Quaternary Ammonium Fluoride Catalysed Halogenation of Carbon Acids by Polyhaloalkanes†

Yoel Sasson‡ and Owen W. Webster

Du Pont Central Research and Development, Experimental Station, Wilmington, DE 19880-0328, USA

Monoprotic carbon acids, for example alkylmalonates or phenylacetylene, are halogenated by polyhaloalkanes under mild conditions when catalysed by tetrabutylammonium fluoride.

Common sources for halonium ions in organic synthesis are hypohalite salts or *N*-haloamides.[1] There are, however, some reports on the use of tetrahalomethanes and other polyhalides under strongly basic conditions for the same purpose. Tetrachloromethane was used to chlorinate acidic hydrocarbons in the presence of potassium hydroxide–*tert*-butyl alcohol[2] and under phase conditions, using sodium hydroxide–triethylbenzylammonium chloride.[3,4] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) promoted carbon acid chlorination by tetrachloromethane[5] and bromination by bromotrichloromethane.[6] Owing to the strongly basic conditions, these procedures suffer from competing side reactions, such as α-elimination with formation of dihalocarbenes and hydrolysis.[7] We have now observed that quaternary ammonium fluorides are very effective homogeneous catalysts for the halogenation of carbon acids by polyhaloalkanes under essentially neutral conditions and at ambient temperature. The reaction proceeds according to the general stoichiometry shown in eqn. (1) where RH is a carbon acid with one active hydrogen, X is

$$RH + ZCX_3 \rightarrow RX + ZCHX_2 \quad (1)$$

a halide (chloride, bromide or iodide) and Z is an electron withdrawing substituent; *e.g.* halide, carboxylic ester or perhalogenated alkyl. The reaction is catalysed by 1–2 mol% of tetrabutylammonium fluoride trihydrate at room temperature. Unlike those reactions carried out in the presence of a stoichiometric base,[2–6] our catalytic system is reversible in nature with the position of the equilibrium depending mainly on the relative acidity of the substrates.

In a typical example, 1.46 g (10 mmol) dimethyl methylmalonate, 1.69 g (11 mmol) tetrachloromethane and 63 mg (0.2 mmol) tetrabutylammonium fluoride trihydrate (TBAF) were stirred for 10 min at room temperature. An exothermic reaction developed instantly with the temperature rising from 24 to 33 °C. Gas chromatographic (coupled with high resolution mass spectrometry) analysis of the mixture showed the formation of chloroform and of dimethyl α-chloro-α-methylmalonate in 63% conversion and over 99% yield [eqn. (2)]. Assay of the reaction mixture after 30 and 60 min showed no further reaction.

$$CCl_4 + MeCH(CO_2Me)_2 \rightleftharpoons CHCl_3 + MeCCl(CO_2Me)_2 \quad (2)$$

Substituting bromotrichloromethane for the tetrachloromethane in the same procedure yielded dimethyl α-bromo-α-methylmalonate in 84% conversion with identical selectivity.§ Other diesters of monoalkylmalonates and monoalkylmalonitriles reacted similarly.

Ethyl trichloroacetate was also found to be an active chlorinating agent under the above conditions (some hydrolysis and decarboxylation of the donor took place), tetrabromomethane and dibromofluoromethane showed some activity in bromination, but hexachloroethane, 1,1,1-trichloroethane and benzotrichloride were inactive.

We confirmed that reaction (2) is reversible. Dimethyl α-chloro-α-methylmalonate reacted with chloroform in the presence of TBAF to yield some dimethyl methylmalonate and tetrachloromethane. Excess tetrachloromethane increased the final conversion in reaction (2) while adding chloroform to the initial mixture dramatically impaired the progress of the reaction. The lifetime of the catalyst is very short (1–2 min)—too short a time for equilibrium to be reached. Equilibrium can be obtained only by repeated additions of fresh portions of catalyst. It is surmised that three side reactions bring about the deactivation of the catalyst.

