ANALYTICAL AND THERMODYNAMIC STUDIES ON SOME HALOGENATED BENZENOID COMPOUNDS

A thesis submitted by

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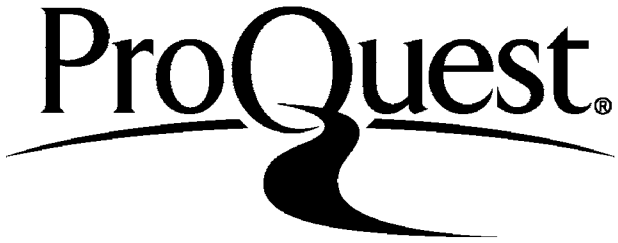

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ABSTRACT

The bromination of 2-fluorophenol, 3-fluorophenol, 4-fluorophenol, 2-fluoroaniline, 3-fluoroaniline and 4-fluoroaniline was carried out in aqueous medium using an acidified mixture of potassium bromate and potassium bromide as a source of bromine. The chlorination of these compounds was carried out using sulphuryl chloride as a chlorinating agent in chloroform or diethyl ether. Anhydrous aluminium chloride was used as a catalyst in the chlorination of the fluoroanilines. All the reaction products obtained were analyzed by fluorine-19 nuclear magnetic resonance spectroscopy (^{19}F n.m.r. spectroscopy), gas liquid chromatography (GLC) and high-performance liquid chromatography (HPLC). The identification and the structure of these products were established by comparison with the authentic compounds.

For the thermodynamic studies:-

(a) The enthalpies of solution (at saturation) of 2,4,6-tribromophenol ($Br_3C_6H_2OH$),4-bromoaniline ($BrC_6H_4NH_2$), 2,6-dibromoaniline ($Br_2C_6H_3NH_2$) and 2,4,6-tribromoaniline ($Br_3C_6H_2NH_2$) in toluene and n-propanol were determined from solubility measurements.

$\Delta_{sol}H^{\ominus}$ ($Br_3C_6H_2OH$) in Toluene = 33.90 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($Br_3C_6H_2OH$) in n-Propanol = 24.01 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($BrC_6H_4NH_2$) in Toluene = 65.94 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($BrC_6H_4NH_2$) in n-Propanol = 61.95 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($Br_2C_6H_3NH_2$) in Toluene = 46.65 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($Br_2C_6H_3NH_2$) in n-Propanol = 44.93 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($Br_3C_6H_2NH_2$) in Toluene = 28.09 kJ mol^{-1}

$\Delta_{sol}H^{\ominus}$ ($Br_3C_6H_2NH_2$) in n-Propanol = 20.22 kJ mol^{-1}

Entropies of solution, enthalpies of transfer, free energies of transfer and the entropies of transfer between the two solvents were also calculated.

(b) Enthalpies of reaction of the bromination of 2-chloroaniline, 4-bromo-2-chloroaniline and 4-chloroaniline in aqueous medium (perchloric acid/sodium bromide) with aqueous bromine (sodium bromide/sodium bromate) were found using reaction calorimetry.

$\Delta_rH^{\ominus}$ (2-chloroaniline,$_c$ + bromine,$_{aq}$) = -207.84 $\pm$ 0.63 kJ mol^{-1}

$\Delta_rH^{\ominus}$ (4-bromo-2-chloroaniline,$_c$ + bromine,$_{aq}$) = -91.29 $\pm$ 0.96 kJ mol^{-1}

$\Delta_rH^{\ominus}$ (4-chloroaniline,$_c$ + bromine,$_{aq}$) = -189.61 $\pm$ 0.90 kJ mol^{-1}.

(c) A titration calorimetric technique was used to determine the enthalpies of bromination of 2-nitroaniline and 4-nitroaniline in aqueous medium (perchloric acid/sodium bromide) with aqueous bromine (sodium bromide/sodium bromate).

