Reactions of Potassium Fluoride in Glacial Acetic Acid with Chlorocarboxylic Acids, Amides, and Chlorides. The Effect of Very Strong Hydrogen Bonding on the Nucleophilicity of the Fluoride Anion

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Although KF is very soluble in glacial acetic acid, the nucleophilicity of the fluoride ion therein is much reduced by the very strong hydrogen bonding which occurs between it and the solvent. The fluoride is in effect enhancing the nucleophilicity of the hydroxyl oxygen atom of the carboxylic acid group. Reaction of chlorocarboxylic acids and their derivatives with this reagent produces acetoxy- instead of the anticipated fluoro-derivatives. The acid chlorides $Cl(CH_2)_nCOCl$, acids $Cl(CH_2)_nCO_2H$, and some amides $Cl(CH_2)_nCONH_2$ (n = 1,2,3, *etc.*) have been investigated and their reactions with KF in acetic acid elucidated. In addition to substitution, lactonization and elimination reactions may also occur. Some new products have been isolated and characterized. Related reactions involving KF alone are reported; in some of these polymerization takes place.

POTASSIUM FLUORIDE has for many years been accepted as a useful reagent in synthesis. Although it is better known as a fluorinating agent, especially in halogen-exchange reactions,[1,2] it can also act as a base.[3] Maynard [4] in his studies with KF in high b.p. polar aprotic solvents, such as *NN*-dimethylformamide, tetrahydrothiophen 1,1-dioxide, and *N*-methylpyrrolidin-2-one, concluded that such systems were exceedingly powerful agents for the fluorination of highly chlorinated materials. However, in some cases complex reactions occurred in which very different products to those of the starting material were obtained. The solubility of KF in solvents of this class is low, *e.g.* in *N*-methylpyrrolidin-2-one, the solvent giving the best yields, the solubility is *ca.* 3% at the temperatures at which the reactions took place (190—200 °C).

On the other hand KF is extremely soluble in glacial acetic acid [5] and this opens the door to the possibility of carrying out homogeneous fluorinations of organic substances of the chlorinated aliphatic type. Unfortunately the price paid for the high solubility of KF in this solvent is very high; its nucleophilicity is greatly reduced and it appears capable of substituting only such activated C–Cl bonds as those of carboxylic acid chlorides. In addition to these it was hoped to test the fluorinating ability of KF towards C–Cl bonds which were one or more positions removed from the activating carbonyl group, and to this end studies were made with the series of ω-chlorocarboxylic acids, $Cl[CH_2]_nCO_2H$ (n = 1—4), and some of their derivatives such as the amides. The outcome of these reactions was far from that expected; lactone formation, elimination, and acetoxylation occurred, but not fluorination.

The reason for the reduced nucleophilicity of the fluoride ion under these conditions is the very strong hydrogen bond formed between it and the solvent, $F^- \cdots H{-}O_2CMe$.[6-8] Indeed, the results of some of the reactions reported in this paper are further indirect evidence of the strength of this remarkable H bond. The nucleophilicity of the fluoride is much reduced by this H-bond formation, while at the same time the nucleophilicity of the hydroxyl oxygen is greatly increased. The result is that these solutions behave as strong acetoxylating but only mild fluorinating agents.

EXPERIMENTAL

Instruments.—The n.m.r. spectra were recorded on Perkin-Elmer R12B (60 MHz) or Bruker HFX90 (90 MHz) spectrometers. I.r. spectra were recorded on a Perkin-Elmer 457 spectrometer using CsBr optics (liquids and mulls) or a NaCl gas cell.

Materials.—Fluorides and acetates were commercial samples dried at 100 °C *in vacuo* for several hours. AnalaR or AristaR grade glacial acetic acid was dried over molecular sieves. Other reagents were generally commercial samples used as obtained. Potassium trifluoroacetate, potassium 4-chlorobutyrate, and fluoroacetamide were prepared by standard methods or as described in the text.

Reactions.—Potassium fluoride has a solubility at 20 °C of greater than 4 mol kg^{-1}(4M) in $MeCO_2H$, but in most reactions 2M solutions were used on the scale of 11.6 g KF (0.2 mol) in 100 g $MeCO_2H$.† Reactions were carried out under anhydrous conditions with facilities for trapping volatile products (mostly MeCOF). Reactions were monitored by sampling and ^1H n.m.r. analysis and the extent of reaction measured by filtering off precipitated KCl and determining the chloride content *via* AgCl. The work-up of reaction mixtures was preceded by the addition of excess of diethyl ether to the filtered solution to effect removal of unchanged KF as the monosolvate, $KF{\cdot}MeCO_2H$, which precipitated almost quantitatively.

Acetyl chloride and KF *in* $MeCO_2H$. Acetyl chloride (7.85 g, 0.10 mol) on addition to a 2M solution of KF in $MeCO_2H$ (100 g) at room temperature gave an immediate and quantitative precipitate of KCl and MeCOF was evolved. Warming the solution and condensing the escaping gas gave acetyl fluoride (6.0 g, 0.97 mol, 97%) [confirmed by gas-i.r. spectroscopy; [9] the ^1H n.m.r. spectrum showed a doublet, ^3J(FCCH) 7.0 Hz, with second-order splitting at 60 but not at 90 MHz].

