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A Complete and Sustained Clemmensen Reduction Mechanism

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Abstract The mechanism for the Clemmensen reduction is not yet fully understood and there are two principal proposals: the ‘Carbanionic Mechanism’ and the ‘Carbenoid Mechanism’. After a critical review, we present a complete and coherent reaction mechanism that involves the formation of a free carbene as well as a zinc carbene and two different carbanionic species as intermediates. This point of view is based on well known reactivities and eliminates all the wrong, dubious or hindered intermediates suggested in previous proposals.

Keywords Carbanions, Carbenes, Carbonyl deoxygenation, Ionic sequence, Organometallic intermediates

1. Introduction

The Clemmensen reduction of carbonyl compounds to alkane analogs by means of amalgamated zinc and hydrochloric has been studied with many substrates. Aliphatic and aromatic compounds have been employed and have shown different chemical deportments. Thus, the original reaction giving methylene analogs is not strictly followed by the aryl derivatives since other products are also formed.

Other point of interest has been the reaction mechanism because with the aliphatic compounds the reduction does not go through the alcohol. There is not a detailed presentation on this subject. We present a complete and clear reaction mechanism, with the respective comment in each step.

Our sequence is a unified theory of the carbanionic mechanism and the carbenoid proposal. There must not be two very different mechanisms in order to explain the same reaction, but a complete and coherent one. This way the two theories are conciliated.

This will also fill a gap in Chemical Education.

2. Early Approaches and Modern Theories

The Clemmensen reaction consists in the reduction of a carbonyl compound to a methyl or methylene group by means of zinc amalgam and hydrochloric acid. There are two reviews [1, 2] and general information [3-8].

We will comment only pertinent studies that are subsequent to the 1942 review.

Brewster [9] studied the Clemmensen reduction. He considers the solid metal as an “electron pump”, this mechanical simile can be misleading since zinc has been interpreted by other authors as a source of free electrons in the reaction medium. He represents the metal as - $(:M)_x^+$. This is inadmissible because there is no reason to polarize the reagent. There is no such dipole in Zn^0.

In other communication [10], Brewster studied the reduction of some sterically hindered ketones and proposes as intermediary the structure in Figure 1. This is in contradiction with his previous paper in which he considers there is no carbonium ion. If so, how the proposed intermediate can be formed?

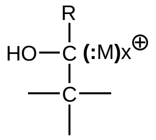

Figure 1. Brewster’s outmoded representation of a reaction intermediate

Staschewski [11] repeated Brewster’s wrong representation of zinc, but he included the needed carbocation previous to the interaction with the metal. The next two steps are confusing due to the unusual distribution of the electrons and electrical charges which is totally inadequate today.

Nakabayashi [12] gave evidence for the formation of an intermediate carbonium ion in the Clemmensen reduction. He studied the initial stages with acetophenone and t-butylphenyl ketone. A scheme related to the mechanism was provided in his previous paper [13].

After the formation of a cationic intermediate he proposes further reaction with another zinc atom giving a dipole with negative zinc, Figure 2.

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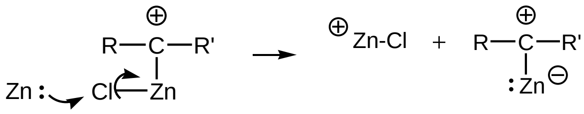
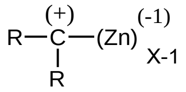


Figure 2. Unfeasible electrophilic reaction

This is completely unlikely, in the chloro-zinc bond chlorine has a δ^- and thus it is not electrophilic. So, there is not either negative zinc. Moreover, in the zincate anions the negative charge arises from the ligands, i.e., oxygen, chlorine, etc., not from the zinc.

The reduction of certain 2-benzoylbenzoic acids and esters was discussed by Risinger and Thomson [14]. This study revealed neighboring group participation and the formation of bimolecular reduction products. However, this theme is far away from the original Clemmensen reaction.

Reusch [15], in Augustine's book 'Reduction', comments the Clemmensen reduction in the section on 'Deoxygenation of Carbonyl Compounds'. He presents a modified version of the Brewster's mechanism. A proposed intermediate is in Figure 3, which is unacceptable because active metals form positive ions, not negative ones. Also, there are missing steps in order to have an understandable and coherent reaction mechanism, as we will see in the Discussion.



$$R-\underset{R}{\overset{(+)}{C}}-(Zn)^{(-1)}_{X-1}$$

Figure 3. A variant of the previously rejected intermediate

Ten years later, Horner and Schmitt [16] proposed a reaction mechanism for the Clemmensen reduction. Two zinc atoms were differentiated as Zn' and Zn''. The step after the carbocation formation is in Figure 4. In this representation the electric charges are missing, the halogen and the zinc must be negative and positive, respectively, as indicated below. Then the zinc atom must leave the metal surface and form a covalent bond with a chloride ion.