(*a*) Formation of ammonium bifluoride: small amounts of hydrochloric acid are formed in the system *via* elimination and/or hydrolysis of the products.[8,9] Each molecule of HCl released neutralizes two catalyst equivalents according to eqn. (3). Tetrabutylammonium bifluoride is catalytically inactive in

$$2\ Bu_4NF + HCl \rightarrow Bu_4NHF_2 + Bu_4NCl \quad (3)$$

reaction (2). The conversion of fluoride to bifluoride according to reaction (3) was monitored by ^{19}F NMR.[10]

(*b*) Halide exchange with polyhalomethane: both chloroform and tetrachloromethane exchange halides with TBAF. ^{19}F NMR showed that the exchange reactions shown in eqns. (4) and (5) are taking place within minutes at room temperature. Similar exchange of tetramethylammonium fluoride with chloroform was reported by Christie and Wilson.[11]

$$Bu_4NF + CCl_4 \rightarrow Bu_4NCl + CCl_3F + CCl_2F_2 + CClF_3 \quad (4)$$

$$Bu_4NF + CHCl_3 \rightarrow Bu_4NCl + CHCl_2F + CHClF_2 + CHF_3 \quad (5)$$

(*c*) Halide exchange with the chlorinated product: fluoride–chloride exchange also takes place with the chloromalonate [eqn. (6)]. The α-fluoromalonate was positively identified in the mixture by GC–MS.

$$Bu_4NF + MeCCl(CO_2Me) \rightarrow Bu_4NCl + MeCF(CO_2Me)_2 \quad (6)$$

Tetrabutylammonium chloride (as well as bromide, iodide and hydrogen sulfate) were all found to be inactive in reaction (2). Higher hydrates of TBAF were also inactive. Thus, ten equivalents of water added to the system (relative to the catalyst) stopped the process altogether.

No direct evidence could be found for Hofmann decomposition of the fluoride catalyst under the reaction conditions.

The first deactivation process, reaction (3), can be essentially eliminated by the introduction of a base to neutralize free hydrochloric acid. Thus, the above procedure was considerably improved by addition of 270 mg (2 mmol) of dry, solid potassium carbonate. In the presence of the added solid base, reaction (2) could be driven to completion with a single batch of catalyst, both with tetrachloromethane and with bromotrichloromethane. Another alternative along this line is the use of the commercially available TBAF supported on silica gel or on alumina. With these heterogeneous catalysts, reaction (2) advanced much slower but without apparent deactivation. It is reasonable to assume that the solid supports

† Contribution No. 6152.

‡ *Present address*: Casali Institute of Applied Chemistry, Hebrew University, Jerusalem, Israel.

§ A parallel disproportionation reaction of bromotrichloromethane took place in this experiment with formation of all five possible bromochloromethanes. In this process the chloroform formed in reaction (2) serves as a halonium acceptor which initiates a complete scrambling of the halogens.

adsorb traces of both water and HCl, thus avoiding poisoning of the catalyst.

Interestingly, in the presence of solid base; *e.g.* potassium or sodium carbonate as well as hydrogen carbonate, reaction (2) proceeded with other tetrabutylammonium catalysts including bromide, chloride and hydrogen sulfate. The observed rate is, however, more than an order of magnitude slower than the reaction under the fluoride catalysis.

Attempts to chlorinate substrates with two acidic hydrogens under similar conditions failed. Thus diethyl malonate, malononitrile, benzyl cyanide and fluorene did not react to a significant degree unless stoichiometric quantities of TBAF were used. We attribute this phenomenon to the large amounts of HCl released by these substrates *via* dimerization of the monochlorinated product as was reported for the base catalysed halogenations.[4–6] When an excess of TBAF was used; for example, with CCl_4–phenylbenzonitrile or CCl_4–diethyl malonate, mixtures of products from both dihalogenation and dimerization were identified.

