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THE HYDROLYSIS OF DIBROMOFLUOROMETHYLTRIPHENYLPHOSPHONIUM BROMIDE

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SUMMARY

Hydrolysis of $[Ph_3\overset{+}{P}CFBr_2]Br^-$ afforded a high yield of dibromofluoromethane and triphenylphosphine oxide. Hydrolysis in the presence of a radioactive isotope of bromine gave evidence that the mechanism of this reaction proceeds *via* the dibromofluoromethide ion and not *via* a bromofluorocarbene intermediate.

INTRODUCTION

Halo-*F*-methylphosphonium salts have been demonstrated to be useful synthetic intermediates for the generation of halo-*F*-methyl carbanions [1] or halofluorocarbenes [2]. They also serve as important precursors to the halofluoromethylene phosphonium ylides and have achieved wide utility in the synthesis of halofluoromethylene olefins [3].

The nature of the substituents attached to phosphorus in the halo-*F*-methyl phosphonium salts determines their ease of hydrolysis. For example, the triphenyl analogs are easily and rapidly hydrolyzed by both water and alcohol (Scheme 1) [4].

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$[Ph_3\overset{+}{P}CFXY]Z^-$ + H_2O or EtOH ⟶ Ph_3PO + CFHXY + HZ

X = F; Y = Br; Z = Br,I
X = Br; Y = Br; Z = Br
X = Cl; Y = Cl; Z = Cl

Scheme 1

The corresponding derivatives in which alkyl groups (such as n-Bu) are attached to phosphorus are hydrolyzed by water but are not hydrolyzed readily by alcohols [4]. When the substituent on phosphorus is a dialkylamino group (Scheme 2), the salt is stable to hydrolysis by both water and alcohol* [4].

$[(R_2N)_3\overset{+}{P}CFXY]Z^-$ + H_2O or EtOH ⟶ No Reaction

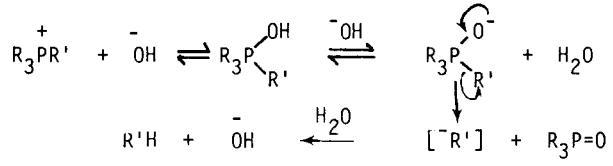
R = Me, Et
X = F; Y = Br; Z = Br
X = Br; Y = Br; Z = Br
X = Cl; Y = Cl; Z = Cl

Scheme 2

Recently, we presented evidence that the hydrolysis of bromo-F-methyltriphenylphosphonium bromide occurs via a carbene intermediate [5]. In this report we address the mechanism of hydrolysis of dibromofluoromethyltriphenylphosphonium bromide.

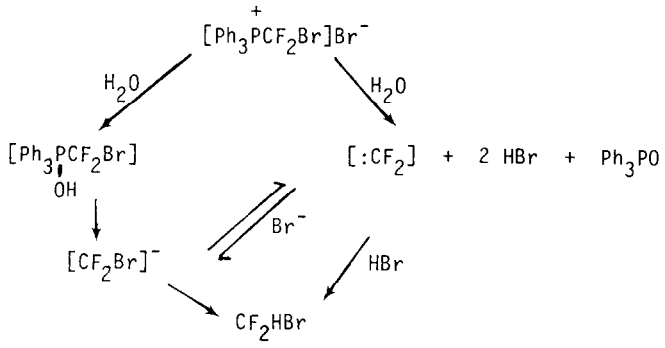
RESULTS AND DISCUSSION

The generally accepted mode of hydrolysis of phosphonium salts is via nucleophilic attack on phosphorus with displacement of the most stable carbanion [6]. Protonation of the resultant carbanion completes the hydrolysis reaction.



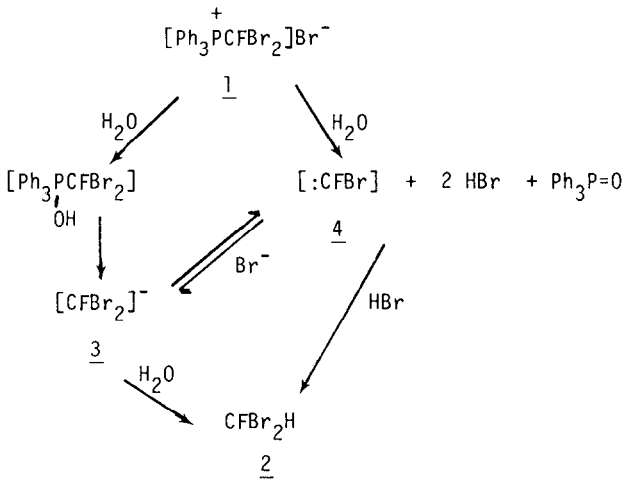
*Although stable to water and alcohol, hydrolysis of these salts can be readily achieved with base, such as hydroxide.

In the case of bromo-F-methyltriphenylphosphonium bromide, however, difluorocarbene formation - not bromo-F-methylcarbanion accounts for the hydrolysis process (Scheme 3) [5].



Scheme 3

A similar mechanistic pathway could account for the hydrolysis of dibromofluoromethyltriphenylphosphonium bromide (Scheme 4).