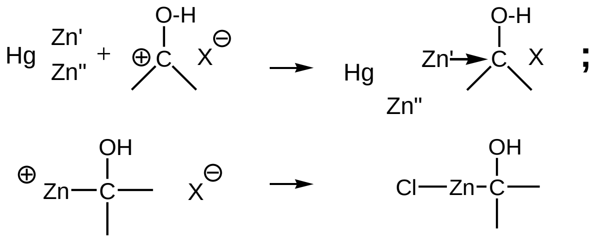


Figure 4. Incorrect and corrected structure after reaction with zinc

The proposed next step is in Figure 5, a double 1,2 migration. This is very improbable since there is no reason for the rupture of two sigma bonds.

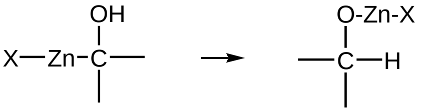


Figure 5. Arbitrary twofold atom tranfer

Other paper is that of Crump and Davis [17], from New Zealand. They studied the Clemmensen reduction of some 1,4-diketones and obtained alcohols which are not normally produced in this reaction. For instance, hexane-2,5-dione gave hexane-2-ol, as well as cis- and trans-hex-4-en-2-ol, Figure 6. Obviously, neighboring group participation deviates completely the normal reactivity.

The Clemmensen reduction of 2-acetylflourene [18] is abnormal since it yields not only 2-ethylflourene but also the carbinol, 2-(α-hydroxyethyl)fluorene, and eight derivatives of this alcohol. What is interesting from the mechanistic point of view is the ease of the proposed metallic intermediate to form the alcohol, Figure 7.

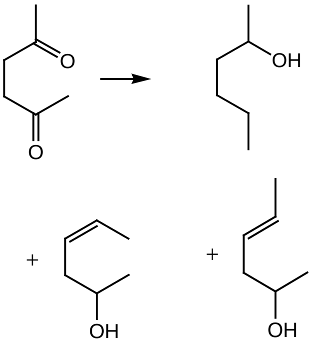


Figure 6. An example of I,4 diketone reduction by Clemmensen reaction

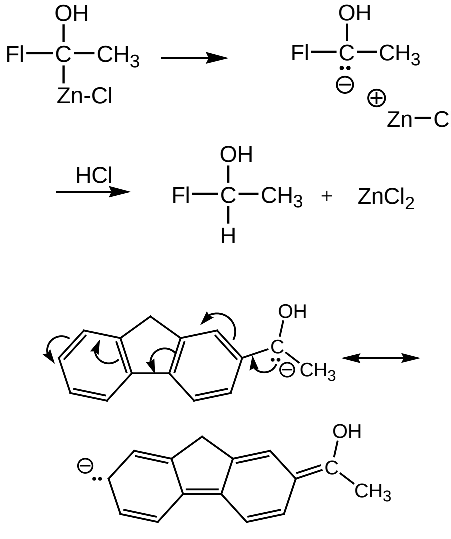


Figure 7. Formation of methyl-2-fluorylcarbinol and carbanion stabilization

The stability of this carbanion can be explained by the extended cross conjugated double bond system that results from electron delocalization by resonance. This is not the case in ordinary Clemmensen reductions and results in a different chemical deportment.

Burdon and Price [19] evidenced the presence of carbene intermediates since they were captured by an alkene to give a cyclopropane. The authors studied the reaction of substituted acetophenones with amalgamated zinc in homogeneous (50% aq. EtOH) solution at 20°C and HCl. They propose direct formation of a zinc-carbene from the ketone, Figure 8.

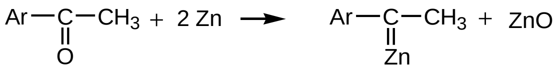


Figure 8. Main reaction of the so-called ‘Carbenoid mechanism’

The viability or not of this proposal is discussed later in ‘The Carbenoid mechanism’. We consider that the carbene is formed through previous intermediates as we will see in the Discussion.

The free carbene was captured by reaction with added styrene as indicated in Figure 9.

