Reactions of Carboxylic Acids with Dichloro- and Dibromo-alkanes in the Presence of Fluoride Ions: Effects of Very Strong Hydrogen Bonding

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Although carboxylic acids do not react with simple dihalogenated alkanes under reflux conditions, in the presence of potassium fluoride they form diesters. The role of the fluoride is to activate the nucleophilicity of the carboxylic acid by the formation of a very strong hydrogen bond with the hydroxy-group. A number of combinations of halide and acid have been studied and the important factors influencing the extent of reaction have been deduced.

IN a previous paper [1] we reported on the unusual reactions which occurred when potassium fluoride was heated with ω-chlorinated carboxylic acids, $Cl[CH_2]_n \cdot CO_2H$ ($n = 1$—4), in glacial acetic acid. Potassium fluoride is very soluble in this medium,[2] owing to the formation of very strong hydrogen bonds of the type $MeC(O)O-H \cdots F^-$, and it was hoped that homogeneous fluorination reactions might occur. As it turned out, the nucleophilicity of the fluoride ion is much reduced in this solvent, but on the other hand the formation of this hydrogen bond enhances the nucleophilicity of the hydroxylic oxygen of the acetic acid. The products were the acetates $MeCO_2 \cdot [CH_2]_n \cdot CO_2H$.

The reactions of the ω-chlorinated carboxylic acids by themselves with potassium fluoride are also capable of giving complex ester products, again explicable by the intermediate formation of a hydrogen bonded complex between the carboxy-group and the fluoride ion. Polymeric esters of the type $Cl[CH_2]_n\{CO_2[CH_2]_n\}_x \cdot CO_2H$ were produced.

We have lately turned our attention to the reaction of dihalogenated alkanes with carboxylic acids in the presence of potassium fluoride.

EXPERIMENTAL

N.m.r. spectra were taken for samples in $CDCl_3$ with a Perkin-Elmer R12B (60 MHz) spectrometer ($SiMe_4$ stan-

dard). I.r. spectra were measured with a Perkin-Elmer 457 spectrometer (CsBr optics) for liquid films.

Potassium fluoride was commercial grade, dried at 100 °C *in vacuo*. AnalaR carboxylic acids were dried over molecular sieves. Other reagents were generally commercial grade samples used without further purification.

Reactions.—The technique used in each case was virtually the same, with only minor modifications. The halogenated hydrocarbon was added to a *ca.* 1 : 2 molar mixture of potassium fluoride and carboxylic acid. This is in effect the disolvate, $KF,2RCO_2H$, which forms a solution on heating. The mixture was kept under reflux conditions for up to 40 h, depending upon the halide. After cooling, diethyl ether was added and the solution filtered to remove potassium chloride and any unchanged potassium fluoride. Distilled water was then added to the filtrate, which was neutralized ($NaHCO_3$), and the organic layer was separated. The aqueous layer was extracted with ether several times. The ethereal solution was dried ($MgSO_4$) and evaporated. The products were distilled under reduced pressure.

The progress of some reactions was monitored by [1]H n.m.r. spectroscopy.

1,2-Dichloroethane and acetic acid. 1,2-Dichloroethane (19.8 g, 0.2 mol), acetic acid (120 g, 2.0 mol), and potassium fluoride (58.1 g, 1.0 mol) were heated under reflux. [1]H N.m.r. spectroscopy showed 10% replacement of Cl by $MeCO_2$ after 2 h, 25% after 5 h, 30% after 9 h, and 35% after 10 h. Analysis for KCl also showed 35% reaction. The

[1] J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1975, 2129.
[2] J. Emsley, *J. Chem. Soc., (A)* 1971, 2511.

mixture was separated and gave ethylene diacetate, (10.0 g, 0.068 mol, 34%), b.p. 165 °C, δ 2.08 (6 H, s, CH₃), and 4.27 (4 H, t, CH₂O); ν_{CO} 1 737 cm⁻¹.

1,2-Dichloroethane and propionic acid. 1,2-Dichloroethane (15.5 g, 0.157 mol), propionic acid (84.6 g, 1.14 mol), and potassium fluoride (33.5 g, 0.58 mol) were heated under reflux. The reaction was monitored by ¹H n.m.r. spectroscopy which showed 12% replacement of Cl by EtCO₂ after 20 h, 20% after 23 h, and 41% after 33 h. The mixture was separated and gave *ethylene dipropionate* (2.20 g, 0.013 mol, 8%), b.p. 213—214 °C (Found: C, 54.8; H, 8.15. C₈H₁₄O₄ requires C, 55.1; H, 8.1%), δ 1.14 (6 H, t, CH₃), 2.35 (4 H, q, CH₂CO₂), and 4.25 (4 H, s, CH₂O).