Scheme 4

In order to delineate the mechanistic pathway for the hydrolysis of 1, we employed the use of $^{82}Br^-$ as an isotopic label to determine if carbanion 3 or carbene 4 was the primary transient intermediate involved in the formation of 2.

Three possible limiting cases can be rationalized when the hydrolysis of 1 is carried out in the presence of $^{82}Br^-$.

Case I: Capture of 3 is faster than loss of Br^- to form 4 (cf. Scheme 4).

In this case no radioactive bromine is incorporated into 2. All the label appears in the HBr. Thus, the distribution of radioactivity will be 0/100 between 2 and HBr.

Case II: Rapid equilibrium between 3 and 4:

$$[CFBr_2]^- \underset{Br^-}{\overset{K_1}{\rightleftharpoons}} [:CFBr] + Br^-$$

3 4

H_2O | k_2

2

If $K_1 >>> k_2$ then both bromines in 3 can potentially enter the radiopool (obviously only one at a time) and the statistical distribution of radioactivity for total equilibration will be $66\frac{2}{3}$ / $33\frac{1}{3}$ between 2 and HBr.

Case III: Capture of 4 via HBr: (cf. Scheme 4).

In this case one bromine remains unique (relative to 1) and does not contribute to the radiopool; thus in the limit we would expect a 50/50 split of Br-82 between 2 and HBr.

Experimentally, when the hydrolysis of 1 is carried out in the presence of $^{82}Br^-$, the majority of the activity appears in the HBr fraction. The results of three separate experiments are summarized in Table I.

TABLE I

$$[Ph_3\overset{+}{P}CFBr_2]Br^- + H_2O + {}^{82}Br^- \longrightarrow Ph_3PO + {}^{82}Br\text{-}HBr + {}^{82}Br\text{-}CFBr_2H$$

Trial	^{82}Br-HBr (%)*	^{82}Br-$CFBr_2H$ (%)*
1	91	9
2	94	6
3**	80	20

*%'s refer to % of original activity incorporated in the HBr and $CFBr_2H$ fractions, respectively; **No added pyridine.

The average of the ^{82}Br-$CFBr_2H$ activity in trials 1 and 2 is 7.5%. This result is in best agreement with Case I and falls far short of the 50-66$\frac{2}{3}$% incorporation of Br-82 expected if carbene 4 were involved in the major mechanistic pathway to 2.

In trial 3 above, the reaction was carried out in the absence of pyridine which serves as a scavenger for the HBr produced in the reaction. Under these conditions it is difficult to remove 2 without contamination of the volatile fraction with HBr- hence the high activity of Br-82 in this trial. Indeed, it's tempting to conclude that the small amount of activity in ^{82}Br-$CFBr_2H$ fraction in trials 1 and 2 is also due to some contamination by HBr - however, we cannot unequivocally distinguish between such low levels of contamination vs. leakage via a competitive mechanistic pathway.

CONCLUSION

The absence of any significant incorporation of Br-82 into 2 when the hydrolysis of 1 is carried out in the presence of $^{82}Br^-$ demonstrates that the hydrolysis proceeds predominately via formation and capture of 3. Carbene 4 as a predominant transient intermediate is excluded. Thus, mechanistically hydrolysis of 1 occurs in a similar fashion to the non-fluorinated phosphonium salts.

From these results and our previous report [5] we would expect only the halo-F-methylphosphonium salts to hydrolyze via a carbene intermediate, and that fluorinated phosphonium salts that do not contain the $-CF_2X$ group to hydrolyze via the normal carbanion intermediate.

EXPERIMENTAL

Br-82 (as bromide) was obtained in 1.0 M NH_4OH solution with an initial activity of 1.0 mCi/ml upon shipment from New England Nuclear. All experiments involving Br-82 were carried out behind 4 x 8 x 16 cm lead bricks. Measurement of Br-82 activity was accomplished by use of a Capintec Radioisotope Calibrator.

1 + H_2O + Br-82

All the Br-82 experiments were carried out in identical sets of apparatus. Trial 1 will be used as a representative example. An aliquot

(0.35 ml) of the Br-82 solution (0.49 mg Br/ml) was placed in a 30 ml brown serum vial equipped with a magnetic stir bar and sealed with a rubber septum. The aqueous solution was evaporated to dryness under a stream of argon. 1 (0.456 g, 0.856 mmole) was placed in the vial and dissolved with 10.0 ml of dry $CHCl_3$. After ten minutes, water (0.062 ml, 3.44 mmole) was syringed into the solution and the vial connected with plastic tubing to an identical vial cooled in dry ice/isopropanol. The mixture was stirred vigorously for one hour. At the end of this time, pyridine (0.078 g, 0.987 mmole) was added and the solution distilled directly into the cooled receiver until only about one milliliter was left in the vial. The serum vials were then removed and the Br-82 content determined in the radioisotope calibrator.

Control experiments in the absence of $^{82}Br^-$ showed (via ^{19}F NMR) that all 1 was consumed in the reaction; that all of 2 appeared in the volatile fraction and that no 2 could be detected in the non-volatile fraction. Examination of decayed samples after hydrolysis in the presence of $^{82}Br^-$ were in total agreement with the initial controls. Earlier work in this laboratory [7] had established (via NMR and mass spectrometry) that the hydrolysis product was 2 and that the hydrolysis was essentially quantitative.

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