Tetramethylammonium chloride as a selective and robust phase transfer catalyst in a solid–liquid halex reaction: the role of water

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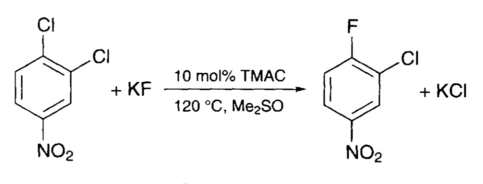
Tetramethylammonium chloride (TMAC) is an effective phase transfer catalyst for the selective chloride/fluoride exchange reaction of activated aryl chlorides with potassium fluoride provided that the amount of water in the system is limited and controlled.

Aromatic halide displacement by fluoride (Halex reaction) is an attractive alternative to other modes of aromatic fluorination such as the Balz–Schiemann reaction or related diazotization procedures.[1] Numerous activated aryl chlorides were exchanged with potassium fluoride (by far the preferred fluoride ion source) to yield the corresponding aryl fluorides. Since the nucleophilicity of the fluoride ion is sufficiently high only in non-hydrogen bonding donor solvents, where the solubility of potassium fluoride is relatively low, these systems are heterogeneous (solid–liquid) in nature. Major efforts have thus been devoted to the physical modification of the potassium fluoride reagent in order to increase its surface area and improve its accessibility (or rather the mass transfer rate) to the reaction zone. Typical procedures include freeze drying,[2] spray drying,[3] solid support such as calcium fluoride[4] and enhanced mixing methods such as ultrasound[5] and application of iron balls in the reaction vessel.[6] Since the solubility of potassium fluoride in polar aprotic solvents is low (0.6 mmol dm^{-3} in Me_2SO) the obvious approach to increase the reaction rate (besides temperature raise) has been the application of phase transfer catalysts. Crown ethers were introduced for that purpose by Liotta[7] and were followed by utilization of lipophilic quaternary ammonium salts[8] and temperature stable phosphonium salts (Ph_4PBr),[9] pyridinium salts[10] or polyethylene glycols (PEGs).[11] Mixtures of catalysts were also examined *e.g.* Ph_4PBr–18-crown-6[12] and Ph_4PBr–PEG[13] and, in solid–solid–liquid systems, polymer anchored pyridinium[14] and phosphonium[15] salts.

It was realised early on that traces of water are essential for effective transport of the reagent from the solid KF surface into the bulk of the organic phase either in the presence[16] or in the absence of a phase transfer catalyst.[17] A controlled amount of water was advocated for best results in many other solid–liquid systems,[18,19] but in the phase transfer catalysed Halex reactions the role of water is much more complicated due to the susceptibility of most ammonium salts to decomposition in the presence of fluoride counter-ions and the promotion of hydrolysis side reactions. Gallo and colleagues have thus observed the formation of phenols and ethers upon attempting the Halex reaction with hydrated ammonium fluoride salts. These authors concluded that anhydrous fluoride ammonium salts are a 'myth'.[20]



Scheme 1

We have examined the Halex reaction of 3,4-dichloronitrobenzene (DCNB) with potassium fluoride in the presence of tetramethylammonium chloride (TMAC) (Scheme 1)

A typical example was performed using a heterogeneous mixture of 6.0 g of DCNB (31.25 mmol), 3.63 g potassium fluoride (62.5 mmol, oven dried at 110 °C under vacuum for 10 h, containing 0.2% *w*/*w* water), 0.68 g of TMAC (6.25 mmol) and 20 cm^3 of Me_2SO at 120 °C. GC analysis of the organic phase, cross checked with titration of the solid phase, showed that the reaction reached 99.8% conversion after 3.5 h. A selectivity of 99% to 3-chloro-4-fluoronitrobenzene (FCNB) was calculated. In the absence of TMAC, conversion of 51% was measured after 8 h under otherwise identical conditions. The reaction followed first order kinetics in both cases with a rate constant 1.436 h^{-1} in the presence of the catalyst and 0.167 h^{-1} in its absence. These results clearly suggest that the concentration of the fluoride anion in the reaction environment is in steady state throughout the reaction both in the catalytic and in the non-catalytic systems. The rate constant of the catalytic reaction was found to be linear with the TMAC concentration. This is shown in Fig. 1, which leads to the overall rate equation at 120 °C shown in [eqn. (1)], where k_1 is

$$-d[\mathrm{DCNB}]/dt = k_1\,[\mathrm{DCNB}] + k_2\,[\mathrm{DCNB}][\mathrm{TMAC}] \quad (1)$$

the rate constant of the non-catalytic reaction and k_2 is the apparent second order rate constant, calculated to be 7.5 h^{-1} mol^{-1}. The figuring of the intrinsic rate constant requires the visualization of the fluoride concentration in the organic phase, which is the summation of the free fluoride and the ion paired fluoride produced by the anion exchange process, eqn. (2).

$$KF_{(\mathrm{solid})} + Me_4NCl_{(\mathrm{org})} \rightleftharpoons KCl_{(\mathrm{solid})} + Me_4NF_{(\mathrm{org})} \quad (2)$$

As could be expected, Me_4NBr gave lower catalytic activity (k = 0.6 h^{-1}) due to the inferior selectivity coefficient of the couple Br^-/F^- in comparison with Cl^-/F^-[21] resulting in a lower steady state concentration of fluoride in the reaction