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To my Family, my Relatives

and my Friends

PART I: HPLC, GLC AND ^{19}F n.m.r. SPECTROSCOPY ANALYSIS

CHAPTER I

I: INTRODUCTION

I. INTRODUCTION

I.A Literature Review

A large number of fluorinated derivatives were synthesized for testing as plant growth regulators.[1,2] Finger et al[1] have described the preparation and properties of 41 fluorophenoxyacetic acids, 4 fluorophenoxy propionic acids, 2 fluorobenzoic acids, several indole derivatives and a number of miscellaneous compounds. Among these preparations were some halogenated fluorophenols and fluoroanilines which are listed in Table I.1.

I.A.1 Halogenated Phenols

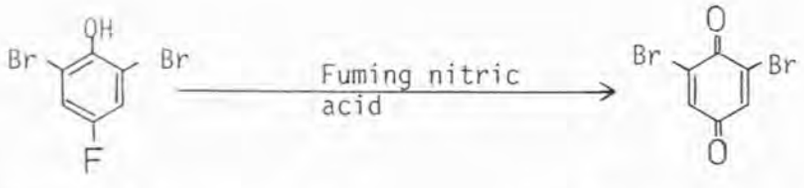
The bromination of the three isomeric monofluorophenols under various conditions was studied by Raiford et al,[3] who prepared as well 4,6-dibromo-2-fluorophenol; 2,4,5,6-tetrabromo-3-fluorophenol and 2,4,6-tribromo-3-fluorophenol bromide (Fig. I.1.a). While the preparation of 4,6-dibromo-3-fluorophenol; 2,4,6-tribromo-3-fluorophenol and 2,6-dibromo-4-fluorophenol was described elsewhere.[4]

2-Chloro-4-fluorophenol was prepared by the chlorination of an alkali metal salt of 4-fluorophenol by an alkaline hypochlorite,[5] as well as by the chlorination of 4-fluorophenol with sulphuryl chloride.[6,7] This compound was used in the preparation of 2-chloro-4-fluorophenyl trans-4̀-substituted cyclohexane carboxylates,[8] (Fig. I.1.b); 2,4-dihalophenyl 4̀-(trans-4̀-alkylcyclohexyl) benzoate[9] (Fig. I.1.c) and 2̀-chloro-4̀-fluorophenyl-3-chloro-4-hydroxybenzoate derivatives[10] (Fig. I.1.d), which are useful as liquid crystals.

Also it was used in the preparation of cyclopropyl-methyl-(thio)-phosphoric acid amides which are useful as insecticides[11] (Fig. I.1.e) and in the preparation of benzofuran derivatives which are useful as inflammation inhibitors[12] (Fig. I.1.f).

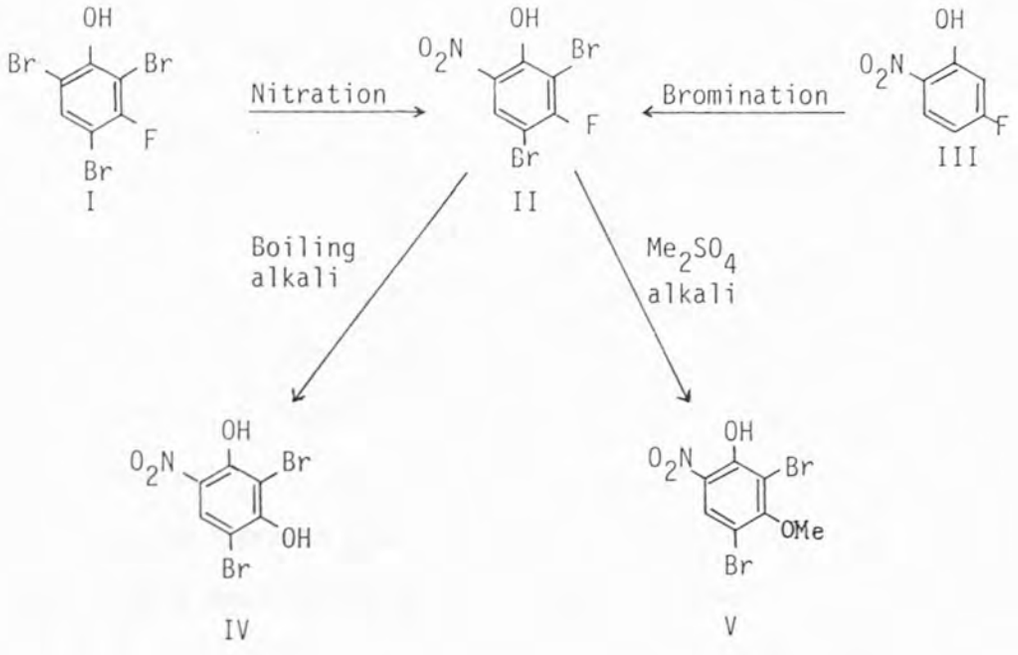
The chlorination of 3-fluorophenol with sulphuryl chloride produces 4,6-dichloro-3-fluorophenol.[6]

