

ISSN Print: 2664-6781  
 ISSN Online: 2664-679X  
 IJACR 2023; 5(1): 47-49  
[www.chemistryjournals.net](http://www.chemistryjournals.net)  
 Received: 15-11-2022  
 Accepted: 20-12-2022

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## The mechanism of Hager's test for glucose

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**DOI:** <https://doi.org/10.33545/26646781.2023.v5.i1a.143>

### Abstract

There are several colour tests for glucose detection, not being the case for glucose estimation. Thus, the quantitative test for glucose due to Hager is fairly important. The test is based on an oxide reduction process. It employs mercury oxide, sodium chloride, and sodium acetate in a slightly acidic medium (2.5% acetic acid). In the presence of glucose, this reagent precipitates the very insoluble dimercy dichloride which is related to glucose content and concentration. Since the reaction route has not been described, and less the reaction mechanism, both are provided in this communication. Each step is fully commented and the electron flow is given. The reactive intermediate is  $\text{H-O-Hg}^+$  which reacts with nucleophilic species. This way hydroxymercury glucose-enolate is formed, as well as, chloromercury hydroxide. Proteolysis of both intermediates and reaction with chloride ions gives the two key intermediates, chloromercury glucose-enolate and the cation  $\text{Cl-Hg}^+$ . A bimolecular reaction between these intermediates occurs via a concerted mechanism (redox reaction). The oxidation product is 2-ketoglucose (Glucosone), whereas the reduced compound is dimercy dichloride.

**Keywords:** Chloromercury glucose-enolate, electrodotic properties, 2-keto glucose, mercuric oxide, organ mercuric intermediate, protolysis

### Introduction

Glucose is the most widely used aldohexose in most living organisms. Reaction of glucose with the amino groups of proteins-glycation-impairs or destroys the function of many proteins.

Thus, glucose is an analyte. Glycosuria-glucose in urine-can result from hyperglycemia because the kidneys are working to get rid of some of the excess sugar circulating in the blood. So, a urinalysis is very important. In this paper, we describe the route and the mechanism of the Hager test for glucose, not previously advanced. The electron flow is given in each step and the reaction is fully commented. It is important and interesting to know what is happening during the test, not only its application.

This communication is a follow-up of our studies on reaction mechanism, <sup>[1-5]</sup>.

### Study Method and Process

This is a Theoretical Organic Chemistry Study. It is based on the chemical department of reagents and substrate. All is in accordance with the reaction medium, the nature of the oxidizer and catalyst employed. The several steps leading to dimercy dichloride and 2-keto-glucose (Glucosone) are fully commented and the electron flow is given in each reaction.

### Antecedents

The German chemist Herman Hager (1816-1897) proposed an analytical test for glucose quantification, <sup>[6]</sup>. He also wrote a book on Pharmaceutical Analysis, <sup>[7]</sup>. His test was recorded in Germany <sup>[8]</sup>, and in the United States <sup>[9]</sup>. The test is as follows. The reagent is a solution of 3 g of red mercuric oxide, 3 g of sodium acetate, 5 g of sodium chloride, 2.5 g glacial acetic acid, and 40 mL of water, diluted to 100 mL. Diabetic urine boiled with reagent yields a precipitate of mercuries chloride. This is weighed and related to glucose according to known concentrations.

The principal reagent, mercury oxide,  $\text{HgO}$ , is a red or orange solid. The difference in colour is due to particle size. Oxygen is released by heating it <sup>[10]</sup>.