1,2-Dibromoethane and propionic acid. 1,2-Dibromoethane (27.1 g, 0.14 mol), propionic acid (28.2 g, 0.38 mol), and potassium fluoride (21.0 g, 0.36 mol) were heated under reflux for 32 h. The mixture was separated and gave ethylene dipropionate (5.05 g, 0.029 mol, 21%). The ¹H n.m.r. spectrum showed a yield of less than 5% after 5 h. This reaction was repeated in the absence of fluoride; after refluxing 1,2-dibromoethane (18.3 g, 0.1 mol) and the acid (18.3 g, 0.25 mol) for 30 h there was no evidence of ester formation.

1,3-Dichloropropane and acetic acid. 1,3-Dichloropropane (22.6 g, 0.2 mol), acetic acid (120.0 g, 2.0 mol), and potassium fluoride (58.1 g, 1.0 mol) were heated under reflux for 24 h. ¹H N.m.r. spectroscopy showed 34% replacement of Cl by MeCO₂ after 3 h, 70% after 6 h, 75% after 8 h, 80% after 12 h, and 100% after 24 h. Analysis for KCl confirmed 100% conversion into diacetate. The mixture was separated and gave *trimethylene diacetate* (29.5 g, 0.185 mol, 93%), b.p. 196 °C (Found: C, 52.8; H, 7.4. C₇H₁₂O₄ requires C, 52.5; H, 7.5%), δ 2.05 (2 H, quint, CH₂·C*H*₂·CH₂), 2.07 (6 H, s, CH₃), and 4.20 (4 H, t, CH₂O), ν_{CO} 1 739 cm⁻¹.

1,3-Dibromopropane and propionic acid. 1,3-Dibromopropane (31.4 g, 0.16 mol), propionic acid (54.2 g, 0.73 mol), and potassium fluoride (20.0 g, 0.34 mol) were heated under reflux; ¹H n.m.r. spectroscopy showed 65% replacement of Br by EtCO₂ after 5 h, 70% after 13 h, 72% after 22 h, and 74% after 30 h. The mixture was separated and gave *trimethylene dipropionate*, (13.3 g, 0.071 mol, 41%), b.p. 125—126 °C at 21 mmHg (Found: C, 57.05; H, 8.5. C₉H₁₆O₄ requires C, 57.5; H, 8.55%), δ 1.10 (6 H, t, CH₃), 1.98 (2 H, quint, CH₂·C*H*₂·CH₂), 2.30 (4 H, q, CH₂CO₂), and 4.11 (4 H, t, CH₂O); ν_{CO} 1 740 cm⁻¹.

1,2-Dichloropropane and acetic acid. 1,2-Dichloropropane (11.3 g, 0.1 mol), acetic acid (60.0 g, 1.0 mol), and potassium fluoride (25.05 g, 0.5 mol) were heated under reflux for 20 h. The mixture was separated and gave propylene diacetate, (0.35 g, 0.002 mol, 2%), b p. 190—192 °C, ν_{CO} 1 727 cm⁻¹, δ 1.22 (3 H, d, *J* 6.5 Hz, C*H*₃·CH), 2.05 (3 H, s, C*H*₃·CO₂·CH), 2.08 (3 H, s, C*H*₃·CO₂·CH₂), *ca.* 4.04 (2 H, m, CH₂), and *ca.* 5.10 (1 H, m, CH). The ¹H n.m.r. spectrum of 1,2-dichloropropane showed the same complexity of the CH₂ (at δ *ca.* 3.7) and CH (δ *ca.* 4.1) signals.

1,2-Dibromopropane and propionic acid. 1,2-Dibromopropane (12.84 g, 0.064 mol), propionic acid (11.32 g, 0.15 mol), and potassium fluoride (8.00 g, 0.14 mol) were heated under reflux for 41 h. The mixture was separated and gave *propylene dipropionate* (1.76 g, 0.009 mol, 14%), b.p. 135 °C at 45 mmHg (Found: C, 57.95; H, 8.75. C₉H₁₆O₄ requires C, 57.45; H, 8.55%), δ 1.12 (6 H, t, C*H*₃·CH₂), 1.26 (3 H, d, C*H*₃·CH), 2.32 (4 H, q, CH₂CO), 4.06 (2 H, m, CH₂O), and 5.05 (1 H, m, CH).