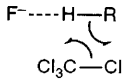
The acidity of the substrate in reaction (1) is no doubt a factor in the mechanism but there are probably other elements involved. We have failed in our attempts to halogenate methyl isobutyrate and even 2-nitropropane, but did succeed in halogenating the relatively weak acid, phenylacetylene (pK = 25).[6] Thus, when 1.1 g (10 mmol) of phenylacetylene, 315 mg (1 mmol) TBAF, 1.4 g (10 mmol) potassium carbonate and 6 ml of tetrachloromethane were stirred at 24 °C for 1 h, chloro(phenyl)ethyne was formed in >99% conversion and 99% yield [eqn. (7)]. A maximum conversion of 59% was

$$C_6H_5C{\equiv}CH + CCl_4 \rightarrow C_6H_5C{\equiv}CCl + CHCl_3 \qquad (7)$$

observed in the above procedure in the absence of potassium carbonate.

Bromo(phenyl)ethyne was obtained also in quantitative yield when bromotrichloromethane was applied as the donor under the same conditions. Even iodo(phenyl)ethyne was formed in 39% conversion (98% yield) when perfluorohexyl iodide was used as a halogen donor in an identical procedure. These reactions did not take place with ammonium catalysts other than the fluoride even on addition of potassium carbonate.

We were unable to trap dichlorocarbene intermediates when either styrene or cyclohexene were added during reaction (2). On the other hand we also did not detect the presence of carbanions by ^1H NMR of TBAF solutions in malonate esters or malononitrile as was recently demonstrated for the *anhydrous* (and obviously more active) tetramethylammonium fluoride.[11] Reaction (2) is apparently taking place *via* nucleophilic attack on the tetrahalomethane.



Scheme 1

We postulate that the attacking nucleophile is the hydrogen-bonded complex of TBAF with the acidic substrate as shown in Scheme 1. Similar hydrogen bond complexes were proposed in other fluoride-catalysed nucleophilic reactions; *e.g.* alkylations and Michael reactions.[9] The formation of hydrogen bond complexes between TBAF and acidic substrates can be conveniently monitored by ^{19}F NMR.[11] Another support for this mechanism can be found in the rapid TBAF-catalysed H–D exchange taking place between deuteriochloroform and carbon acids. In a typical example, 1 mmol of dimethyl methylmalonate and 0.1 mmol of TBAF were dissolved in 1 ml of $CDCl_3$. ^1H NMR of the solution showed complete exchange of the acidic proton. Other malonates and malononitriles reacted similarly. This exchange can be applied to substrates with two adjacent acidic hydrogens as well. Thus, benzyl cyanide, diethyl malonate, ethyl phenylacetate and fluorene exchanged their acidic hydrogens with $CDCl_3$ under the above conditions. The transition state for the H–D exchange reaction apparently resembles the one proposed for halogenation.

Received, 20th March 1992; Com. 2/01472F

References

1 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1969.
2 C. Y. Meyers and V. M. Kolb, *J. Org. Chem.*, 1978, **43**, 1985.
3 M. Maskoza, B. Serafin and I. Gajos, *Rocz. Chem.*, 1969, **43**, 671.
4 A. Jonczyk, A. Kwast and M. Makosza, *J. Org. Chem.*, 1979, **44**, 1192.
5 Y. Hori, Y. Saruno and Y. Nagano, *Rikogakubu Shuho* (*Saga Daigaku*), 1978, **6**, 19.
6 Y. Hori, Y. Nagano, H. Uchiyama, Y. Yamada and H. Taniguchi, *Chem. Lett.*, 1978, 73.
7 E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, Verlag Chemie, Weinheim, 2nd edn., 1983.
8 J. Hyami, N. Ono and A. Kaji, *Tetrahedron Lett.*, 1968, 1385.
9 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429.
10 K. O. Christie, W. W. Wilson, R. D. Wilson, R. Bau and J. Fang, *J. Am. Chem. Soc.*, 1990, **112**, 7619.
11 K. O. Christie and W. W. Wilson, *J. Fluorine Chem.*, 1990, **47**, 117.