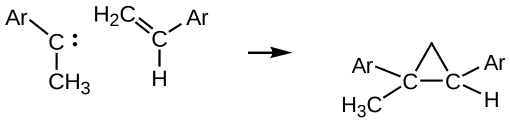


Figure 9. Formation of a cyclopropane derivative with capturing styrene

Actual information online on the Clemmensen Reduction [20] states ‘the mechanism is not yet fully understood’ and there are two principal proposals: the ‘Carbanionic mechanism’ and the ‘Carbenoid mechanism’.

In one presentation of the ‘Carbanionic mechanism’ [21] every carbocation reacts with two free electrons, supposedly emitted by the zinc, forming a carbanion that afterwards is protonated. The resulting short sequence is apparently flawless but it omits the formation of a carbene, a key intermediate that has been detected experimentally. But if a neutral organometallic intermediate is formed in the sequence, as we will see later, there is possibility to form a carbene, otherwise no. The misconception of free electrons in the reaction medium derives from considering literally the zinc as an ‘electron pump’. Besides, this would increase hydrogen formation in the acidic medium.

In the other mechanism presented, the ‘Carbenoid’ [20], the first formed intermediate is a zinc-carbenoid, without hydrogen chloride participation, Figure 10.

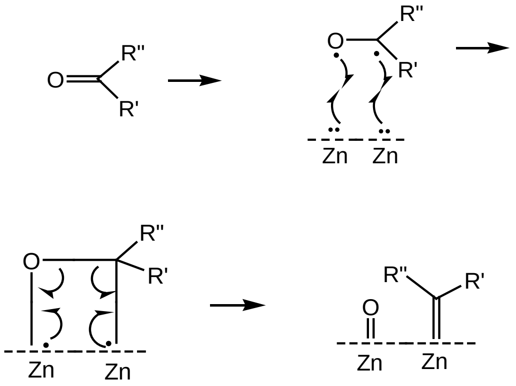


Figure 10. Supposed formation of zinc oxide and a zinc-carbene

The simultaneous interaction of the carbonyl compound with two vicinal zinc atoms in the zinc surface is not probable because the Zn-Zn distance is 2.3 times longer (2.84 Å) than the C=O bond length (1.21 Å). Besides, it is very dubious that would be reaction between a carbonyl compound and zinc alone, i.e., without the intervention of hydrochloric acid.

In the next section we present the formation of a free carbene and a zinc-carbene after other stages and by reaction with a second zinc atom.

In this review, dedicated exclusively to the mechanistic theme, we have pointed out the errors, the false reactivities and the missing links that we have encountered in the communications on the Clemmensen reduction mechanism.

We present our theory in the next section.

3. Discussion

Instead of two different reaction mechanisms, the ‘Carbanionic’ and the ‘Carbenoid’, we present a complete mechanism that includes the formation of both species. This has been possible considering the formation of sigma bonded organometallic intermediates, Figure 11.