Chloroacetyl chloride and KF *in* $MeCO_2H$. Chloroacetyl

† 1M = 1 mol kg^{-1}.

[1] M. Hudlický, 'Chemistry of Organic Fluorine Compounds,' Macmillan, New York, 1962, p. 88.
[2] A. K. Barbour, L. F. Belf, and M. W. Buxton, *Adv. Fluorine Chem.*, 1963, **3**, 181.
[3] L. Rand, D. Haidukewych, and R. J. Dolinski, *J. Org. Chem.*, 1966, **31**, 1272.
[4] J. T. Maynard, *J. Org. Chem.*, 1963, **28**, 112.
[5] J. Emsley, *J. Chem. Soc.* (*A*), 1971, 2511.
[6] J. Emsley, *J. Chem. Soc.* (*A*), 1971, 2702.
[7] J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1973, 2154.
[8] J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1974, 1127.
[9] B. P. Susz and J. J. Winhrman, *Helv. Chim. Acta*, 1957, **40**, 722.

chloride (28.3 g, 0.25 mol) was added to a stirred 2M solution of KF in $MeCO_2H$ (500 g) at 0 °C. Within minutes KCl was precipitated and was filtered off (18.6 g, 0.25 mol). The ^1H n.m.r. spectrum of the solution showed that the original singlet due to $ClCH_2COCl$ at δ 4.50 p.p.m. had been replaced completely by the doublet due to $ClCH_2COF$ at δ 4.23 p.p.m. [^3J(FCCH) 4 Hz]. However, only small quantities of chloroacetyl fluoride, b.p. 77—79 °C, were obtained on distillation. Warming the reaction mixture to 30 °C gave a quantitative yield of chloroacetic acid (m.p. 60—62 °C, δ 4.08 p.p.m.) and acetyl fluoride was evolved (9.3 g, 0.15 mol, 60%) and trapped.

Chloroacetic acid and KF *in* $MeCO_2H$. Chloroacetic acid (4.73 g, 0.05 mol) was heated in a refluxing 2M solution of KF in $MeCO_2H$ (100 g) for 15 h. Precipitated KCl was filtered off, the solvent removed on a rotary evaporator, and the product dissolved in water and extracted into diethyl ether. Drying ($MgSO_4$), evaporation, and recrystallization from $CHCl_3$ gave acetoxyacetic acid, $MeCO_2CH_2CO_2H$ (3.5 g, 0.03 mol, 60%), m.p. 68 °C (lit.,[10,11] 67—68 °C); ^1H n.m.r. resonances at δ 4.58 (s, 2 H, CH_2), 2.10 (s, 3 H, CH_3), and *ca.* 10.6 p.p.m. (br, s, 1 H, OH). This last band was sensitive to concentration changes which is typical of the carboxylic proton; all the ^1H n.m.r. spectra were recorded in $CDCl_3$, and referenced to $SiMe_4$. The i.r. spectrum of acetoxyacetic acid showed two overlapping ν(CO) vibrations centred at 1 740 cm^{-1}.

Chloroacetic acid and KF. Potassium fluoride (58 g, 1.0 mol) and $ClCH_2CO_2H$ (47 g, 0.5 mol) reacted on heating at 150 °C and the reaction was monitored by ^1H n.m.r. spectroscopy. This showed the disappearance of $ClCH_2CO_2H$ and the emergence of (chloroacetoxy)acetic acid, $ClCH_2CO_2CH_2CO_2H$, and later the formation of higher polymers. These appeared before the complete disappearance of the starting material. At no time were there any resonances attributable to fluoroacetic acid present in the spectrum. At the end of 7 h the reaction mixture was cooled, extracted with diethyl ether, filtered, dried, and evaporated. The product was distilled and (chloroacetoxy)acetic acid obtained (10.2 g, 0.066 mol, 27%), b.p. 140 °C (1 mmHg)* (Found: C, 31.6; H, 3.25. $C_4H_5ClO_4$ requires C, 31.4; H, 3.25%); δ 4.22 (s, 2 H, $ClCH_2$), 4.78 (s, 2 H, OCH_2), and *ca.* 9.2 p.p.m. (br, s, 1 H, OH); ν(CO) at 1 735 cm^{-1}.