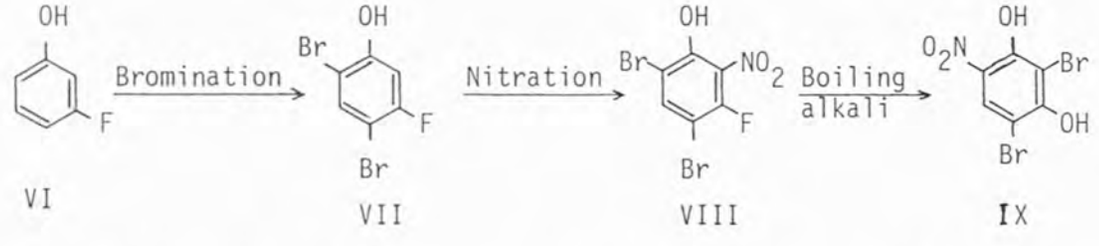
The action of fuming nitric acid on 2,6-dibromo-4-fluoro-phenol and anisole was studied by Hodgson and Nixon.[4] They had found in their study that all 4-halogenated phenols except the 4-iodo-compound (which was destroyed) gave 2,6-dibromo-4-benzoquinone. On the other hand 4-chloro-2,6-dibromoanisole and 2,4,6-tribromo-anisole gave 4-chloro-2,6-dibromo-3-nitroanisole and 2,4,6-tribromo-3-nitroanisole respectively.



2,6-Dibromo-4-fluorophenol 2,6-Dibromo-4-benzoquinone

Although the bromine atom in the 4-position to the hydroxyl group seemed to be labile in the presence of nitric acid, there was an exception in case of 2,4,6-tribromo-3-fluorophenol (I),[4] where the 6-bromo was replaced by the nitro group.





I, 2,4,6-Tribromo-3-fluorophenol; II, 2,4-Dibromo-6-nitro-3-fluorophenol; III, 6-Nitro-3-fluorophenol; IV, 2,4-Dibromo-6-nitroresorcinol; V, 2,4-Dibromo-6-nitroresorcinol 3-methyl ether; VI, 3-Fluorophenol; VII, 4,6-Dibromo-3-fluorophenol; VIII, 4,6-Dibromo-6-nitro-3-fluorophenol; IX, 2,4-Dibromo-3-nitroresorcinol.

When two bromine atoms were present o and p to the phenolic group, either could be removed, yielding isomeric nitrobromophenols. Raiford and LeRosen[3] showed that the fluorine atom was never displaced when bromo-fluorophenols were treated with sodium nitrite in glacial acetic acid, e.g., 2,6-dibromo-4-fluorophenol gave 2-bromo-4-fluoro-6-nitrophenol, and 2-fluoro-4,6-dibromophenol gave both isomers, 2-fluoro-4-nitro-6-bromophenol and 2-fluoro-4-bromo-6-nitrophenol.