1,4-Dichlorobutane and acetic acid. 1,4-Dichlorobutane

(25.4 g, 0.2 mol), acetic acid (120 g, 2.0 mol), and potassium fluoride (58.1 g, 1.0 mol) were heated under reflux for 8 h, after which the ¹H n.m.r. spectrum of the products showed very little Cl[CH₂]₄Cl. Analysis for KCl showed 95% replacement of Cl. The mixture was separated and gave *tetramethylene diacetate* (30 g, 0.17 mol, 87%), b.p. 216—219 °C (Found: C, 54.3; H, 8.05. C₈H₁₄O₄ requires C, 55.15; H, 8.1%), δ 1.67 (4 H, m, CH₂), 1.98 (6 H, s, CH₃), and 4.04 (4 H, t, CH₂O), ν_{CO} 1 743 cm⁻¹.

1,4-Dichlorobutane and propionic acid. 1,4-Dichlorobutane (40.85 g, 0.32 mol), propionic acid (84.5 g, 1.14 mol), and potassium fluoride (36.8 g, 0.63 mol) were heated under reflux. ¹H N.m.r. spectroscopy showed 6% replacement of Cl by EtCO₂ after 1 h, 22% after 2 h, 35% after 5 h, 42% after 11 h, 50% after 17 h, 57% after 25 h, and 59% after 35 h. The mixture was separated and gave *tetramethylene dipropionate* (21.02 g, 0.104 mol, 33%), b.p. 146—147 °C at 22 mmHg (Found: C, 60.0; H, 8.45. C₁₀H₁₈O₄ requires C, 59.4; H, 8.95%), δ 1.14 (6 H, t, CH₃), 1.70 (4 H, m, CH₂·C*H*₂), 2.26 (4 H, q, CH₂CO₂), and 4.10 (4 H, t, CH₂O), ν_{CO} 1 740 cm⁻¹.

1,4-Dibromobutane and acetic acid. 1,4-Dibromobutane (21.6 g, 0.1 mol) was added to acetic acid (60 g, 1.0 mol) and potassium fluoride (29 g, 0.5 mol) at 100 °C. There was an immediate precipitate of potassium bromide and ¹H n.m.r. spectroscopy showed the reaction to be complete in 1 h. This was confirmed by analysis of the KBr. The mixture was separated and gave tetramethylene diacetate (17.4 g, 0.10 mol, 100%).

1,4-Dibromobutane and propionic acid. 1,4-Dibromobutane (31.7 g, 0.147 mol), propionic acid (22.3 g, 0.301 mol), and potassium fluoride (17.0 g, 0.293 mol) were heated under reflux. ¹H N.m.r. spectroscopy showed 34% replacement of Br by EtCO₂ after 1½ h, 52% after 3 h, 56% after 5 h, 60% after 7 h, 67% after 16h, and 72% after 21 h. The mixture was separated and gave tetramethylene dipropionate (10.67 g, 0.053 mol, 36%).

1,4-Di-iodobutane and acetic acid. 1,4-Di-iodobutane (15.5 g, 0.05 mol) was added to potassium fluoride (14.5 g, 0.25 mol) in acetic acid (30 g, 0.5 mol) at 100 °C. There was an immediate precipitate of potassium iodide and ¹H n.m.r. spectroscopy showed the reaction to be complete in 3/4 h. This was confirmed by analysis of the KI. The mixture was separated and gave tetramethylene diacetate (8.6 g, 0.05 mol, 99%).

1,3-Dichlorobutane and acetic acid. 1,3-Dichlorobutane (12.7 g, 0.1 mol), acetic acid (60 g, 1.0 mol), and potassium fluoride (29.1 g, 0.5 mol) were heated under reflux for 10 h, after which the ¹H n.m.r. spectrum showed 80% replacement of Cl by MeCO₂. This was confirmed by KCl analysis. The mixture was separated and gave 1-*methyltrimethylene diacetate* (12 g, 0.07 mol, 70%), b.p. 200—205 °C (Found: C, 54.5; H, 7.9. C₈H₁₄O₄ requires C, 55.15; H, 8.1%), δ 1 25 (3 H, d, C*H*₃·CH), 1.80 (2 H, q. C*H*₂·CH), 2.02 (6 H, s, CH₃·CO₂), 4.11 (2 H, t, CH₂O), and 5.01 (1 H, q, CH), ν_{CO} 1 736 cm⁻¹.

