

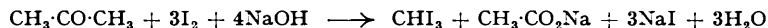
623. *The Iodoform Reaction.*

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The mechanism of the iodoform reaction is discussed. When the reaction is used for the determination of methyl ketones, low results are obtained unless the order and rate of addition and the concentrations of the reagents are properly adjusted. The inaccuracy encountered, when the recommended analytical procedure is not closely followed, may be ascribed, in part, to the competing reaction: $3\text{IO}^- \longrightarrow \text{IO}_3^- + 2\text{I}^-$. Means by which the sources of error may be minimised have been examined, and the optimum conditions for the use of the reaction in quantitative analysis determined.

The haloform reaction, first discovered in 1831 (Liebig, *Annalen*, **23**, 444; Souberian, *Ann. Chim. Phys.*, 1831, **48**, 131), has found extensive use in organic analysis. Though first developed as a gravimetric method by Lieben (*Ann. Chem., Pharm. Suppl.*, 1870, **7**, 218) and Kramer (*Ber.*, 1880, **13**, 1000), it was not until it was adapted to a volumetric procedure by Messinger (*Ber.*, 1888, **21**, 3366) that its full potentialities were realised. As examples of its use, mention may be made of the classical work of Tiemann (*Ber.*, 1895, **28**, 2141; 1900, **33**, 3703) and of Simonsen (*J.*, 1922, **121**, 2292). Recently, it has been employed in this laboratory in investigations of the slow combustion of hydrocarbons and their derivatives (see, *e.g.*, Cullis, *Trans. Faraday Soc.*, 1949, **45**, 709; Bardwell and Hinshelwood, in the press). Despite the wide use of the reaction for the determination of methyl ketones and related substances, it is perhaps not commonly realised that quantitative results are not obtained unless the generally recommended analytical procedure (see, *e.g.*, Thorpe and Whiteley, "Organic Chemical Analysis," Longmans and Green, 1926, p. 192) is closely adhered to.

One of the simplest examples of the haloform reaction is the interaction of acetone and iodine, usually represented by the equation :



Although this reaction is irreversible and rapid even at room temperature, it is easily shown that, when the reactants are mixed in stoichiometric proportions, only a small fraction of the acetone is converted into iodoform.

It is now recognised that reaction takes place through the following stages :

(a) Conversion of the ketone into the enolate ion :



(where B is the basic catalyst, usually the hydroxyl ion). Extensive work on the kinetics of the reaction has shown that this is the rate-determining stage (Bartlett, *J. Amer. Chem. Soc.*, 1934, **56**, 967; Bell and Lidwell, *Proc. Roy. Soc.*, 1946, *A*, **176**, 88; Bell and Longuet-Higgins, *J.*, 1946, 636).

(b) Progressive iodination of this ion, resulting in the eventual formation of tri-iodoacetone. There is little evidence to show which of the various iodine compounds present reacts with the enolate ion, since the rate of reaction is invariably independent of the halogen concentration (Bartlett, *loc. cit.*; Bell and Lidwell, *loc. cit.*). However, in alkaline solutions of iodine, the principal species will be hypoiodite ions (IO^-) and undissociated hypoiodous acid molecules

(HIO); * the latter acid is very weak ($K_a = 4.5 \times 10^{-13}$; Skrabal, *Ber.*, 1942, **75**, 1570), so that there will be an appreciable quantity of HIO even in strongly alkaline solutions. Since iodination involves attack of the negative enolate ion, it would appear that the undissociated hypiodous acid molecule rather than the hypiodite ion is the species involved (cf. Ingles and Israel, *J.*, 1948, 810).

(c) Hydrolysis of tri-iodoacetone according to the equation:



Reactions of this type are catalysed by bases (Richard and Langlais, *Bull. Soc. chim.*, 1910, **7**, 464).