On plant growth regulating, phenols can be active as auxins, when both o-positions were substituted, but when one o-substituent or when two substituents were present in o-positions the phenol was completely inactive.[13]

A lot of studies were made on the o-substituted phenols using Nuclear Magnetic Resonance and Infra-red methods, e.g. a quantitative study of the o-effect,[14] and an investigation of the strengths and relative strengths of the intramolecular halogen bonds in o-halophenols.[15,16,17] The study of intramolecular hydrogen bonds by proton resonance gave quantitative information about the enthalpy of formation of the hydrogen bonds in o-chloro-, bromo- and iodophenol.[18] NMR was used as well for studying the formation of a cis-trans dimer of o-halophenols in dilute CS_2. The stereo-specific spin-spin coupling between hydroxyl protons and ^{19}F nuclei in o-, m- and p-fluorophenol derivatives ($^{o}J_{OH,F}$, $^{m}J_{OH,F}$ and $^{p}J_{OH,F}$) were reported.[19] The coupling constants depend somewhat upon the substituents, but the values were determined mainly by the atomic species themselves and by their relative positions in the benzene ring[20] e.g. ^{19}F n.m.r. spectra of 4,6-dichloro-2-fluorophenol, showed $^{p}J_{HF}$ = 2.1 Hz and $^{o}J_{HF}$ = 9.6 Hz.

The ^{19}F n.m.r. shift of some 3- and 3,5-substituted fluorobenzenes relative to fluorobenzene as internal standard was measured by Hirst et al.[21] when they had found that the correlation of the shifts with various substituent parameters was not good and the comparison of the series showed that the effects of substituents were not additive.

For a series of p-substituted fluorobenzenes it was reported,[22] that the ^{19}F chemical shifts were directly related to changes in π electron density on the carbon atom bonded to the fluorine in terms of Molecular Orbital Theory. Ebraheem and Webb[23] performed Pariser-Parr-Pople (P-P-P) MO Calculations and they carried out INDO MO calculation on some of the substituted fluorobenzenes in an attempt to estimate the substituent electric field effect on the ^{19}F chemical shifts; they found agreement between the experimental results and the theoretical calculations.

^{19}F n.m.r. spectroscopy was used also for the investigation of the intramolecular coordination of 4-fluorophenol derivatives in which the H of the OH group was replaced by substituents such as Me, Et_3 Sn and Ph Hg, while the ring contained 0, 1 or 2 bromine atoms in the 2-position relative to the OH or OR group, in solvents such as CCl_4, $CHCl_3$ and Me_2SO.[24]

It was shown that in aromatic electrophilic substitutions involving neutral molecules of both aromatic substrate and halogen, the Arrhenius activation energies could be correlated with electronic densities on the carbon atoms where halogenation takes place.[25,26]

Arrhenius activation energies for the bromination of 4-methylphenol, 4-fluorophenol, 4-chlorophenol and 4-bromophenol were measured[27] and correlated with charge density distributions for these compounds.[28] When bromine was used as brominating agent, the kinetic features of these reactions seemed to be a second order reaction, first order in 4-substituted phenol and first order in bromine. The reaction mechanism suggested follows[27]:-

$$ArH + Br_2 \underset{}{\overset{k \text{ fast}}{\rightleftharpoons}} ArH \cdot Br_2$$

(π complex)

$$ArH.Br_2 + Solvent \xrightarrow{k_1 \text{ slow}} ArH.Br^+ + Solvent.Br^-$$

(σ-complex)

$$ArH.Br^+ \xrightarrow{\text{fast}} ArBr + H^+$$

$$H^+ + Br^- \xrightarrow{\text{fast}} HBr$$

(where ArH denotes the aromatic substrate)

In the case of 4-fluorophenol the value of the activation energy was less than those of 4-chloro- and 4-bromo-phenol which showed that the electron-density at the 2-position with respect to OH group in 4-fluorophenol was higher than those of 4-chloro- and 4-bromo-phenol.

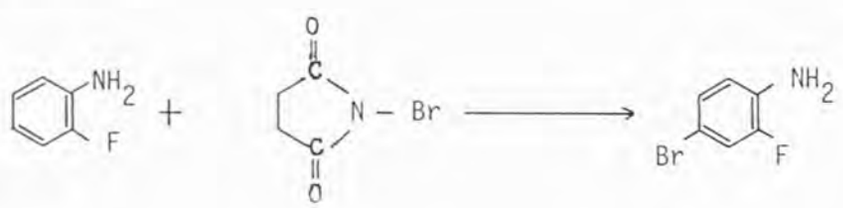
On the other hand, the kinetics of bromination of 4-substituted phenol with N-bromosuccinimide (NBS) as brominating agent in 80% aqueous acetic acid was investigated. The reaction was found to be first order in the aromatic substrate (ArH) and zero order in NBS.