2,3-Dichlorobutane and acetic acid. 2,3-Dichlorobutane (25.4 g, 0.2 mol), acetic acid (120 g, 2.0 mol), and potassium fluoride (58.1 g, 1.0 mol) were heated under reflux for 20 h. The mixture was separated and gave a little 1,2-dimethylethylene diacetate (0.3 g, 0.001 7 mol, 0.85%), b.p. 191—193 °C, δ 1.21 (6 H, dd, C*H*₃·CH), 2.08 (6 H, s, CH₃CO₂), 3.95 (1 H?, m, CH), and 4.93 (1 H?, m, CH).

1,5-Dibromopentane and acetic acid. 1,5-Dibromopentane (11.5 g, 0.05 mol), acetic acid (30 g, 0.5 mol), and potassium

fluoride (14.5 g, 0.25 mol) were heated; within minutes a precipitate of potassium bromide was observed. After heating the reactants under reflux for $\frac{1}{2}$ h the ^{1}H n.m.r. spectrum showed no starting material to be present. Analysis of the KBr indicated a quantitative yield. The mixture was separated and gave *pentamethylene diacetate* (10 g, 0.05 mol, 100%), b.p. 234—240 °C (Found: C, 57.2; H, 8.75. $C_9H_{16}O_4$ requires C, 57.4; H, 8.5%), δ 1.56 (6 H, m, CH_2·CH_2·CH_2), 2.03 (6 H, s, CH_3), and 4.08 (4 H, t CH_2O), ν_{CO} 1 740 cm^{-1}.

1,5-Dibromopentane and propionic acid. 1,5-Dibromopentane (10.5 g, 0.045 mol), propionic acid (33.7 g, 0.45 mol), and potassium fluoride (13.2 g, 0.23 mol) were heated under reflux for 5 h. The mixture was then separated and gave *pentamethylene dipropionate* (9.34 g, 0.043 mol, 96%), b.p. 144—145 °C at 16 mmHg (Found: C, 61.3; H, 9.3. $C_{11}H_{20}O_4$ requires C, 61.05; H, 9.35%), δ 1.07 (6 H, t, CH_3), ca. 1.5br (6 H, m, CH_2·CH_2·CH_2), 2.26 (4 H, q, CH_2CO_2), and 4.01 (4 H, t, CH_2O), ν_{CO} 1 740 cm^{-1}.

1,6-Dichlorohexane and acetic acid. 1,6-Dichlorohexane (31.0 g, 0.2 mol), acetic acid (120 g, 2.0 mol), and potassium fluoride (58.1 g, 1.0 mol) were heated under reflux. ^{1}H N.m.r. spectroscopy showed 15% replacement of Cl by $MeCO_2$ after $\frac{1}{2}$ h, 30% after 1 h, 64% after 3 h, 95% after 8 h, and almost 100% after 12 h. The mixture was separated and gave *hexamethylene diacetate* (38.5 g, 0.19 mol, 95%), b.p. 260—265 °C (Found: C, 59.4; H, 8.9. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.9%), δ 1.47 (8 H, m, CH_2), 2.04 (6 H, s, CH_3), and 4.08 (4 H, t, CH_2O), ν_{CO} 1 740 cm^{-1}.

DISCUSSION

When a dihalogenated alkane is heated in refluxing carboxylic acid for several hours no reaction occurs. This is hardly surprising in view of the weak nucleophilicity of the carboxy-group. Even if a reaction were to take place, the expected products would be alkenes rather than diesters.

Esters are rarely made from the corresponding halides; when they are the reagent is a carboxylate.[3] For example esters can be formed from the chloro-derivatives of n-butane, n-octane, *etc.* and trimethylammonium carboxylates.[4] The alkali metal carboxylates are not suitable since they produce low yields, although silver salts give better results.

