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Haloform reaction

The **haloform reaction** is a chemical reaction where a haloform (CHX_3, where X is a halogen) is produced by the exhaustive halogenation of a methyl ketone ($RCOCH_3$, where R can be either a hydrogen atom, an alkyl or an aryl group), in the presence of a base.[1][2][3] The reaction can be used to transform acetyl groups into carboxyl groups or to produce chloroform ($CHCl_3$), bromoform ($CHBr_3$), or iodoform (CHI_3) and also cyanide.

Haloform reaction	
Named after	Adolf Lieben
Reaction type	Substitution reaction
Identifiers	
Organic Chemistry Portal	haloform-reaction

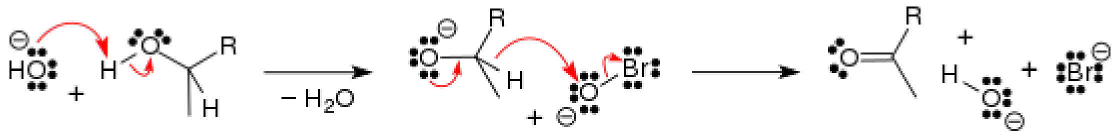
Contents

Mechanism

In the first step, the halogen disproportionates in the presence of hydroxide to give the halide and hypohalite (example with bromine, but reaction is the same in case of chlorine and iodine; one should only substitute Br for Cl or I):

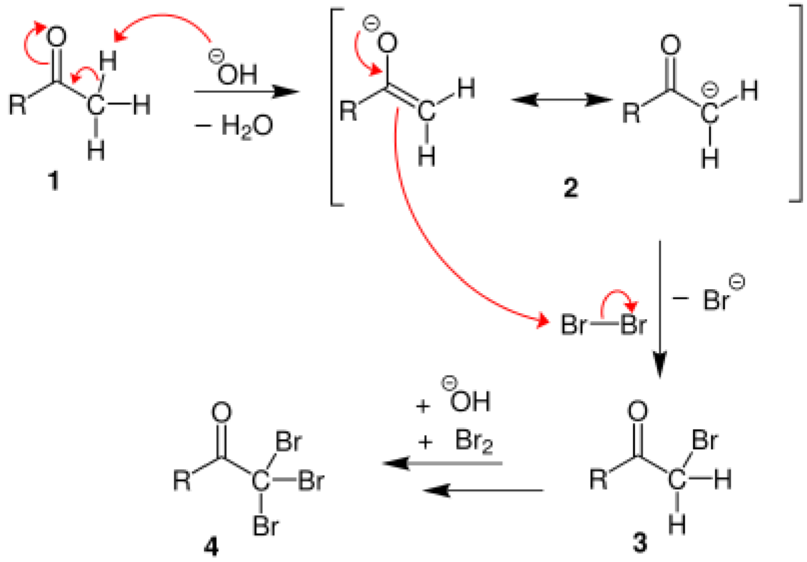
$$\mathrm{Br_2 + 2OH^- \rightarrow Br^- + BrO^- + H_2O}$$

If a secondary alcohol is present,it is oxidized to a ketone by the hypohalite:

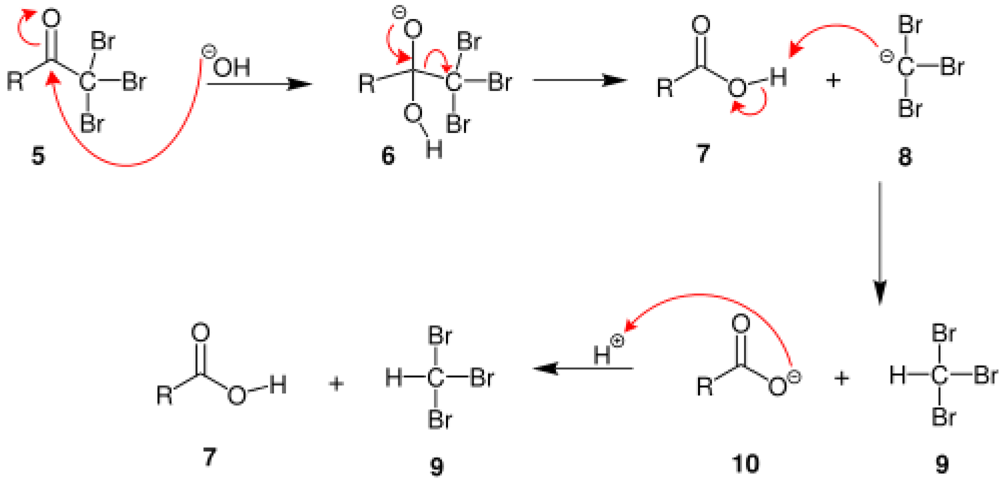


If a methyl ketone is present, it reacts with the hypohalite in a three-step process:

1. Under basic conditions, the ketone undergoes keto-enol tautomerization. The enolate undergoes electrophilic attack by the hypohalite (containing a halogen with a formal +1 charge).