Chromatographic separation of halogenated phenols was widely used, e.g. gas liquid chromatography[29-32] using the appropriate columns and detectors for separation of chlorophenols, and high performance liquid chromatography[33-35] using reverse phase columns for separation and trace determination of phenolic compounds.

I.A.2 Halogenated Anilines

The bromination of anilines using N-bromosuccinimide in an inert organic solvent such as methylene chloride and carbon tetrachloride[36,37] and in acetic acid[38] is well known.

4-Bromo-2-fluoroaniline can be prepared by bromination of 2-fluoroaniline[39,40] with N-bromosuccinimide (NBS) as shown in the following scheme:-



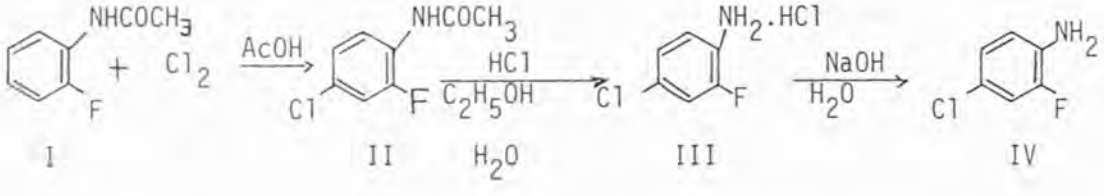
2-Fluoroaniline NBS 4-Bromo-2-fluoroaniline

It can be prepared as well by using 1,3-dibromo-5,5-dimethylhydantoin as brominating agent which was described elsewhere[41,42] and gives 94% of 4-bromo-2-fluoroaniline.

N-Bromosuccinimide was used for preparation of 2-bromo-4-fluoroaniline;[36] while a solution of 4-fluoroaniline in acetic acid was treated with bromine solution in acetic acid to produce 2,6-dibromo-4-fluoroaniline.[43]

6-Bromo-2-fluoroaniline was prepared by Boehninger,[44] from 4-sulphonamido-2-fluoroacetanilide, which was brominated with bromine and treated with acid to desulphonate.

The chlorination of anilines using N-chlorosuccinimide and the chlorination of acetanilides using chlorine gas in acetic acid are well known.[38,45] 4-Chloro-2-fluoroaniline can be prepared from 2-fluoroacetanilide[39] as shown in the following scheme:-



I II III IV

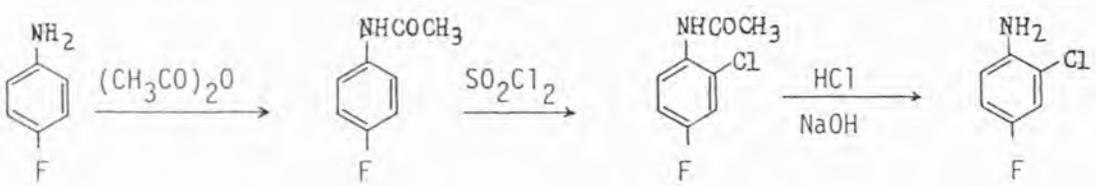
I: 2-Fluoroacetanilide; II: 4-Chloro-2-fluoroacetanilide;
III: 4-Chloro-2-fluoroaniline hydrochloride;
IV: 4-Chloro-2-fluoroaniline.

4-Chloro-2-fluoroaniline was used in the preparation of herbicidal Isoindol-1-one derivatives[40] (Fig. I.2.a), herbicidal 2-(substituted aryl)-3A, 4, 5, 6, 7, 7A-Hexahydro-1H-isoindole-1,3 (2H)-diones[46] (Fig. I.2.b), and herbicidal 2-substituted phenyl 4,5,6,7-tetrahydro-2H-indazoles[47] (Fig. I.2.c).