However a reaction between a dichloro- or dibromo-alkane and acetic or propionic acid to form diesters can be induced by the presence of potassium fluoride. It is believed that the fluoride ion forms a very strong hydrogen bond to the carboxy-group, resulting in a strengthening of the nucleophilicity of the latter sufficient to enable it successfully to attack the halide centre. The nature of the hydrogen bond has been discussed.[2,5,6] More important are the high yields of esters that are obtained. The carboxylic acid–fluoride combination achieves esterification in much higher yields than can be produced by the use of metal carboxylates.

In studying the reaction we have varied the reactants

(i) by employing dichloro-, dibromo-, and di-iodo-alkanes; (ii) by using acetic and propionic acids; (iii) by employing different alkane chain lengths; and (iv) by altering the steric hindrance at one or both halide centres.

(i) The reactions of the 1,4-dihalogenobutanes with acetic acid and potassium fluoride showed that the di-iodide reacted slightly more readily (100% yield in 45 min) than the dibromide (100% in 1 h), which was considerably more reactive than the dichloride (95% in 8 h). This is as expected.

(ii) The reactions of 1,4-dibromobutane and 1,5-dibromopentane with acetic and propionic acids in the presence of fluoride showed the former acid to react much faster than the latter (100% of diacetate in 1 h with $Br[CH_2]_4Br$ and 95% in $\frac{1}{2}$ h with $Br[CH_2]_5Br$, as opposed to 72% dipropionate after 21 h with $Br[CH_2]_4Br$ and 96% after 5 h with $Br[CH_2]_5Br$). The lower reactivity of the propionic acid may be a medium effect, although the higher reflux temperature might have compensated for this. It may reflect the slightly weaker hydrogen bonding ability of this acid, as revealed by δ(OH) of EtC(O)O–H $\cdots$ F$^-$ as compared with MeC(O)O–H $\cdots$ F$^-$.[5]

(iii) The reactions of the dichloroalkanes $Cl[CH_2]_nCl$ ($n = 2, 3, 4,$ or 6) with acetic acid–fluoride and of the dibromoalkanes $Br[CH_2]_nBr$ ($n = 2, 3, 4,$ or 5) and with propionic acid–fluoride showed that the further apart are the halogenated centres the more easily they are substituted. The acetic acid reactions gave yields of diacetate after 8 h of 30% when $n = 2$, 75% when $n = 3$, 95% when $n = 4$, and 96% when $n = 6$. The propionic acid reactions gave yields of dipropionate after 5 h of $<5\%$ when $n = 2$, 65% when $n = 3$, 56% when $n = 4$, and 96% when $n = 5$. Thus the deactivating effect of the first ester group becomes progressively weaker as n increases. The deactivating effect of an ester group on a halogen atom attached to a β-carbon atom is well known.

(iv) Steric hindrance should be clearly shown when the halogen to be substituted is attached to a secondary alkyl group. This is demonstrated by a 35% yield of diacetate from 1,2-dichloroethane after 10 h but only 2% of diacetate after 20 h from 1,2-dichloropropane, and less than 1% of diacetate after 20 h from 2,3-dichlorobutane.

Separating the reactive carbon centres has a more profound effect as witnessed by the 80% yield of diacetate after 10 h from 1,3-dichlorobutane; similar to the 80% of diacetate after 12 h from 1,3-dichloropropane; this suggests that there is no steric hindrance operating. This result is hard to rationalize.

Of all hydrogen bonds the combination O–H $\cdots$ F has been virtually neglected until recently. This combination forms only a very weak hydrogen bond if

[3] M. F. Ansell and R. H. Gigg, ' Rodd's Chemistry of Carbon Compounds,' 2nd edn., ed. S. Coffey, vol. Ic, Elsevier, London, 1965, pp. 139—142.

[4] R. H. Mills, M. W. Farrar, and O. J. Weinkauff, *Chem. and Ind.*, 1962, 2144.
[5] J. Emsley and O. P. A. Hoyte, *J.C.S. Dalton*, in the press.
[6] J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1973, 2154.

the fluorine atom is covalently bonded to another atom or group,[7] however fluoride ion forms one of the strongest hydrogen bonds known.[2] Lately it has been shown that potassium fluoride can activate other compounds that can form hydrogen bonds, such as phenols, benzenethiols, and amines.[8]

[7] D. A. K. Jones and J. G. Watkinson, *J. Chem. Soc.*, 1964, 2366.

[8] J. H. Clark and J. M. Miller, *J.C.S. Chem. Comm.*, 1976, 229.