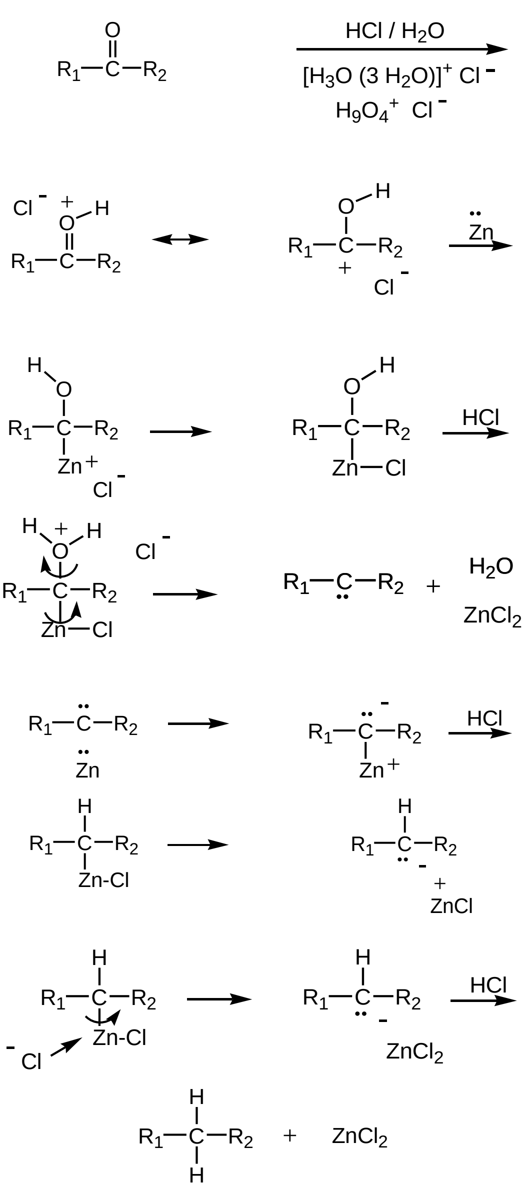


Figure 11. Complete reaction mechanism of the Clemmensen reduction

The first step is interaction of the ketone or aldehyde with a solvated hydroxonium ion [22, 23] coming from the aqueous hydrochloric acid. The resulting oxonium chloride is in resonance with a carbonium ion electromer. This carbocation, in a chemisorption step, reacts with elemental zinc, an electrodoting reagent [24], leading to a two-electron reduction. The obtained organometallic intermediate reacts with hydrochloric acid: a carbene is formed with concomitant water and zinc chloride elimination. The electron deficient species reacts with another zinc atom and a dipolar ion is formed. This metal carbene complex is of Schrock type [25], a carbanion and an electron deficient metal. It can be represented double bonded to zinc, but *ab initio* quantum mechanical methods display a zinc- carbon single bond for $ZnCH_2$ [26].

Reaction of the above zwitter ion with hydrochloric acid yields a deoxy organometallic derivative. Finally, ionization gives a carbanion which by protonation affords the reduction product, i.e., with a methylene instead of the original carbonyl group. The ionization can be assisted by direct formation of zinc chloride due to interaction with a chloride ion. This is supported by the fact that zinc chloride in the presence of hydrochloric acid forms the tetrachlorozincate anion, $ZnCl_4$= [27], showing the zinc receptivity to chloride ions.

The Clemmensen reduction can be summarized in the following equation:

$R_1\text{-CO-}R_2 + 2\ Zn + 4\ HCl \longrightarrow R_1\text{-}CH_2\text{-}R_2 + H_2O$
$+ 2\ ZnCl_2$

In the mechanism presented by Vedejs [2], the hydroxy organometallic intermediate, after protonation and water elimination yields a bis-chlorozinc structure, Figure 12a, and no carbene is formed. However, carbenes are known intermediates whose formation has been confirmed experimentally.

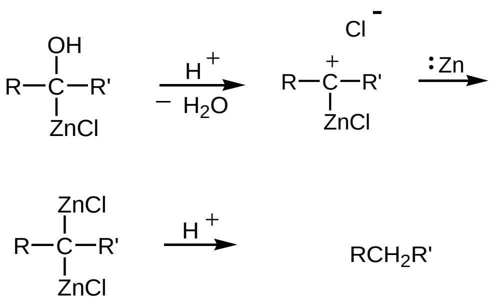


Figure 12a. Improbable protolysis to the hydrocarbon

Moreover, the bis-chlorozinc structure is not prone to the required ionization in order to be protonated and yield the reduction product because a chlorozinc ligand causes a δ^- at the carbon atom and thus a carbanion from the second chlorozinc group would be at the seminegative carbon atom, which is highly unlikely. On the other hand, the carbanions in our reaction sequence are far likely.

Figure 12b shows our alternative to the previous reactions. The protonated hydroxy organometallic intermediate goes ahead with an almost synchronic water elimination, carbene formation and ^+ZnCl displacement.

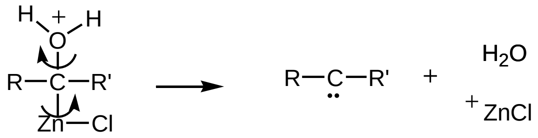


Figure 12b. The required carbene formation via a concerted reaction mechanism

4. Conclusions

- We present a complete and coherent reaction mechanism for the Clemmensen reduction in order to explain the deoxygenation of a carbonyl group to a methylene.
- The sequence is fully commented and is based on facts and well known reactivities.
- This reaction mechanism includes the intermediates proposed by the two actual theories: the ‘Carbanionic Mechanism’ and the ‘Carbenoid Mechanism’.
- The unification of both theories has been possible postulating certain organometallic links instead of free electrons reduction or direct formation of a zinc-carbene.
- The finding that both carbenes and carbanions are formed in the same reaction sequence eliminates the disagreement on the Clemmensen reduction mechanism.

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