6-Chloro-2-fluoroaniline was prepared from 2-chloro-6-fluorobenzoic acid in the preparation of some fluorophenothiazines.[48]

4-Chloro-3-fluoroaniline was obtained by hydrolysing its acetyl derivative[49] with 20% hydrochloric acid for 24 h , while the 4-chloro-, 6-chloro- and 4,6-dichloro-3-fluoroanilines were[50] obtained as mixture from hydrolysing their acetyl derivatives, which were separated by distillation under reduced pressure.

The chlorination of 4-fluoroaniline[43] with gaseous chlorine evolved from potassium chlorate, yielded 2,6-dichloro-4-fluoroaniline which can be obtained as well from deacetylation of the corresponding acetanilide. The preparation of 2-chloro-4-fluoroaniline was developed[51] as a high yield synthesis, as shown in the scheme below ,in comparison with other methods, e.g.,the preparation



I II III IV

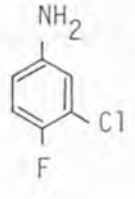
I: 4-Fluoroaniline; II: 4-Fluoroacetanilide;

III: 2-Chloro-4-fluoroacetanilide; IV: 2-Chloro-4-fluoroaniline.

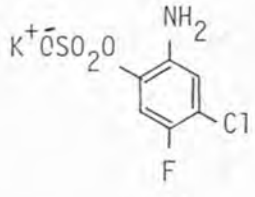
of 2-chloro-4-fluoroaniline from the reaction of 2-chloro-N-phenylhydroxylamine with hydrogen fluoride.[52] 2-Chloro-4-fluoroacetanilide was prepared also[53] from m-chlorofluorobenzene; this was acetylated in carbon disulphide in the presence of aluminium

chloride to give 2-chloro-4-fluoroacetophenone which by Beckmann rearrangement of its oxime gave 2-chloro-4-fluoroacetanilide and deacetylation gave 2-chloro-4-fluoroaniline. In the same way 3-chloro-4-fluoroaniline was prepared, which had been already prepared by Rinkes.[54]

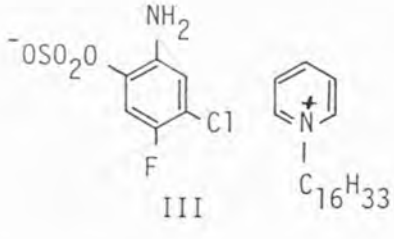
3-Chloro-4-fluoroaniline[55] (I) is an intermediate in the manufacture of two wild oat herbicides, flampropisopropyl (isopropyl-N-benzyl-N-(3-chloro-4-fluorophenyl)-2-aminopropionate) and flampropmethyl (the analogous methyl ester).



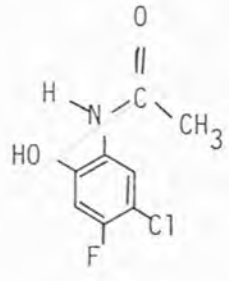
I



II



III



IV

I: 3-Chloro-4-fluoroaniline; II: Potassium 2-amino-4-chloro-5-fluorophenyl sulphate; III: Cetylpyridinium salt of 2-amino-4-chloro-5-fluorophenyl sulphate; IV: N-(5-chloro-4-fluoro-2-hydroxyphenyl)acetamide.

A study of the metabolism of 3-chloro-4-fluoroaniline[55,56] in rat and dog was undertaken as part of an industrial hygiene research programme to indicate the most suitable method to monitor exposure to chlorofluoroanilines.