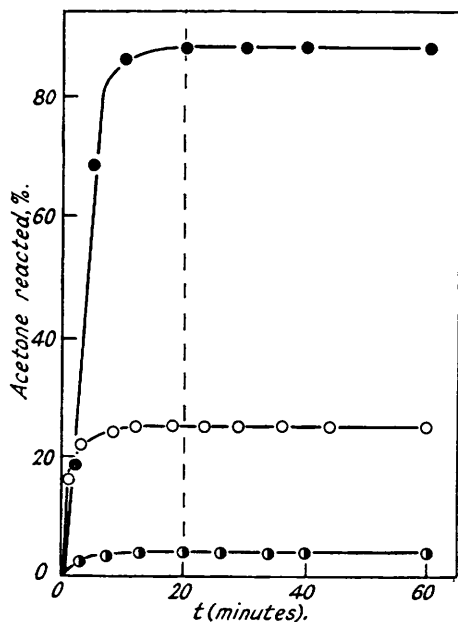
The present investigation was conducted with a view to increasing the reliability of Messinger's iodoform method by ascertaining the limiting experimental conditions needed to obtain quantitative results. Preliminary experiments indicated that among the main factors which must be carefully controlled are the order and rate of addition and the relative concentrations of the reagents. Systematic examination of these factors yielded the results described below.

EXPERIMENTAL.

All experiments were carried out at 25° in an electrically controlled thermostat. The reagents, with the exception of the acetone, were of "AnalaR" purity; the acetone was obtained from the

FIG. 1.

The extent of reaction as a function of time at 25°.



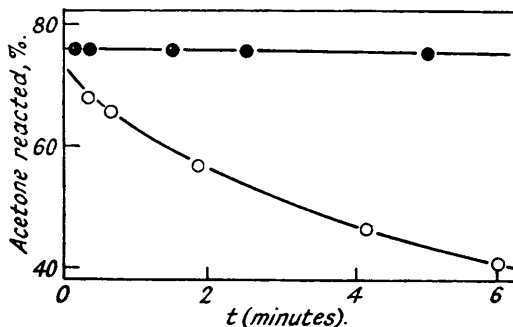
- Acetone, 0.00071M.; iodine, 0.00285M.; NaOH, 0.0285M.
- Acetone, 0.01M.; iodine, 0.04M.; NaOH, 0.50M.
- ◐ Acetone, 0.01M.; iodine, 0.04M.; NaOH, 0.04M.

sodium iodide complex. For the determination of "unreacted" iodine (as both HIO and IO_3^- , see below), the solution was made slightly acid with hydrochloric acid, and titrated with standard thio-sulphate. It was found that a slight excess of acid was sufficient to liberate all the "unreacted" iodine, but that a moderate excess did not interfere in the titration. Careful buffering of the solution before titration, as recommended by Dawson and Leslie (*J.*, 1909, **95**, 1860), was not found to be necessary in this work.

Results.—(1) Rate experiments. A few typical results are shown in Fig. 1, which indicate that at

FIG. 2.

The influence of the order of mixing of reagents on the percentage of acetone reacting.



Acetone, 0.001M.; iodine, 0.004M.; sodium hydroxide, 0.02M.

- Acetone and sodium hydroxide mixed, iodine added after time t.
- Iodine and sodium hydroxide mixed, acetone added after time t.

* Although the role of positive halogen ions in halogenation reactions in acid solution is well established (see, e.g., Derbyshire and Waters, *J.*, 1950, 564), the concentration of I^+ in the strongly alkaline solutions employed will be negligible [$K_s(\text{HIO}) = 3.2 \times 10^{-10}$; Skrabal, *loc. cit.*].