In reactions employing equimolar amounts of KF and $ClCH_2CO_2H$ the proportion of polymeric products was increased and *8-chloro-4,7-dioxy-3,6-dioxaoctanoic acid*, $ClCH_2CO_2CH_2CO_2CH_2CO_2H$, *11-chloro-4,7,10-trioxy-3,6,9-trioxaundecanoic* acid, $ClCH_2CO_2(CH_2CO_2)_2CH_2CO_2H$, and *14-chloro-4,7,10,13-tetraoxy-3,6,9,12-tetraoxatetradecanoic acid*, $ClCH_2CO_2(CH_2CO_2)_3CH_2CO_2H$ were separated by fractional distillation and characterized. $ClCH_2CO_2CH_2CO_2CH_2CO_2H$: b.p. 162—165 °C (1 mmHg); δ 4.19 (s, 2 H, $ClCH_2$), 4.77 (s, 2 H, OCH_2CO_2H), 4.85 (s, 2 H, CH_2), and *ca.* 7.80 p.p.m. (br, s, 1 H, OH); and ν(CO) at 1 745 cm^{-1}. $ClCH_2CO_2(CH_2CO_2)_2CH_2CO_2H$: b.p. 180—185 °C (1 mmHg) (Found: C, 35.5; H, 3.35. $C_8H_9ClO_8$ requires C, 35.7; H, 3.35%); δ 4.16 (s, 2 H, $ClCH_2$), 4.75 (s, 2 H, OCH_2CO_2H), 4.92 (s, 4 H, CH_2), and *ca.* 7.2 p.p.m. (br, s, 1 H, OH); and ν(CO) at 1 740 cm^{-1}. $ClCH_2CO_2(CH_2CO_2)_3CH_2CO_2H$: b.p. 200—205 °C (1 mmHg) (Found: C, 37.2; H, 3.40. $C_{10}H_{11}ClO_{10}$ requires C, 36.7; H, 3.35%); δ 4.19 (s, 2 H, $ClCH_2$), 4.78 (s, 2 H, OCH_2CO_2H), 4.96 (s, 6 H, CH_2), and *ca.* 7.05 p.p.m. (br, s, 1 H, OH); and ν(CO) at 1 748 cm^{-1}. All the ^1H n.m.r. spectra showed traces of an impurity with signals at δ 4.33 and 4.28 p.p.m.

Dichloroacetic acid and KF *in* $MeCO_2H$. Dichloroacetic acid (25.8 g, 0.02 mol) was added to a 3M solution of KF in $MeCO_2H$ (270 g) and the mixture heated under reflux for 15 h at the end of which time almost complete precipitation of KCl had occurred. After filtration the solution was diluted with water and extracted with diethyl ether. The ether layer was dried and evaporated, the product taken up in $CHCl_3$, decolourized, and the solvent removed to yield diacetoxyacetic acid, $(MeCO_2)_2CHCO_2H$ (Found: C, 40.7; H, 4.55. $C_6H_8O_6$ requires C, 40.9; H, 4.55%); δ 2.09 (s, 6 H, CH_3), 5.90 (s, 1 H, CH), and *ca.* 11.0 p.p.m. (br, s, 1 H, OH); ν(CO) at 1 750 cm^{-1}. The compound decomposed above 200 °C.

Dichloroacetic acid and KF. Dichloroacetic acid (25.8 g, 0.2 mol) and KF (5.81 g, 0.1 mol) were heated at 150 °C for 20 h, at the end of which time the products were dissolved in diethyl ether, the solution filtered to remove potassium salts (30% replacement of Cl determined), and the solvent evaporated. The product was purified by distillation and gave *bis(dichloroacetoxy)acetic acid*, $(Cl_2CHCO_2)_2CHCO_2H$, b.p. 140—142 °C (0.6 mmHg) (Found: C, 23.9; H, 1.30; Cl, 44.1. $C_6H_4Cl_4O_6$ requires C, 22.9; H, 1.25; Cl, 45.2%); δ 6.02 (s, ? H, CH) and *ca.* 10.9 p.p.m. (br, s, ? H, OH), *i.e.* only two peaks observed in the integral ratio 0.9 : 1 instead of the expected three in the ratio 2 : 1 : 1, suggesting that exchange among all the protons occurs and that the CH protons are acidic; ν(CO) at 1 740 cm^{-1}.

3-Chloropropionyl chloride and KF *in* $MeCO_2H$. 3-Chloropropionyl chloride (31.75 g, 0.25 mol) was added to a 2M solution of KF in $MeCO_2H$ (500 g) at 0 °C. Potassium chloride was quantitatively precipitated. The ^1H n.m.r. spectrum of the solution showed the characteristic triplet of the CH_2COF group at δ 2.96 p.p.m., and the solution of 3-chloropropionyl fluoride was stable in the solution of KF–$MeCO_2H$ at 0 °C. However, it was slowly converted at room temperature, and rapidly on warming, into 3-chloropropanoic acid (23.9 g, 0.22 mol, 88%), m.p. 63 °C, which was separated and identified, and acetyl fluoride which was evolved and trapped (9.5 g, 0.15 mol, 60%).

3-Chloropropanoic acid and KF *in* $MeCO_2H$. 3-Chloropropanoic acid (5.43 g, 0.05 mol) was added to a 2M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux for 4 h. The ^1H n.m.r. spectrum of the final mixture showed propenoic acid (60%), β-propiolactone (30%), and unchanged acid (10%). Separation of the mixture by filtration, addition of water, extraction into diethyl ether, drying, and distillation with added benzene to remove $MeCO_2H$ as an azeotrope produced propenoic acid (7.3 g 0.10 mol, 50%), b.p. 142 °C, and β-propiolactone (3.3 g, 0.045 mol, 23%), b.p. 160—165 °C, identified by their ^1H n.m.r. and i.r. spectra. ^1H N.m.r. spectroscopy showed the appearance in solution of propenoic acid before β-propiolactone.