2. When the α(alpha) position has been exhaustively halogenated, the molecule undergoes a nucleophilic acyl substitution by hydroxide, with $^-CX_3$ being the leaving group stabilized by three electron-withdrawing groups. In the third step the $^-CX_3$ anion abstracts a proton from either the solvent or the carboxylic acid formed in the previous step, and forms the haloform. At least in some cases (chloral hydrate) the reaction may stop and the intermediate product isolated if conditions are acidic and hypohalite is used.



Scope

Substrates are broadly limited to methyl ketones and secondary alcohols oxidizable to methyl ketones, such as isopropanol. The only primary alcohol and aldehyde to undergo this reaction are ethanol and acetaldehyde, respectively. 1,3-Diketones such as acetylacetone also give the haloform reaction. β-ketoacids such as acetoacetic acid will also give the test upon heating. Acetyl chloride and acetamide don't give this test. The halogen used may be chlorine, bromine, iodine or sodium hypochlorite.[4] Fluoroform (CHF_3) cannot be prepared by this method as it would require the presence of the highly unstable hypofluorite ion. However ketones with the structure $RCOCF_3$ do cleave upon treatment with base to produce fluoroform; this is equivalent to the second and third steps in the process shown above.

Applications

Laboratory scale

This reaction forms the basis of the iodoform test which was commonly used in history as a chemical test to determine the presence of a methyl ketone, or a secondary alcohol oxidizable to a methyl ketone. When iodine and sodium hydroxide are used as the reagents a positive reaction gives iodoform, which is a solid at room temperature and tends to precipitate out of solution causing a distinctive cloudiness.


Negative and positive iodoform test

In organic chemistry, this reaction may be used to convert a terminal methyl ketone into the analogous carboxylic acid.

Industrially

It was formerly used to produce iodoform, bromoform, and even chloroform industrially.

As a by-product of water chlorination

Water chlorination can result in the formation of haloforms if the water contains suitable reactive impurities (e.g. humic acid).[5][6] There is a concern that such reactions may lead to the presence of carcinogenic compounds in drinking water.[7]

History

The haloform reaction is one of the oldest organic reactions known.[8] In 1822, Georges-Simon Serullas added potassium metal to a solution of iodine in ethanol and water to form potassium formate and iodoform, called in the language of that time *hydroiodide of carbon*.[9] In 1832, Justus von Liebig reported the reaction of chloral with calcium hydroxide to form chloroform and calcium formate.[10] The reaction was rediscovered by Adolf Lieben in 1870.[11] The iodoform test is also called the **Lieben haloform reaction**. A review of the Haloform reaction with a history section was published in 1934.[2]

References

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10. Liebig, Justus von (1832). "Ueber die Verbindungen, welche durch die Einwirkung des Chlors auf Alkohol, Aether, ölbildendes Gas und Essiggeist entstehen" (https://babel.hathitrust.org/cgi/pt?id=wu.89048351662&view=1up&seq=861) [On the compounds which arise by the reaction of chlorine with alcohol [ethanol], ether [diethyl ether], oil-forming gas [ethylene], and spirit of vinegar [acetone]]. *Annalen der Physik und Chemie*. 2nd series. **100** (2): 243–295. Bibcode:1832AnP...100..243L (https://ui.adsabs.harvard.edu/abs/1832AnP...100..243L). doi:10.1002/andp.18321000206 (https://doi.org/10.1002%2Fandp.18321000206).
On pages 259–265, Liebig describes *Chlorkohlenstoff* ("carbon chloride", chloroform), but on p. 264, Liebig incorrectly states that the empirical formula of chloroform is C_2Cl_5. From p. 259: *"Chlorkohlenstoff. Man erhält diese neue Verbindung, wenn man Chloral mit ätzenden Alkalien, Kalkmilch oder Barytwasser in Ueberschuss vermischt und das Gemenge destillirt."* (Chloroform. One obtains this new compound when one mixes chloral with an excess of caustic alkalies, milk of lime [solution of calcium hydroxide] or barite water [solution of barium hydroxide], and [then] distills the mixture.)
11. See:
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    - Lieben, Adolf (1870). "Nachschrift zur Abhandlung über Entstehung von Jodoform und Anwendung dieser Reaction in der chemischen Analyse" (https://babel.hathitrust.org/cgi/pt?id=uiug.30112018225695&view=1up&seq=389) [Postscript to the article on the formation of iodoform and the application of this reaction to chemical analysis]. *Annalen der Chemie. Supplementband.* (in German). **7**: 377–378.

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