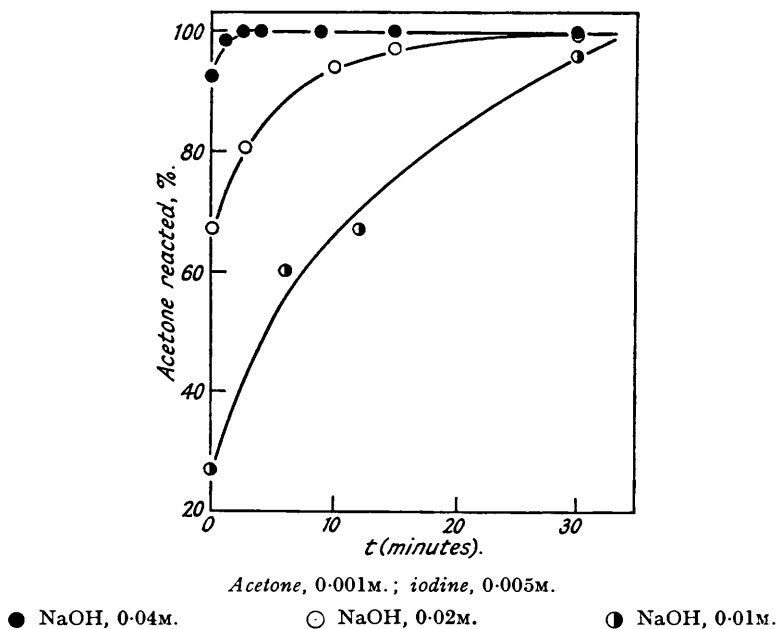
the reagent concentrations employed no further iodine is, in general, taken up by the acetone after 20 minutes. This time was taken as the standard reaction period in all subsequent experiments.

2. *The order of mixing of the reagents.* The procedure in these experiments was to mix two of the components and then to add the third after various times. The results of greatest interest are those in which (a) the acetone is added last, and (b) the iodine is added last. Some data are given in Fig. 2, which indicate the importance of the order in which the reagents are mixed. It is seen that the yield of iodoform is decreased when the alkali and iodine are mixed and set aside before the acetone is added. This result is most easily explained in terms of a side reaction involving the alkali and iodine. On the other hand, when the alkali and acetone are "pre-mixed," the amount of the latter converted into iodoform is independent of the time which elapses before the iodine is added.

(3) *The rate of addition of iodine.* In this series of experiments, the iodine was added slowly with constant agitation to the "pre-mixed" acetone and alkali, and its rate of addition was varied. The results given in Fig. 3 show that the yield of iodoform is increased by slow addition of the iodine; the effect is most pronounced when the alkali : acetone ratio is comparatively small.

FIG. 3.

The influence of the rate of addition of iodine on the percentage of acetone reacting. [The abscissæ represent the time taken for the addition of a fixed volume of iodine solution (40 c.c.).]



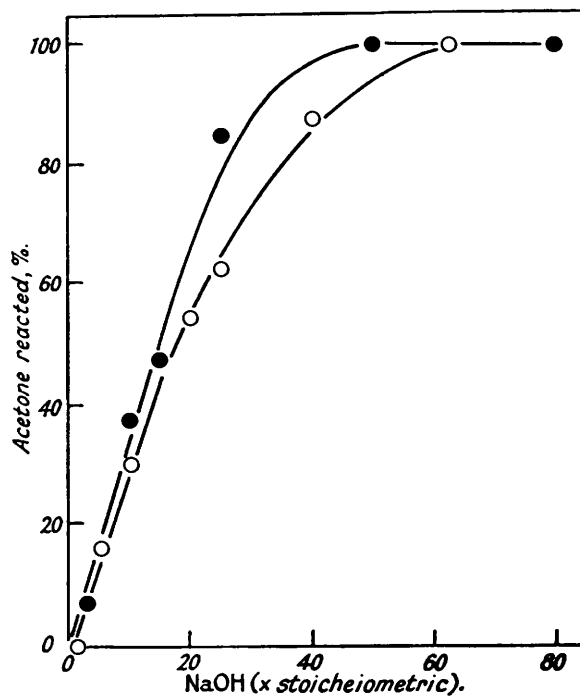
(4) *The influence of alkali concentration.* The effect of varying the concentration of alkali was investigated in a series of experiments in which all three reagents were mixed rapidly; in this way, variations due to order and rate of addition were eliminated. Some typical results are shown in Fig. 4, from which it is clear that, under the particular conditions employed for these experiments, complete conversion of all the acetone into iodoform is achieved only in presence of a very large excess of alkali (about 50 times that required by the stoichiometry of the reaction). It is evident from Fig. 2 that, when the iodine is added slowly to the other reagents, considerably less than this quantity of alkali is needed. Even under such favourable conditions, however, several times the theoretical amount of the latter must be used. The marked influence of the alkali concentration may also be seen from the results given in Figs. 3 and 5.

Similar results to the above were obtained when barium hydroxide was used in place of sodium hydroxide.