β-Propiolactone and KF *in* $MeCO_2H$. β-Propiolactone (3.6 g, 0.5 mol) was added to a 2M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux for 1 h. At the end of this time the yield of propenoic acid was 20% (^1H n.m.r.), after 2 h it was 35%, and after 3 h it was 45%.

2-Chloropropanoic acid and KF *in* $MeCO_2H$. 2-Chloro-

* 1 mmHg ≈ 13·6 × 9·8 Pa.

[10] S. Olsen, E. Aalrust, A. Henkisen, and B. Alstad, *Annalen*, 1959, **627**, 96.

[11] J.-C. Micheau and A. Lattes, *Bull. Soc. Chim. France*, 1970, 4018.

propanoic acid (5.4 g, 0.05 mol) was added to a 4M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux and monitored by ^1H n.m.r. analysis. This showed 50% reaction after 1 h, 90% after 2 h, and almost complete reaction after 3 h. The solution was cooled, filtered (quantitative amount of KCl), and the filtrate diluted with water and extracted with diethyl ether, which after drying and evaporating yielded 2-acetoxypropanoic acid (DL) (5.8 g, 0.045 mol, 90%), m.p. 58—60 °C (lit.,[12] 57—60 °C) (Found: C, 43.5; H, 6.05. Calc. for $C_5H_8O_4$: C, 45.0; H, 6.05%); δ 1.53 (d, 3 H, CH_3CH), 2.12 (s, 3 H, CH_3CO_2), 5.12 (q, 1 H, CH), and *ca.* 10.2 p.p.m. (br, s, 1 H, OH); ν(CO) at 1 710 cm^{-1}.

2-*Chloropropanoic acid and* KF. 2-Chloropropanoic acid (43.2 g, 0.4 mol) and KF (11.6 g, 0.2 mol) were shaken together at room temperature; the mixture became warm as the KF dissolved. The solution was then heated at 120 °C for 3 h. After cooling, diethyl ether was added and the mixture filtered to remove KCl, *etc.* (analysis showed 70% reaction). The filtrate was dried, evaporated, and distilled to give unchanged 2-chloropropanoic acid, b.p. 95 °C (1.3 mmHg), and 2-(2-*chloropropionyloxy*)*propanoic acid*, $MeCH(O_2CCHClMe)CO_2H$, b.p. 155—160 °C (1.3 mmHg) (Found: C, 39.3; H, 5.05. $C_6H_9ClO_4$ requires C, 40.0; H, 5.00%); δ 1.66 (t or 2d, 6 H, CH_3), 4.48 (q, 1 H, CHCl), 5.20 (q, 1 H, CHO), and *ca.* 6.8 p.p.m. (br, s, 1 H, OH); ν(CO) at 1 740 cm^{-1}.

4-*Chlorobutyryl chloride and* KF *in* $MeCO_2H$. 4-Chlorobutyryl chloride (28.2 g, 0.20 mol) was added to a 2M solution of KF in $MeCO_2H$ (500 g) at 0 °C. Potassium chloride precipitated quantitatively. ^1H N.m.r. spectroscopy revealed that only $Cl(CH_2)_3COF$ was present in solution as shown by its triplet at δ 2.77 p.p.m. [^3J(HCCF) 6.6 Hz] due to CH_2COF. This triplet showed the reported fine splitting. Computer-simulation techniques on this and related compounds, however, showed this to be a purely second-order effect and not due to long-range coupling. A small sample of the solution was extracted with diethyl ether, and 4-chlorobutyryl fluoride (2.1 g) was obtained, purified by distillation, and characterized.

On warming the solution of $Cl(CH_2)_3COF$ in KF–$MeCO_2H$, conversion into 4-chlorobutanoic acid occurred, slowly at room temperature and rapidly at 50 °C. Acetyl fluoride was evolved, trapped, and identified. The yield of acid was 92%, b.p. 196 °C. In the absence of KF, 4-chlorobutyryl chloride in $MeCO_2H$ showed no reaction at room temperature. On heating under reflux, evolution of HCl occurred and ceased after *ca.* 2 h, when the product of the reaction was the mixed anhydride, $Cl(CH_2)_3CO{\cdot}O{\cdot}CO{\cdot}Me$.

4-*Chlorobutanoic acid and* KF *in* $MeCO_2H$. 4-Chlorobutanoic acid (30.6 g, 0.25 mol) was added to a 2M solution of KF in $MeCO_2H$ (500 g) and the solution heated under reflux. The reaction was monitored by ^1H n.m.r. spectroscopy and this revealed the presence of γ-butyrolactone after 5 min, and complete conversion into this after 1 h. The solution was filtered to remove KCl (100%), diluted with water, extracted with diethyl ether, and γ-butyrolactone finally obtained pure by distillation (20.0 g, 0.23 mol, 92%), b.p. 402 °C, identified by its ^1H n.m.r. and i.r. spectra.

