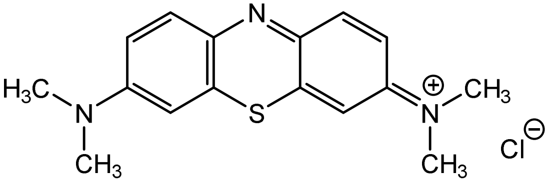


Figure 1. Graphic formula of methylene blue.

It is important notice that in this preparation intervene an oxidant, $FeCl_3$, and a reducer, H_2S, that can react with precipitation of sulphur [9, 10], as follows:

$$2\ FeCl_3 + H_2S \longrightarrow 2\ FeCl_2 + 2\ HCl + S, \quad \text{or}$$

$$2\ FeCl_3 + 3\ H_2S \longrightarrow 2\ FeS + S + 6\ HCl$$

These reactions compete with the organic compound in the tertiary combination and are counterproductive. However, a not mentioned half reaction between Fe3+ and H_2S can be useful, that is, electron transfer oxidation of H-S-H produces a radical ion which yields a sulfhydryl radical by deprotonation. This intermediate radical species reacts with the organic compound, as it will be seen in the next section.

The synthesis was adapted by E. Fischer for hydrogen sulphide identification, observing the blue colour obtained due to methylene blue formation, [11, 12]. The test was registered in the United States, [13].

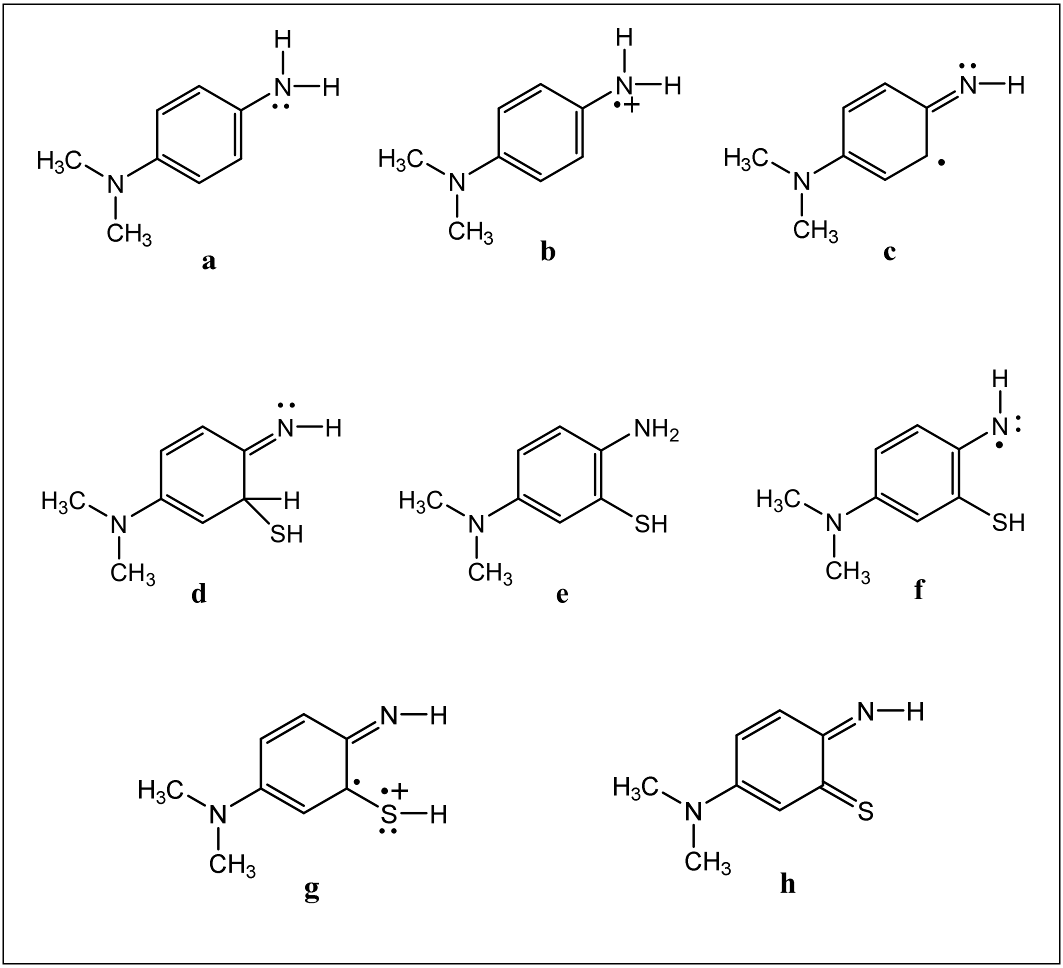
The hydrogen sulphide may be determined colorimetrically by the Caro-Fischer method, [14, 15], the blue colour is due to the indamine structure, [16]. There is a book about H. Caro, [17].

