Finkelstein Reaction with Aqueous Hydrogen Halides Efficiently Catalysed by Lipophilic Quarternary Onium Salts

Dario Landini,* Domenico Albanese, Sabrina Mottadelli and Michele Penso
Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy

The rate of halogen metathesis between halogenoalkanes RX **1–4** (X = F, Cl, Br, I) and aqueous concentrated hydrogen halides HY (Y = Cl, Br, I) is strongly accelerated under phase-transfer catalysis conditions, without solvent. The amount and nature of the nucleophilic species in the organic phase were determined.

The importance of simple and effective methods for the synthesis of alkyl bromides and iodides, reagents of choice for alkylations and for the preparation of various organometallic derivatives, was recently pointed out by Barrio and co-workers.[1] These authors described a new and interesting way of carrying out the classical Finkelstein halogen–halogen exchange by using concentrated aqueous hydrogen halides (HY, Y = Cl, Br, I), instead of the conventional alkali halides,[2,3] in a heterogeneous system without organic solvent.

Some years ago we found that reactions involving concentrated aqueous HY, *e.g.* hydrochlorination of alcohols,[4] cleavage of ethers[5] and esters[6] with hydrobromic acid, and addition of hydrohalogenic acids to alkenes,[7] are effectively catalysed by lipophilic quaternary onium salts under phase-transfer catalysis (PTC) conditions.

Here we report that halogen exchange reactions between halogenoalkanes and hydrohalogenic acids are also strongly accelerated by catalytic amounts of a phase-transfer (PT) agent.†

Results and Discussion

Typically halogenoalkanes **1–4** (1 mol) and concentrated hydrohalogenic acids, HY (Y = Cl, Br, I) (4 mol) were heated at 25–130 °C with stirring in the presence of the PT catalyst **5–7** (0.05 mol) until almost complete conversion of the starting material (GLC analysis) was reached (Scheme 1).

$$\underset{\textbf{1–4}}{RX} + HY_{aq} \xrightarrow{i} \underset{\textbf{2–4}}{RY} + HX_{aq}$$

1 X = F **3** X = Br
2 X = Cl **4** X = I

Scheme 1 *Conditions:* i, RX (1 mol), **5–7** (0.05 mol) (**5**, $C_{16}H_{33}P^+$-Bu_3Br^-; **6**, Aliquat. 336; **7**, $Bu_4N^+Br^-$), HY_{aq} (4 mol) (HY, 37% HCl, 47% HBr, 57% HI), 25–130 °C

A number of structurally different alkyl halides were examined in order to define the scope and limitations of the catalytic process. As shown in Table 1, 1-iodooctane **4a** was obtained in almost quantitative yields starting from the corresponding 1-fluoro-, 1-chloro- and 1-bromo-octane **1a**, **2a** and **3a** (entries 1, 4 and 6). The catalytic effect of the PT agent was particularly relevant in the case of the chloride **2a** (entries 4 and 5) and bromide **3a** (entries 6 and 7). Benzyl chloride **2c** and bromide **3c** were quantitatively converted into benzyl iodide **4c** in 5 min by working at 105 and 60 °C, respectively (entries 10 and 12). The reaction of 1-bromo-2,2-dimethylpropane **3b** with HI, at 105 °C in the presence of **5** reached a 92% conversion in 60 h, affording 2,2-dimethyl-1-iodopropane **4b** in 73% yield and minor amounts (14%) of the rearranged derivative 2-iodo-2-methylbutane **4g** (entry 9); without catalyst and after a similar reaction time, the conversion of **3b** was 19% only, giving 13% of **4b** together with 6% of **4g**. High catalytic effect was observed also in the case of 2-bromooctane **3d** (entry 13) and bromocyclooctane **3f** (entry 17), while it was less pronounced in the reactions of chloro- and bromo-cyclohexane **2e** and **3e** (entries 14, 15 and 16), 2-bromo-2-methylbutane **3g** (entry 18) and 1-bromoadamantane **3h** (entry 19). The catalytic process was very effective also in the reactions of hydrobromic acid with **1a** and **2a** (entries 2 and 5) as well as in the reaction of hydrochloric acid with **1a** (entry 3). Almost complete conversion of the starting octyl halide was obtained in the chloride–bromide transhalogen exchange by using a larger excess of the appropriate hydrohalogenic acid (8 mol instead of 4 mol/mol alkyl halide) (entries 5 and 7).‡

As expected for PT-catalysed processes,[8,10] the reaction rate increased by increasing the amount of the catalyst (Table 2, entries 1–4).§ The more lipophilic hexadecyltributylphosphonium bromide **5** and Aliquat 336 **6** were found to be the most efficient (Table 2, entries 5 and 6).