Under the same conditions but in the absence of KF, a solution of 4-chlorobutanoic acid in $MeCO_2H$ gave 23% conversion into the lactone after 3 h, 36% after 4 h, with virtually no increase beyond this even after 7 h. The addition of KCl to the solution had no effect. Potassium acetate solution (2M) gave 80% lactone after 4 h together with acetic anhydride by-product. Potassium trifluoroacetate solution (2M) gave 95% lactone after 2 h. Heating $Cl(CH_2)_3CO_2K$ in refluxing $MeCO_2H$, in which it is surprisingly only slightly soluble, converted it into 50% lactone in 30 min and 100% lactone in 1 h.

4-*Chlorobutanoic acid and* CF_3CO_2K *in* CF_3CO_2H. 4-Chlorobutanoic acid (14.1 g, 0.1 mol) was added to a 2M solution of CF_3CO_2K in CF_3CO_2H (200 g). No immediate precipitation of KCl occurred but this came down on warming. The solution was heated under reflux for 12 h and a volatile component trapped; this was $(CF_3CO)_2O$ (15.5 g, 0.077 mol, 77%), b.p. 40 °C, identified by its i.r. spectrum. The reaction mixture was filtered, diluted with diethyl ether to precipitate other salts, filtered, evaporated, stripped of solvent, and distilled under reduced pressure to yield 4-(*trifluoroacetoxy*)*butanoic acid*, $CF_3CO_2CH_2CH_2CH_2CO_2H$ (14.0 g, 0.07 mol, 70%), b.p. 98—100 °C (1.0 mmHg) (Found: C, 36.2; H, 3.70. $C_6H_7F_3O_4$ requires C, 36.0; H, 3.50%), δ 2.46 (m, 4 H, CH_2), 4.39 (t, 2 H, OCH_2), and *ca.* 8.3 p.p.m. (br, s, 1 H, OH) and γ-butyrolactone (1.7 g, 0.02 mol, 20%), b.p. 206 °C, identified by its ^1H n.m.r. and i.r. spectra.

3-*Chlorobutanoic acid and* KF *in* $MeCO_2H$. 3-Chlorobutanoic acid (6.13 g, 0.05 mol) was added to a 2M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux for 30 min at the end of which time the precipitated KCl (0.05 mol) showed total-chloride replacement had taken place. After removal of unchanged KF and solvent the products were purified by distillation and gave *trans*-but-2-enoic acid (3.7 g, 0.043 mol, 86%), m.p. 70—72 °C, b.p. 35—40 °C (1.2 mmHg), identified by its ^1H n.m.r. and i.r. spectra, and 3-acetoxybutanoic acid (DL), $MeCH(O_2CMe)CH_2CO_2H$ (0.51 g, 0.0035 mol, 7%), b.p. 108—110 °C (1.0 mmHg) [lit.,[13] 93—94 °C (0.5 mmHg)] (Found: C, 48.9; H, 6.85. Calc. for $C_6H_{10}O_4$: C, 49.3; H, 6.85%); δ 1.29 (d, 3 H, CH_3CH), 1.99 (s, 3 H, CH_3CO_2), 2.50 (d, 2 H, CH_2), 5.27 (sxt, 1 H, CH), and *ca.* 13.2 p.p.m. (br, s, 1 H, OH). Heating 3-chlorobutanoic acid at 100 °C for 2 h produced no change. Refluxing the acid in $MeCO_2H$ for 5 h produced 22% *trans*-but-2-enoic acid.

5-*Chloropentanoic acid and* KF *in* $MeCO_2H$. 5-Chloropentanoic acid (6.83 g, 0.05 mol) was added to a 2M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux. Traces of precipitated KCl appeared within a few minutes. The reaction was monitored by ^1H n.m.r. spectroscopy which showed 25% conversion into δ-valerolactone after 20 min, 80% after 2 h, and 95% after 4.5 h. The final yield of KCl confirmed 95% chloride displacement. The solvent was removed on a rotary evaporator, diethyl ether was added, and the precipitated potassium salts were filtered off. The ether solution was dried, evaporated, and distilled to give δ-valerolactone (3.0 g, 0.03 mol, 60%), b.p. 215—220 °C, identified by its ^1H n.m.r. and i.r. spectra, and a trace of 5-hydroxypentanoic acid. With a greater ratio of acid : KF in the solution, *i.e.* 0.05 : 0.04, the yield of lactone was 100% after 1.5 h.

Chloroacetamide and KF *in* $MeCO_2H$. Chloroacetamide (93.5 g, 1.0 mol) was added to a 2M solution of KF in $MeCO_2H$ (500 g) and the solution heated under reflux for 8 h. Precipitated KCl (52.0 g, 0.7 mol) was filtered off and the solvent removed on a rotary evaporator. The solid products were extracted with $CHCl_3$, and the addition of hexane and diethyl ether to this solution precipitated acetoxyacetamide, $CH_3CO_2CH_2CONH_2$ (73.2 g, 0.55 mol, 55%), m.p. 92—94 °C

[12] P. Auger, *Compt. rend.*, 1905, **140**, 938.
[13] R. Anschutz and O. Motschmann, *Annalen*, 1912, **392**, 100.