3. Discussion

The reaction site for electron subtraction by ferric ion is the unshared electron pair at nitrogen, Figure 2, **a**. The dimethylamino group does not react due to steric hindrance, thus reaction occurs at the amino group. The resulting radical ion is stabilized by deprotonation and radical coupling, **b, c.**

The unpaired electron at C-2 reacts with a sulfhydryl radical coming from partial reduction of hydrogen sulphide, **d.** Protonation of the imino group produces aromatization, **e.** Ferric chloride reacts with the restored amino group as before, **f,** and the mercapto group is reduced to a free radical that couples with the electron at C-2, **g.** This way an imine and a thioxo group are formed, **h.**

Acid catalyzed addition of unreacted as-dimethyl-p-phenylenediamine to the imino group yields a transient aminal, **i,** that eliminates ammonia, **j**. An ortho quinonoid structure results, and the two phenyl groups are linked by a nitrilo radical, [18. 19].



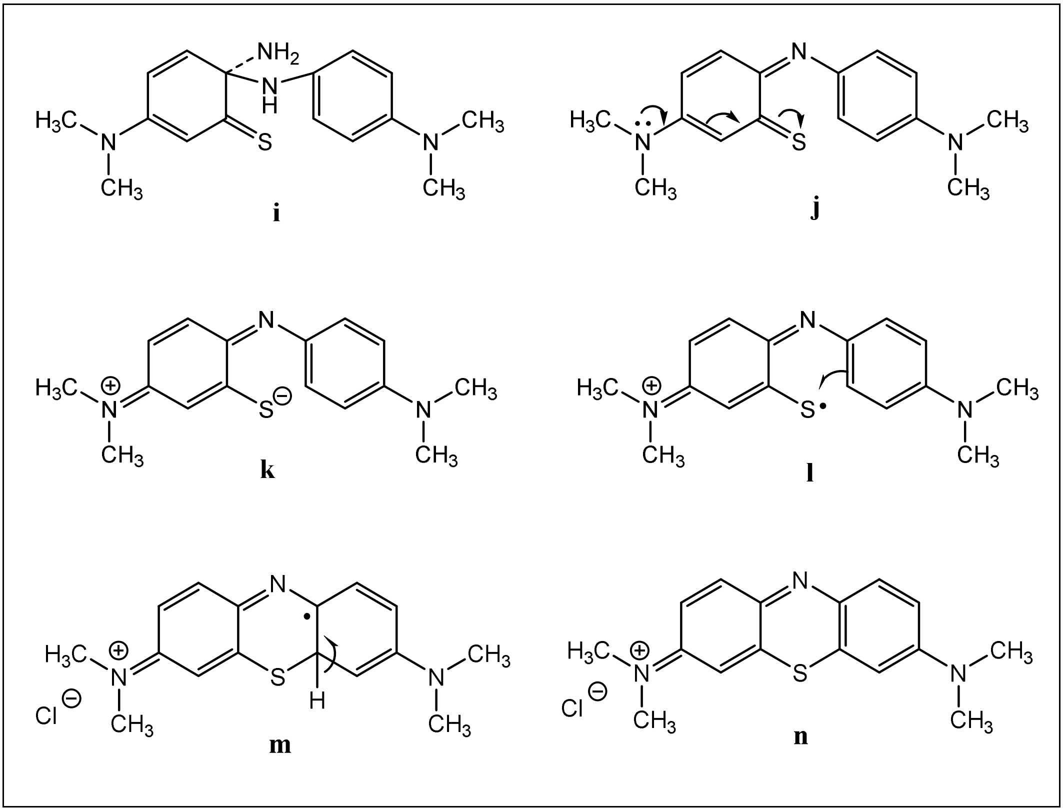


Figure 2. Reaction route of Caro synthesis of methylene blue.

There is an enamine conjugated with a thioxo group and this produces a push-pull electron shift from the dimethylamino group to the thioketone, and a p-diiminoquinone structure results, **k.**

The zwitter ion intermediate is reduced by ferric chloride to a radical on sulphur, **l.** The last step is ring closure via free radicals to the thiazine derivative, **m, n.**

In this synthesis of methylene blue the sulphur species must react with the organic compound in an early stage, that is, before complete reaction of hydrogen sulphide with ferric ions occurs, forming insoluble sulphur.

The oxidation of 1-amino-2-naphtol to 1,2-naphtoquinone by means of ferric chloride [20], can be explained by the mechanism indicated in the initial steps of our description.

4. Conclusion

The route and the mechanism of the Caro synthesis of methylene blue have been cleared up. The oxidation of N,N-phenylene diamine and hydrogen sulphide by ferric chloride in acidic medium takes place by radical ion intermediates. Deprotonation and radical coupling occur for stabilization. A sulfhydryl derivative is first obtained and further oxidations leads to an o-imino thione. Condensation with unreactive as-dimethylphenylenediamine yields an aminal, followed by elimination of ammonia. The last steps are isomerization, oxidation, and ring closure to the indamine dye.

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