(5) *The influence of iodine concentration.* The influence of iodine concentration was investigated in a series of experiments in which a fixed volume of various iodine solutions was added at a standard rate to an acetone-alkali mixture. It is seen from Fig. 5 that, with a high concentration of alkali (*i.e.*, 20 times the stoichiometric), the proportion of acetone converted into iodoform at first increases as more iodine is added, quantitative conversion occurring when slightly more than the stoichiometric amount of iodine is used. At lower alkali concentrations, it will be noticed that a large excess of iodine has an unfavourable effect, the percentage of acetone which reacts passing through a maximum and then decreasing as further iodine is added. This decrease usually occurs when the iodine concentration approaches that of the alkali.

FIG. 4.

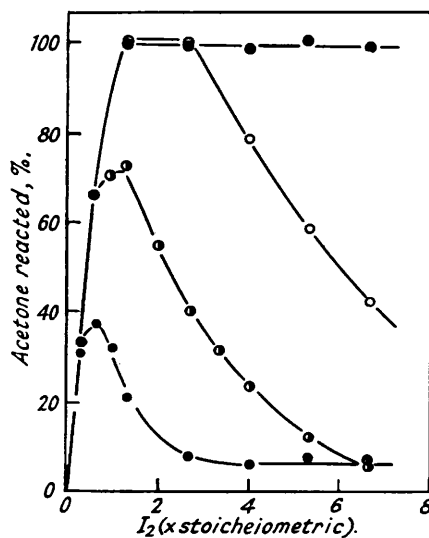
The influence of alkali concentration on the percentage of acetone reacting, under conditions of rapid mixing of reagents.



● Acetone, 0.002M.; iodine, 0.008M. ○ Acetone, 0.001M.; iodine, 0.004M.

FIG. 5.

The influence of iodine concentration on the percentage of acetone reacting.



Acetone: 0.0016M.

● NaOH, 0.128M. (20 × stoichiometric). ◐ NaOH, 0.032M. (5 × stoichiometric).
○ NaOH, 0.064M. (10 × stoichiometric). ⊕ NaOH, 0.0128M. (2 × stoichiometric).

It is suggested that the unfavourable influence of a large excess of iodine is due to its causing a considerable depletion of the hydroxyl-ion concentration as a result of the reaction: $I_2 + OH^- \rightarrow HIO + I^-$. As might be expected from the results given earlier, any factor which seriously reduces the effective concentration of alkali will also tend to decrease the efficiency of the iodoform reaction.

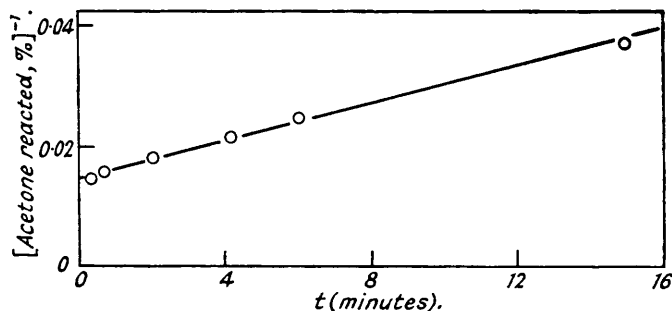
(6) *The effect of added barium nitrate.* The results given in Fig. 2 suggest that the reactive iodinating species may be converted into some unreactive compound by a side reaction; a possibility is a reaction of the type: $IO^- \rightarrow IO_3^-$. Such a process would interfere with the iodoform reaction only if it were irreversible. Since barium forms an insoluble iodate, addition of excess of barium ions to the reaction system should, if the reaction is reversible, increase the rate of removal of hypoiodite by the side reaction, and so lower the yield of iodoform. Some experiments were therefore carried out in presence of a high concentration of barium nitrate, together with parallel experiments in which an equivalent quantity of sodium nitrate was used (to eliminate salt effects). In no case could any appreciable difference be detected in the amounts of acetone converted into iodoform in the two series of experiments.

DISCUSSION.