(lit.,[14] 94 °C) (Found: C, 41.25; H, 6.00; N, 11.8. Calc. for $C_4H_7NO_3$: C, 41.0; H, 6.00; N, 12.0%); δ 2.15 (s, 3 H, CH_3), 4.58 (s, 2 H, CH_2), and *ca.* 6.35 p.p.m. (br, s, 2 H, NH_2); ν(CO) at 1 737 and 1 680 cm^{-1}. The yield of acetoxyacetamide could be increased to 85% by heating chloroacetamide with a two-fold excess of KF·$MeCO_2H$ for 10 min. The use of $CaCl_2$ solution in $MeCO_2H$ in place of KF gave no reaction.

Chloroacetamide and KF. Chloroacetamide (9.96 g, 0.106 mol) and KF (30.86 g, 0.530 mol) were intimately ground together and heated at 130 °C for 50 min. Almost from the start of the heating fine white needles sublimed on to the exposed sides of the vessel. These were pure fluoroacetamide, FCH_2CONH_2 (Found: C, 32.3; H, 5.2; N, 17.9. Calc. for C_2H_4FNO: C, 31.2; H, 5.2; N, 18.2%); δ 4.75 [d, 2 H, CH_2, ^2J(FCH) 47 Hz] and *ca.* 6.3 p.p.m. (br, s, 2 H, NH_2). Heating a mixture of chloroacetamide (9.35 g, 0.1 mol) and potassium acetate (49 g, 0.5 mol) for 1 h gave a better than 95% yield of acetoxyacetamide which was extracted with $CHCl_3$ and precipitated on addition of diethyl ether.

Fluoroacetamide and KF *in* $MeCO_2H$. Fluoroacetamide (7.7 g, 0.1 mol) was added to a 3M solution of KF in $MeCO_2H$ (165 g) and the solution heated under reflux for 5 h. ^1H N.m.r. analysis of the resulting solution showed 25% conversion into acetoxyacetamide. The reaction solution formed two layers with CCl_4 in which the latter was the more soluble and could thereby be separated. Recrystallization from $CHCl_3$–hexane gave pure acetoxyacetamide (1.2 g, 0.01 mol, 10%).

3-Chloropropionamide and KF *in* $MeCO_2H$. 3-Chloropropionamide (21.5 g, 0.2 mol) was added to a 2M solution of KF in $MeCO_2H$ (100 g) and the solution heated under reflux and monitored by ^1H n.m.r. analysis. This showed that after 5 min the mol ratio of 3-chloropropionamide : acrylamide (CH_2:CH·$CONH_2$) : 3-acetoxypropionamide was 85 : 15 : 0, after 15 min 55 : 40 : 5, after 45 min 35 : 40 : 25, after 1 h 33 : 40 : 27, after 1.5 h 30 : 40 : 30, after 2 h 26 : 40 : 34, after 3 h 12 : 40 : 48, and after 4 h 6 : 40 : 54. The mixture was separated by filtration and removal of the solvent, followed by extraction of the products into $CHCl_3$. The addition of dry diethyl ether to this solution gave fine white needles of *3-acetoxypropionamide*, $MeCO_2CH_2CH_2CONH_2$, m.p. 95 °C (Found: C, 44.7; N, 10.6. $C_5H_9NO_3$ requires C, 45.0; N, 10.5%); δ 2.05 (s, 3 H, CH_3), 2.55 (t, 2 H, CH_2), 4.37 (t, 2 H, CH_2), and *ca.* 6.1 p.p.m. (br, s, 2 H, NH_2); ν(CO) at 1 730 and 1 656 cm^{-1}; ν(NH_2) at 3 360 and 3 180 cm^{-1}.

DISCUSSION

Reactions involving KF *alone.*—Potassium fluoride by itself is capable of exchanging C–Cl bonds for C–F as, for instance, in the case of chloroacetamide. On the other hand when chlorocarboxylic acids are treated with KF the products are entirely different. The interaction between RCO_2H and the fluoride ion is that of a very strong H bond, which has the effect of reducing the nucleophilicity of F^- and at the same time increasing that of the hydroxyl oxygen atom. In these reactions the behaviour of the fluoride ion is more akin to that of a base, although perhaps it is more realistic to differentiate this situation from the role of purely a proton acceptor.