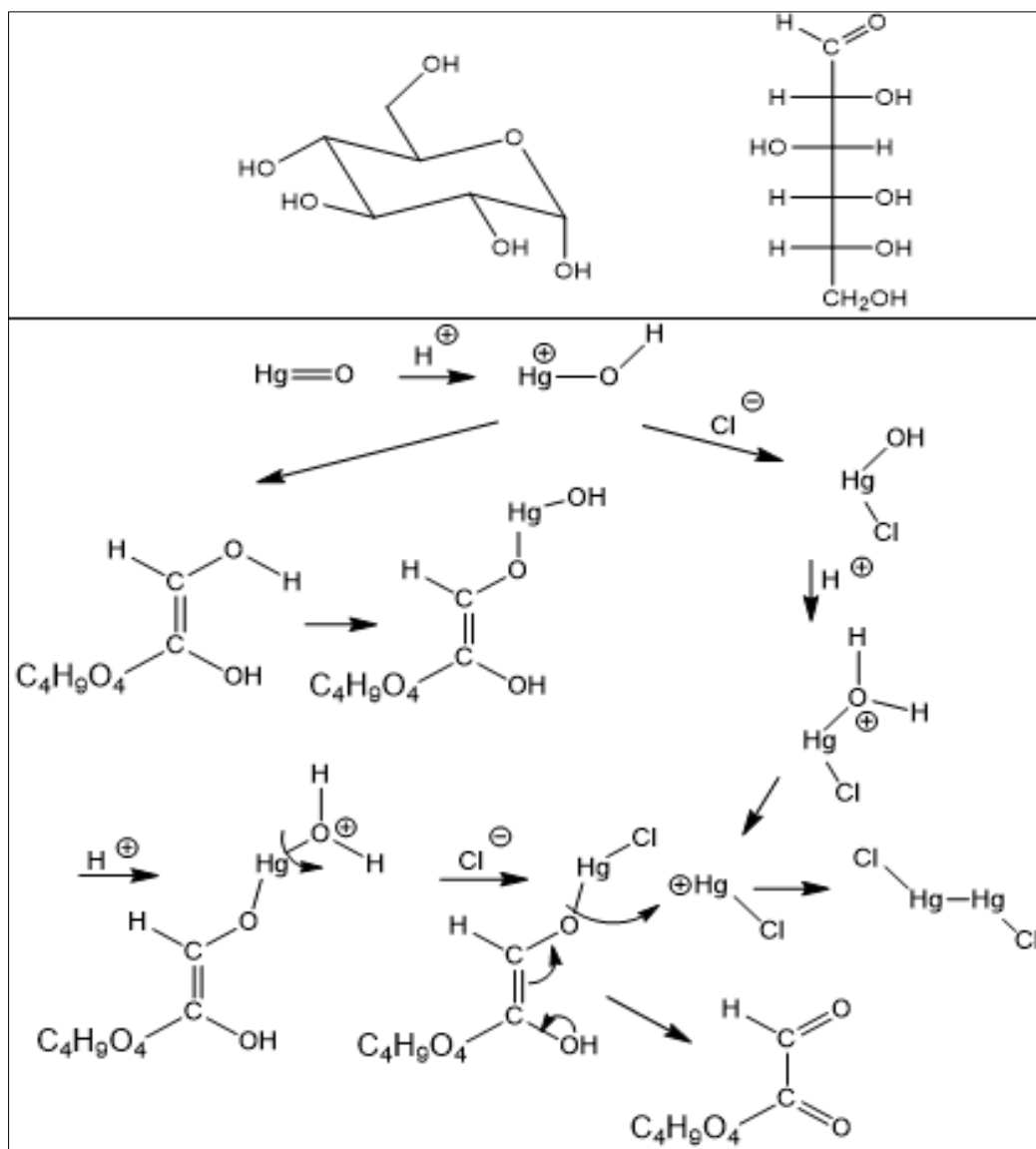
The end product, mercurous chloride or mercury sub chloride is a colourless solid also known as calomel. Mercury (I) chloride is really  $\text{Hg}_2\text{Cl}_2$ , with the connectivity  $\text{Cl-Hg-Hg-Cl}$ , indicative of its tendency to bond to itself. Mercury is in d-block, group 12, period 6. Its electron configuration is:  $[\text{Xe}] 4f^{14}5d^{10}6s^2$ , <sup>[11]</sup>.  $\text{Hg}^+$  has a  $5d^{10}6s^1$ . Thus,  $\text{HgCl}$  would be expected to be paramagnetic as it has an impaired electron. However, the compound is diamagnetic since it combines with another ion and must exist as  $\text{Hg}_2\text{Cl}_2$ . The existence of the metal-metal bond in  $\text{Hg}$  (I) compounds was established using X-ray diffraction in 1927 <sup>[12]</sup>, and Raman Spectroscopy in 1934 <sup>[13]</sup>.

Calomel was taken internally and used as a laxative, and disinfectant, as well in the treatment of syphilis <sup>[14]</sup>. In

homeopathy, calomel is known as *Mercurius dulcis* due to its sweet taste. It has marked effect on catarrhal inflammation of ear, and useful in Eustachian catarrh, deafness, and prostatitis <sup>[15]</sup>. Calomel is practically insoluble in water; the greater the covalent character, the lower will be the solubility (Fajan's rule of solubility).

### Discussions

Glucose does not react as  $\alpha$ -D-glucopyranoside but in the reactive open-chain form. This aldohexose is a carbon acid and isomerizes to the enolic form in an acidic medium or to the corresponding enolate in basic conditions. The test for glucose occurs in a slightly acidic medium (2.5% acetic acid).



**Fig 1:** Reaction route of Hager's test for glucose, formation of dimercury dichloride and 2-ketoglucose

The reactive species,  $\text{H-O-Hg}^+$ , comes from protonation of mercuric oxide, the principal reagent. This cation can react with an acetate ion, with a chloride ion, or with the enol at C-1 in the enediol formed in glucose; the oxygen at C-2 is more hindered. Protonation of this organo mercuric intermediate facilitates reaction with a chloride ion, either by a  $\text{S}_{\text{N}}1$  or by a  $\text{S}_{\text{N}}2$  mechanism. The  $\text{S}_{\text{N}}1$  mechanism is preferred since protolysis of chlorohydroxy mercury yields the key cationic species with which the chloromercury

enolate reacts.

A bimolecular reaction starts with the electrophilic <sup>[16]</sup> properties of the enol at C-2. A concerted mechanism takes place, affording the end products: 2 ketoglucose (Glucosone), the oxidation product, and dimercury dichloride, the reduction product. Thus, the proposed mechanism is in accordance with the inorganic information (experimental data) given in the previous section.

The very insoluble  $\text{Hg}$  (I) chloride is filtered, dried, weighed

and related to glucose concentrations.

### Conclusion

The reaction mechanism of the Hager test for glucose quantification has been cleared up. Information related to the end inorganic product has been provided since its chemical structure, dimercury dichloride, is of utmost importance in order to understand and confirm the reaction mechanism of this test.

The reaction starts from a cationic species that combines with different nucleophiles giving hydroxymercury intermediates. Protolysis of these compounds followed by reaction with chloride ions give chloromercury glucose-emulate and chloromercury caption. These two key intermediates react and there is a bimolecular electron transfer (oxido-reduction step), affording 2-ketoglucose and dimercury dichloride this very insoluble product is weighed and related to glucose content and concentration.

### Acknowledgment

Thanks are given to Martha Berros for support.

### Disclosure of conflict of interest

There is no conflict of interest among the authors or any other person.

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