These results show that application of PTC to the acid-promoted halogen exchange represents a useful tool for the synthesis of alkyl iodides and bromides starting from the cheaper and readily available alkyl chlorides.

In order to better understand the role of the PT agent in the catalysed process, we studied the partition equilibria of hexadecyltributylphosphonium bromide **5** in the heterogeneous system under the reaction conditions (Scheme 2). When a

$$Q^+Br^-_{org} + 2\,HY_{aq} \rightleftharpoons z\,Q^+Y^-_{org} + (1-z)\,Q^+HY_2^-{}_{org} + z\,HY_{aq} + HBr_{aq}$$

$Q^+ = C_{16}H_{33}P^+$

Scheme 2

solution of **5** in 1-bromooctane **3a** (~0.2 mol dm^{-3}) was equilibrated with concentrated hydroiodic acid at 130 °C, the quaternary onium salt **5** was almost quantitatively partitioned in the organic phase. Acid–base and argentometric titrations of aliquots of the organic phase showed the presence of acidic

† Some years ago Starks *et al.* reported that quaternary onium salts catalyse chloride–bromide exchange between an alkyl halide and gaseous hydrogen chloride or bromide under anhydrous conditions.[8]

‡ The complete conversion of alkyl chlorides into bromides in a process catalysed by $FeBr_3$ under homogeneous conditions[9] required a similar excess of anhydrous hydrogen bromide.

§ In our hands, the reaction times of the uncatalysed runs were found to be longer than those reported by Barrio *et al.*[1]

Table 1 Products RY **2–4** of the Finkelstein reaction of alkyl halides RX **1–3** in the presence of hydrohalogenic acids HY[a] under PTC conditions[b]

Entry	Substrate RX	Product RY	R	T/°C	Yield (%)[c] Catalysed	Yield (%)[c] Uncatalysed
1	**1a** RF	**4a** RI	C_8H_{17}	130	98 (25 h) *97*	88 (25 h)
2	**1a** RF	**3a** RBr	C_8H_{17}	130	95 (8.5 h) *86*	26 (15 h)
3	**1a** RF	**2a** RCl	C_8H_{17}	130	90 (80 h) *81*	<1 (55 h)
4	**2a** RCl	**4a** RI	C_8H_{17}	130	98 (2 h) *95*	85 (37 h)
5	**2a** RCl	**3a** RBr	C_8H_{17}	130	98 (4 h)[d]	17 (26 h)
6	**3a** RBr	**4a** RI	C_8H_{17}	130	96 (45 min) *95*	95 (10 h)
7	**3a** RBr	**2a** RCl	C_8H_{17}	130	90 (3 h)[e]	26 (41 h)
8	**4a** RI	**2a** RCl	C_8H_{17}	130	38 (8 h)	17 (22 h)
9	**3b** RBr	**4b** RI	Me_3CCH_2	105	73 (60 h)[f,g]	15 (60 h)[f,h]
10	**2c** RCl	**4c** RI	$PhCH_2$	105	100 (5 min) *100*	100 (1 h)
11	**2c** RCl	**3c** RBr	$PhCH_2$	105	100 (40 min)	85 (40 min)
12	**3c** RBr	**4c** RI	$PhCH_2$	60	100 (5 min) *99*	100 (1 h)
13	**3d** RBr	**4d** RI	$C_6H_{13}CHCH_3$	130	100 (20 min) *97*	97 (19 h)
14	**2e** RCl	**4e** RI	c-C_6H_{11}	105	95 (7 h) *90*	96 (8 h)
15	**2e** RCl	**3e** RBr	c-C_6H_{11}	105	80 (7 h)	78 (8 h)
16	**3e** RBr	**4e** RI	c-C_6H_{11}	105	94 (1.75 h) *90*	92 (3 h)
17	**3f** RBr	**4f** RI	c-C_8H_{15}	70	96 (1.5 h) *88*	95 (6 h)
18	**3g** RBr	**4g** RI	$CH_3CH_2CMe_2$	25	92 (15 min)	92 (30 min)
19	**3h** RBr	**4h** RI	adamant-1-yl	105	100 (1.75 h) *98*	100 (1.5 h)

[a] HY = 57% HI; 48% HBr; 37% HCl. [b] RX (1 mol), HY (4 mol), **5** (0.05 mol). [c] GLC yields and, in italics, isolated yields; in parenthesis time of the highest conversion reached. [d] Using 8 mol of HBr, in the presence of 4 mol of HBr, after 4 h 70% of **2a** was detected from the equilibrium mixture. [e] Using 8 mol of HCl; in the presence of 4 mol of HCl, after 3 h 77% of **2a** was detected from the equilibrium mixture. [f] Determined by ^{1}H NMR. [g] 92% conversion; together with **4b**, $Me_2C(I)CH_2Me$ (14%) was detected. [h] 19% conversion; $Me_2C(I)CH_2Me$ (6%) was detected.