There are almost no examples reported of fluorination of chlorocarboxylic acids. The one reaction of this type, that of Cl_3CCO_2H and KF, was the first time that the base behaviour of KF was recognized.[15] The products of this reaction were $CHCl_3$ and CO_2. We have studied the reaction of KF and chlorocarboxylic acids; mono- and di-chloroacetic acid and 2-chloropropanoic acid give *ca.* 30% yields of carboxylated products [equations (1), (2), and (3)], those from reactions (2) and (3) being

$$ClCH_2CO_2H \xrightarrow{KF} ClCH_2CO_2CH_2CO_2H\ (27\%) \quad (1)$$

$$Cl_2CHCO_2H \xrightarrow{KF} (Cl_2CHCO_2)_2CHCO_2H\ (30\%) \quad (2)$$

$$MeCHClCO_2H \xrightarrow{KF} MeCH(O_2CCHClMe)CO_2H\ (35\%) \quad (3)$$

new compounds. Reaction (1) can also be made to yield higher polymers since (chloroacetoxy)acetic acid is capable of behaving in the same fashion. Prolonged heating of chloroacetic acid with KF led to lower polymers [equation (4)] which were separated by fractional distillation and characterized. Under similar conditions,

$$ClCH_2CO_2H \xrightarrow{KF} Cl(CH_2CO_2)_nCH_2CO_2H\ (n = 2—4) \quad (4)$$

but using KCl or KBr as catalysts and at higher temperatures (180—200 °C), Asaraha *et al.*[16] produced a polymeric mixture with n = 8—17, although no individual members of the series were separated.

Reactions involving KF–$MeCO_2H$.—The primary purpose of our work was to study reactions of KF in glacial acetic acid solutions. In view of what has just been said, fluorination in this medium is expected to be poor. However, carboxylic acid chlorides are rapidly and quantitatively converted into the corresponding fluorides, but these are not stable in $MeCO_2H$ and are transformed to the acid and acetyl fluoride [equation (5)]. Thus as a

$$RCOF + MeCO_2H \longrightarrow RCO_2H + MeCOF\uparrow \quad (5)$$

method for preparing acetyl fluoride from the chloride this compares quite well with other methods [17-19] although it is unsuitable for other acid fluorides. Moreover, if the acid produced by step (5) is a chlorocarboxylic acid, further reaction takes place.

Chloroacetic acid formed from chloroacetyl chloride *via* reaction (5) is subsequently acetoxylated when the solution is heated under reflux [equation (6)]. Acetoxy-

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acetic acid, originally prepared from acetyl chloride and hydroxyacetic acid,[20] has recently been prepared by

$$ClCH_2CO_2H + KF\text{–}MeCO_2H \longrightarrow MeCO_2CH_2CO_2H\ (60\%) + KCl\downarrow \quad (6)$$

hydrogenation of its benzyl ester, obtained from acetic acid and benzyl chloroacetate [11] [equation (7)]. This

$$MeCO_2H + ClCH_2CO_2CH_2Ph \longrightarrow MeCO_2CH_2CO_2CH_2Ph \xrightarrow{H_2\text{–}PdC} MeCO_2CH_2CO_2H \quad (7)$$

method was extended to preparing $ClCH_2CO_2CH_2CO_2H$ and the higher polymers, $Cl(CH_2CO_2)_nCH_2CO_2H$, mentioned above, although these were not separated and characterized.[21] Dichloroacetic acid produced diacetoxyacetic acid [22] on heating under reflux in KF–$MeCO_2H$ [equation (8)]. In both reactions (6) and (8) there was

$$Cl_2CHCO_2H + KF\text{–}MeCO_2H \longrightarrow (MeCO_2)_2CHCO_2H + KCl\downarrow \quad (8)$$

no evidence of the chloroacetoxy-derivatives produced in reactions (1) and (2).

2-Chloropropanoic acid behaved similarly in KF–$MeCO_2H$, producing 2-acetoxypropanoic acid [equation (9)]. On the other hand, 3-chloropropanoic gives a

$$MeCHClCO_2H + KF\text{–}MeCO_2H \longrightarrow MeCH(O_2CMe)CO_2H + KCl\downarrow \quad (9)$$

mixture of the β-lactone and propenoic acid [equation (10)]. The latter is in the greater proportion presumably

$$ClCH_2CH_2CO_2H + KF\text{–}MeCO_2H \longrightarrow \underset{(30\%)}{\overline{OCH_2CH_2CO}} + \underset{(70\%)}{CH_2{:}CHCO_2H} \quad (10)$$

because α–β unsaturated conjugated carbonyl-double-bond systems are formed easily and are usually fairly stable, whereas four-membered rings like the β-lactone form slowly and under these reaction conditions are converted into propenoic acid anyway. The formation of the lactone can be seen as self carboxylation, but whether this is facilitated by H bonding between the hydroxyl proton of the acid and F^- is not certain. However, there was no indication of 3-acetoxypropanoic acid being produced.