It is evident from the foregoing that the conversion of acetone into iodoform is quantitative only when the experimental conditions are properly adjusted to minimise the occurrence of side reactions. Two types of competitive reaction may be considered: (a) those involving acetone and iodine, (b) those involving some iodine compound formed by interaction with alkali. In either case, the products must be such that on acidification all the iodine not combined as iodoform is liberated as the element. This criterion in itself renders unlikely any side reaction involving acetone and iodine, since under the conditions employed, fission

FIG. 6.

The rate of disproportionation of hypoiodite ions as determined by the conversion of acetone into iodoform; the variation of $[\% \text{ acetone reacted}]^{-1}$ with time [cf. Fig. 2 (open circles)].



of a C-I bond is highly improbable. However, a reaction of type (b), such as the disproportionation of IO^- into IO_3^- , may well occur, for iodate ions react with iodide ions in acid solution to yield iodine; the presence of sufficient iodide ions is assured both by their formation during the reaction and by their presence in the original iodine solution (I_2 in KI). The results presented in Fig. 2 also favour the above hypothesis. For the disproportionation reaction to be effective in removing hypoiodite ions from the system, it must, however, be irreversible. It seems probable that this is so in alkaline solution, particularly in view of the experimental results obtained in presence of barium nitrate (section 6). Li and White (*J. Amer. Chem. Soc.*, 1943, **65**, 335) have shown that the rate of disproportionation may be represented by the equation:

$$-d[IO^-]/dt = k[IO^-]^2[I^-]/[OH^-]$$

(see also Forster, *J. Physical Chem.*, 1903, **7**, 640); $[I^-]$ and $[OH^-]$ being assumed to be constant, this expression may be integrated to give $1/[IO^-] = k't + \text{const}$. The experimental results plotted in Fig. 2 (open circles) refer to a series of experiments in which $[I^-]$ and $[OH^-]$ are both effectively constant. From these data, the amount of acetone reacted may be obtained; this will, on the basis of the reaction mechanism outlined earlier, be proportional to the concentration of undissociated hypoiodous acid, which in turn will be proportional to the concentration of hypoiodite ions, *i.e.*, $\% \text{ acetone reacted} \propto [HIO] \propto [IO^-]$. When the reciprocal of the first quantity is plotted against time (Fig. 6), a straight line is obtained, as the integrated form of the rate equation predicts. Moreover, from the expression governing the rate of disproportionation of hypoiodite to iodate, it appears that hydroxyl ions exert a retarding influence on the reaction. This explains, in part, the improved yield of iodoform when the alkali concen-

tration is increased (Figs. 4 and 5). However, it is desirable that other means should also be sought of minimising the extent of the side reaction. These include (a) increasing the concentration of the enolate ion $[\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3]^-$, (b) decreasing the rate of disproportionation of hypiodite to iodate in comparison with that of iodination of the enolate ion. With regard to (a), the concentration of $[\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3]^-$ can obviously only be increased to a certain limiting concentration governed by the keto-enol equilibrium. On the other hand, (b) may be effected, not only by using a high concentration of alkali, but also by maintaining a high degree of dispersion of hypiodite ions; for, as the rate equation shows, the disproportionation is of the second order with respect to such ions, while the iodination is of zero order with respect to halogen (Bartlett, *loc. cit.*; Bell and Lidwell, *loc. cit.*). The dispersion is effected by using a slow rate of addition of iodine accompanied by vigorous stirring (cf. Fig. 3).

It will be seen from the foregoing that, in order to obtain quantitative yields of iodoform, the experimental conditions should be adjusted as follows:

1. The acetone and alkali should be "pre-mixed" and the iodine added slowly with constant agitation. This minimises, for any given conditions, the rate of the disproportionation reaction.

2. A large excess of alkali must be used, preferably of the order of twenty times that required according to the stoichiometric equation. This (a) assists the formation of the enolate ion, (b) retards side reactions leading to loss of the active iodinating species, (c) catalyses the final C-C bond fission.

3. A moderate excess of iodine (about $1.5 \times$ stoichiometric) should be employed. A larger excess may reduce the efficiency of the reaction by decreasing the hydroxyl ion concentration.

4. The reactants should be set aside for at least twenty minutes (at 25°) before acidification, to ensure completion of the reaction.

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