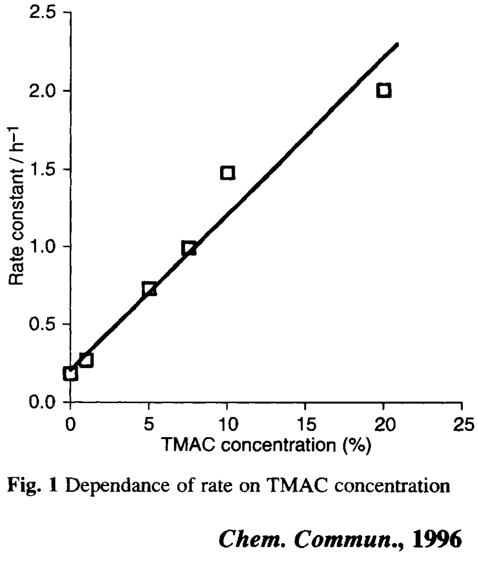


Fig. 1 Dependance of rate on TMAC concentration

phase. The reaction, in presence of TMAC, was found to be largely insensitive to the stirring rate above 250 rpm. Surprisingly, even in a static system, *without mixing at all*, a rate constant of 0.5 h^{-1} was resolved. The process is very sensitive to temperature change and the activation energy was calculated to be 27.0 kcal mol^{-1} (1 cal = 4.184 J). These last results clearly show that the solid–liquid mass transport does not contribute to the overall rate. Accordingly, miscellaneous surface alteration of potassium fluoride is apparently not critical for effective fluorination under these conditions.

Dimethylsulfoxide is, by far, the best solvent for both the catalytic and the non-catalytic[22] Halex reaction. The decreasing order of activity in the presence of TMAC is Me_2SO > *N,N*-dimethylformamide (DMF) > *N,N*-dimethylacetamide (DMA) > *N*-methylpyrrolidin-2-one (NMP) > sulfolane. The catalytic effect is, however, more conspicuous in the less effective solvents. The rate enhancement (catalytic : non-catalytic first order rate constants ratio) for different solvents is as follows: sulfolane (78.7), NMP (20.7), DMF (14.3), DMA (14) and Me_2SO (8.6). A similar order of solvents was analysed and elucidated by Clark.[22]

The choice of TMAC as a catalyst in this study is not fortuitous. This thermally stable and highly cost effective quaternary ammonium salt has been overlooked by most researchers in the field presumably due to its poor solubility in apolar solvents. TMAC, as well as its fluoride exchanged counterpart TMAF, has an inherent superiority over the widespread, more lipophilic quaternary ammonium phase transfer catalysts including the recently developed phosphonium or pyridinium salts. TMAC is characterized by high stability in a diversity of harsh conditions including strong aqueous bases as well as high temperatures.[23] This stability towards strong bases or nucleophiles was attributed to the absence of β-hydrogens.[24] TMAC catalysis in polar protic[25] and aprotic[26] solvents was revealed in several patents. TMAF was recently utilized by Clark as a stoichiometric reagent in a remarkably selective fluorodenitration of activated nitroarenes.[27] In our study of the reaction shown in Scheme 1, other ammonium salt catalysts exhibited inferior performance due to profound decomposition in the course of the reaction. Customary catalysts such as tetrabutylammonium chloride, bromide or hydrogen sulfate, triethylbenzylammonium chloride and Aliquat 336 gave lower initial rates relative to TMAC and were totally deactivated before the reaction was completed.

Water molecules are beneficial to the stability of ammonium salts by partially offsetting the nucleophilicity of the counter ion *via* hydration. Unfortunately, with fluoride counter anion, the water of hydration acquires nucleophilic properties of its own (*via* hydrogen bonding) and tends to participate in the reaction. We have now observed that when the reaction is conducted using vacuum dried potassium fluoride containing less than 0.2% *w/w* water under the conditions specified above, no hydrolysis products are observed. The intermediate TMAF is evidently formed as an anhydrous salt and consequently a selective fluorination reaction is perceived. Upon addition of small amount of water both the rate and the selectivity of the process are notably diminished. Thus with 5% water (relative to KF) less than 50% selectivity to FCNB is measured. The major product in this experiment was 2,2′-dichloro-4,4′-dinitrodiphenyl ether (51%) along with 2% of 2-chloro-4-nitrophenol. The product FCNB is particularly sensitive to the presence of water molecules combined with fluoride anion. Under the above reaction conditions FCNB reacts instantly and completely with hydrated TMAF to yield almost identical amounts of the above ether and phenol. In presence of excess of water (*e.g.* 20% solution of KF in water) no reaction was observed at all under the above conditions, evidently because the exchange step [eqn. (2)] is completely stagnant in presence of water solution. The convoluted role of water in the solid–liquid phase transfer catalysed halex reactions can be summarized as follows. Firstly, traces of water (0.2–0.3% *w/w*) are essential for effective transport of fluoride anion from the surface of the solid potassium salt into the bulk of the reaction phase. This is valid for both the catalysed and the non catalyzed reaction. Secondly, water of hydration is beneficial for the stabilization of the ammonium salt catalyst *via* partial neutralization of the reactive fluoride counter ion. Enhanced nucleophilicity of these water molecules, induced by hydrogen bonding to the naked fluoride, might result in unwanted hydrolysis reactions. The activated aryl fluorides are particularly liable for such hydrolysis. Thirdly, excess of water which forms partial dissolution of potassium fluoride results in inhibition of the initial exchange step and in total deactivation of the catalysis.

This procedure was extended to other substrates. Under identical conditions the following yields of fluorinated products were obtained from the corresponding aryl chlorides: 2,4-dinitrofluorobenzene (94%), 4-fluoro-2-nitrobenzonitrile (92%) 2,4-difluoronitrobenzene (70%, 25% monofluorinated products) and 4-fluoronitrobenzene (81%).

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