Table 2 Influence of concentration and nature of PT catalyst on the formation of alkyl iodides **4** from bromides **3** or chlorides **2**[a]

Entry	RX	PT Catalyst [eq. mol. (%)[b]]	T/°C	t/h, min	GLC Yield of **4a** (%)
1	**2a** $C_8H_{17}Cl$	**5** (10)	130	1 h	97
2	**2a** $C_8H_{17}Cl$	**5** (5)	130	2 h	98
3	**2a** $C_8H_{17}Cl$	**5** (2.5)	130	3 h	98
4	**2a** $C_8H_{17}Cl$	—	130	37 h	85
5	**3a** $C_8H_{17}Br$	**5** (5)	130	45 min	96
6	**3a** $C_8H_{17}Br$	**6** (5)	130	75 min	97
7	**3a** $C_8H_{17}Br$	**7** (5)	130	4 h	96
8	**3a** $C_8H_{17}Br$	—	130	10 h	95

[a] RX (1 mol), HI 57% (4 mol). [b] **5**, $C_{16}H_{33}P^+Bu_3Br^-$; **6**, Aliquat 336; **7**, $Bu_4N^+Br^-$.

species (0.36 mol per mol of **5**) and a corresponding increase of halide ion concentrations (Table 3, entry 1).

Both the acidic species as well as the halide ion concentration rose up to ~0.8 mol per mol of **5** when 1-bromo- **3a** or 1-chloro-octane **2a** solutions of **5** were equilibrated with concentrated hydrobromic acid (Table 3, entries 2 and 3).* Only traces of acid and of halide anions were detected in the absence of the PT catalyst. Moreover, as expected for extraction processes under liquid–liquid PTC conditions,[8,10] some molecules of water are partitioned in the organic phase (Table 3).

On the basis of these results the well known mechanism of liquid–liquid PTC[8,10] seems to be operating also in the transhalogen exchange promoted by hydrohalogenic acids in the presence of lipophilic onium salts: *i.e.*, the PT agent Q^+Br^-, **5**, by contact with concentrated aqueous HY, extracts into the organic phase the appropriate anionic reagent, Y^-, in part as Q^+Y^- and in part as hydrogen dihalides, $Q^+HY_2^-$;† both Q^+Y^- and $Q^+HY_2^-$ react with the substrate RX in the bulk of the organic phase. According to the relative affinities of halide anions for lipophilic quaternary cations in apolar media ($I^- \gg Br^- \geq Cl^- \gg F^-$),[8,10,13] the exchange of alkyl fluorides, chlorides or bromides with hydroiodic acid is complete under the above conditions, while a larger excess of hydrohalogenic acid is required to realize almost complete conversion of the alkyl chlorides into bromide, and *vice versa*.

The presence in the organic phase of some molecules of water, as well as acidic species, produces a highly polar microenvironment where tertiary and partially secondary substrates undergo halogen exchange *via* an S_N1 mechanism.[14] This behaviour accounts for the reactivity sequence found: tertiary > secondary > primary.[14]

Experimental

Starting halogenoalkanes **1a**, **2a**, **c**, **e**, **3a–c**, **e**, **g**, **h** and **4a** are commercially available and were distilled or recrystallized before use; 2-bromooctane **3d**[23] and bromocyclooctane **3f**[24] are known compounds and were prepared by literature procedures. Solvents, hydrohalogenic acids, and hexadecyltributylphosphonium bromide **5** were used as purchased. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AC 300 (at 300 MHz) or WP 80 (at 80 MHz) spectrometers, using tetramethylsilane as external standard; GLC analyses were obtained with Alltech RSL-150 (10 m × 0.35 mm, polymethylsiloxane, 0.25 μm thickness) and OV 101 (0.5 m, O. D. 1/8″, material SS, mesh 100/120, support Chrom-WHP) columns; argentometric and acid–base titrations were performed on a Metrohm 670 titroprocessor. Karl–Fischer analyses were obtained with a Metrohm 684 KF coulometer; refractive indexes were determined with an Atago 1T refractometer; melting points were determined with a Buchi 535 apparatus.