The reaction of 3-chlorobutanoic acid in KF–$MeCO_2H$ might have been expected to give also a mixture of β-lactone and unsaturated acid. In fact no lactone is formed and the products are *trans*-but-2-enoic acid and a little 3-acetoxybutanoic acid [equation (11)], the latter

$$MeCHClCH_2CO_2H + KF\text{–}MeCO_2H \longrightarrow \underset{(90\%)}{MeCH{:}CHCO_2H} + \underset{(10\%)}{MeCH(O_2CMe)CH_2CO_2H} \quad (11)$$

having previously been reported from the reaction of 3-hydroxybutanoic acid and acetyl chloride.[13]

When 4-chlorobutyryl chloride was heated with KF at 130 °C in polar aprotic solvents such as tetrahydrothiophen 1,1-dioxide a 50% yield of $Cl(CH_2)_3COF$ was obtained.[23] At 190 °C the product was cyclopropanecarbonyl fluoride, $\overline{CH_2CH_2CH}COF$, and it was surmised that this was produced by F^- abstracting a β-hydrogen atom from $Cl(CH_2)_3COF$ to form the carbanion $ClCH_2\text{-}CH_2\bar{C}HCOF$ which cyclized to give the product. In $MeCO_2H$, 4-chlorobutyryl chloride gave an immediate and quantitative yield of the fluoride and KCl but the second reaction, (5), then occurred to produce 4-chlorobutanoic acid. On refluxing this in KF–$MeCO_2H$ there was total conversion into γ-butyrolactone [equation (12)].

$$Cl(CH_2)_3CO_2H + KF\text{–}MeCO_2H \longrightarrow \overline{OCH_2CH_2CH_2CO}\ (100\%) + KCl\downarrow \quad (12)$$

The KF is essential to the speedy and complete cyclization to the lactone; in its absence there is only 36% conversion after 4 h. Whether this reaction is as fast as cyclization of the 4-chlorobutyrate anion itself could not be adequately tested because of the low solubility of potassium 4-chlorobutyrate in $MeCO_2H$. Both reactions appear to progress at about the same rate. The use of other strong H-bonding anions such as acetate and trifluoroacetate also promotes the cyclization, although use of the latter in trifluoroacetic acid as solvent resulted in mainly 4-(trifluoroacetoxy)butanoic acid, $CF_3CO_2\text{-}(CH_2)_3CO_2H$, a new compound, rather than the lactone.

Lactone formation occurred solely with 5-chloropentanoic acid [equation (13)] and as a general reagent

$$Cl(CH_2)_3CO_2H + KF\text{–}MeCO_2H \longrightarrow \overline{OCH_2CH_2CH_2CH_2CO}\ (95\%) + KCl\downarrow \quad (13)$$

for lactone formation the combination KF–$MeCO_2H$ has been used to form the seven-membered ring 1,4-oxathiepan-2-one, cyclized from 6-chloro-3-thiahexanoic acid [equation (14)].[24]

$$Cl(CH_2)_3SCH_2CO_2H + KF\text{–}MeCO_2H \longrightarrow \overline{SCH_2CH_2CH_2OC(:O)CH_2} + KCl \quad (14)$$

The products of reaction of the acids $Cl(CH_2)_nCO_2H$ and KF–$MeCO_2H$ depends chiefly on n. For a given n, however, the results indicate that the course of the reaction will be lactonization preferred to elimination which in turn is preferred to acetoxylation. Both lactonization and acetoxylation are assisted by formation of a very strong H bond and both are essentially nucleophilic attack of the hydroxyl oxygen on the chlorine-carrying carbon atom. It would seem that either $RCO_2H \cdots F^-$ or $MeCO_2H \cdots F^-$, but not both forms together, is effective in that the former is much

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more reactive than the latter when cyclization is possible, otherwise the latter is more reactive. However, in the case of CF_3CO_2K in CF_3CO_2H both lactone and the trifluoroacetoxylated product are formed.

Going from carboxylic acids to amides removes the possibility of lactone formation. Chloroacetamide when treated with KF–$MeCO_2H$ produced acetoxyacetamide [equation (15)], a compound previously reported from the reaction of $MeCO_2CH_2CN$ and methanol.[14] Fluoroacetamide undergoes the same reaction. Heating

$$ClCH_2CONH_2 + KF\text{–}MeCO_2H \longrightarrow MeCO_2CH_2CONH_2\ (55\%) + KCl\downarrow \quad (15)$$

chloroacetamide with KF by itself produces fluoroacetamide in excellent yield [equation (16)]. Originally

$$ClCH_2CONH_2 + KF \longrightarrow FCH_2CONH_2\ (95\%) + KCl \quad (16)$$

xylene was used as the solvent for this reaction [25] but improved yields were obtained with polar solvents such as polyethylene glycol [26] and ethylene glycol.[27] Clearly $MeCO_2H$ is an unsuitable medium. The best method is to use no solvent at all, although this was previously dismissed as impracticable because of difficulties in separating the product from the starting material.[28] Sublimation surmounts this obstacle and the ' dry-state ' reaction has a great deal to recommend it.

3-Chloropropionamide and KF–$MeCO_2H$ gave acrylamide and the new compound 3-acetoxypropionamide [equation (17)]. The yield of the former rapidly levels

$$ClCH_2CH_2CONH_2 + KF\text{–}MeCO_2H \longrightarrow CH_2{:}CH{\cdot}CONH_2\ (40\%) + MeCO_2CH_2CH_2CONH_2\ (54\%) \quad (17)$$

off at 40% while that of the latter increases slowly. In the absence of KF, 3-chloropropionamide gives only acrylamide when heated under reflux in $MeCO_2H$. Cyclization does not occur.

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