General Procedure for the Metathesis of Halogenoalkanes.—In a screw-capped vial, a mixture of halogenoalkane **1–4** (2

* The extraction of hydrogen halides by quaternary ammonium salts into dichloromethane under PTC conditions was reported some years ago by Dehmlow *et al.*[11]

† The synthesis and/or the existence of quaternary onium hydrogen dihalides, $Q^+HY_2^-$ (Y = I, Br, Cl) in non polar organic media have been well documented in literature.[12]

Table 3 Extraction of hydrogen halides into nonpolar organic media by $C_{16}H_{33}P^+Bu_3Br^-$ **5** in $C_8H_{17}X$/HY systems[a]

Entry	$C_8H_{17}X$/HY	t/min	In organic phase			
			$C_{16}H_{33}P^+Bu_3$/ mol dm^{-3}	H^+/ mol dm^{-3} [b]	Y^-/ mol dm^{-3} [c]	H_2O/ mol dm^{-3} [d]
1	$C_8H_{17}Br$/HI	5	0.22	0.08	0.30	0.28
2	$C_8H_{17}Cl$/HBr	5	0.26	0.19	0.45	0.88
3	$C_8H_{17}Br$/HBr	5	0.25	0.21	0.46	0.85

[a] **5** (0.05 mol), $C_8H_{17}X$ (1 mol), HY (4 mol), at 130 °C. [b] By acid–base titration. [c] By argentometric titration. [d] Karl–Fischer analysis.

Table 4 Physical data and selected proton chemical shifts of halides RY, **2–4**

RY	n_D^{20} [or m.p. T/°C[a]]	δ CHY (J/Hz)
2a	1.4309 (1.4306[15])	3.51 (t, J 6.7)
3a	1.4530 (1.4527[15])	3.38 (t, J 6.8)
4a	1.4886 (1.4889[16])	3.15 (t, J 6.4)
4b	1.4894 (1.4890[17])	*b*
3c	1.5751 (1.5742[18])	4.50 (s)
4c	1.6670 (1.6667[19])	4.47 (s)
4d	1.4899 (1.4896[20])	4.12 (m)
3e	1.4957 (1.4953[21])	4.17 (m)
4e	1.5479 (1.5477[21])	4.30 (m)
4f	oil	4.59 (m)[c]
4g	1.4985 (1.4981[20])	*d*
4h	[74.4–75.2 (74–76[22])]	*e*

[a] In parenthesis literature data. [b] δ_H 1.05 (9 H, s), 3.15 (2 H, s). [c] Other signals: δ_H 1.50 (10 H, m) and 2.16 (4 H, m). [d] δ_H 1.04 (3 H, t, J 6.6), 1.62 (2 H, m), 1.90 (6 H, s). [e] δ_H 1.80 (6 H, m), 1.91 (3 H, m), 2.62 (6 H, m).

mmol), HY (8 mmol; HY = 57% HI, 47% HBr, 37% HCl) and **5** (51 mg, 0.1 mmol) was stirred at the temperature indicated in Table 1 until the starting material was no longer detectable (GLC and/or TLC analysis). The crude reaction mixture was diluted with Et_2O (15 cm^3) and water (10 cm^3). The organic phase was washed three times with 5% $NaHCO_3$ and brine (4 cm^3), then dried ($MgSO_4$) and evaporated under reduced pressure. The products obtained were pure compounds (≥99% by GLC and ^{1}H NMR analyses) and their physical and spectroscopic characteristics matched those reported in literature. Reaction times, temperatures and yields are reported in Table 1. Physical and selected ^{1}H NMR spectroscopic data of reaction products are reported in Table 4.

Determination of Partition Equilibria.—A solution (A) of **5** (3.27 g, 6.5 mmol) in 1-bromooctane **3a** (25.00 g, 129.0 mmol) was stirred at 130 °C. A sample of solution (A) (1 cm^3) was withdrawn at 130 °C and diluted in a volumetric flask at 25 °C to 10 cm^3 with anhydrous PhCl. The molar concentration of **5** in **3a** was determined by argentometric titration of 2 cm^3 of this diluted solution, using 0.01 mol dm^{-3} $AgNO_3$.

A mixture of solution (A) (4 cm^3) and 57% HI (10.6 cm^3) had been stirred at 130 °C for 5 min. A sample of the organic phase (1 cm^3) was diluted as described above. The halide content of this solution was determined by argentometric titration as usual, while the amount of acidic species was determined by acid–base titration using 0.01 mol dm^{-3} NaOH, and water content by Karl–Fischer analysis (Table 3, entry 1). The same procedure was performed with **5** (3.55 g, 7.0 mmol), 1-chlorooctane (20.00 g, 135 mmol) and 47% HBr (Table 3, entry 2) or **5** (2.64 g, 5.2 mmol), 1-bromooctane (20.01 g, 104 mmol) and 47% HBr (Table 3, entry 3).

Acknowledgements

This work was supported in part by the MURST (Rome).

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Paper 2/02663E
Received 21*st May* 1992
Accepted 10*th June* 1992