In the light of ^{19}F n.m.r. spectroscopy, among the study of many of substituted fluorobenzenes, the ^{19}F chemical shifts of 3-fluoroaniline and 4-fluoroaniline were reported.[21,23] In 4-fluoroaniline[57] $^{m}J_{HF}$ = 5.1 Hz and $^{o}J_{HF}$ = 8.6 Hz, while in 4-fluorotoluene[58] $^{m}J_{HF}$ = 5.8 Hz and $^{o}J_{HF}$ = 8.7 Hz. The proton nuclear magnetic resonance spectra of selected 4-substituted fluorobenzenes, including 4-fluoroaniline, were investigated.[59]

Other analytical studies were made on 4-fluoroaniline and aniline in the vapour phase by microwave[60] and far infrared[61] spectroscopy. The observation from combined microwave and far infrared studies showed that the amino group is more nonplanar in 4-fluoroaniline than in aniline.

Table I.1

Phenol and aniline derivatives investigated, as plant growth regulators

2,6-Dibromo-4-fluorophenol	3,5-Dichloro-4-fluorophenol
3-Chloro-2-fluorophenol	2,4-Dichloro-5-fluorophenol[b]
4-Chloro-2-fluorophenol	3-Chloro-2-fluoroaniline
4-Chloro-3-fluorophenol	2-Chloro-4-fluoroaniline
2-Chloro-4-fluorophenol[a]	3,5-Dichloro-4-fluoroaniline
3-Chloro-4-fluorophenol	4-Chloro-3-fluoroaniline
2-Chloro-5-fluorophenol	3-Chloro-4-fluoroaniline
4,5-Dichloro-2-fluorophenol	4,5-Dichloro-2-fluoroaniline
2,6-Dichloro-4-fluorophenol	5-Chloro-2-fluoroaniline
2,5-Dichloro-4-fluorophenol	2,5-Dichloro-4-fluoroaniline

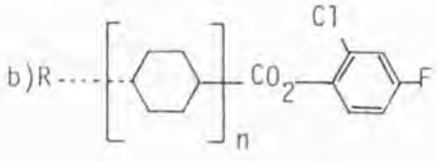
The preparations of (a) and (b) (were mentioned elsewhere[6]) by the chlorination of 4-fluorophenol and 3-fluorophenol with SO_2Cl_2 as chlorinating agent, *.

Fig. 1.1

a) 

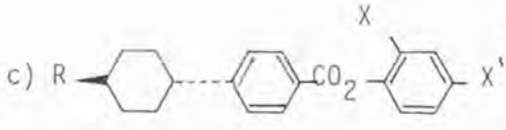
"C_6HBr_4OF"

2,4,6-Tribromo-3-fluorophenol bromide or 3-Fluoro-2,4,4,6-tetrabromocyclohexa-2,5-dienone.

b) 

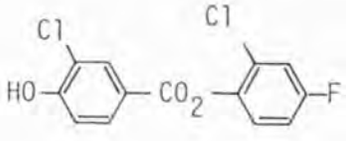
2-Chloro-4-fluorophenyl trans-4`-substituted cyclohexane carboxylates

R = Et ; n = 2.

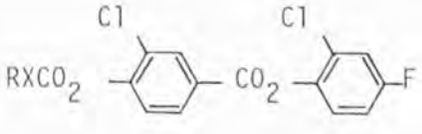
c) 

2,4-Dihalophenyl 4`-(trans-4"-alkylcyclohexyl)benzoates.

X = Cl, F; X' = F, Cl; R = Et.

d) 

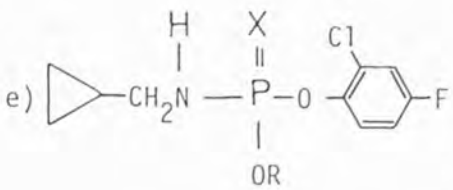
2'-Chloro-4'-fluorophenyl 3-chloro-4-hydroxy benzoate



It's derivative

R = Pr, Bu, C_5H_{11}, Pr, C_5H_{11}, BuO, $C_6H_{13}O$.

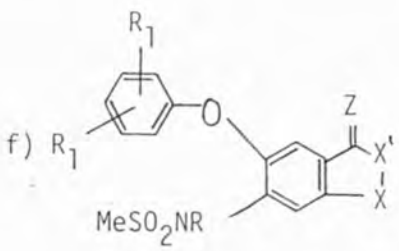
X = Trans-1,4-cyclohexylidene (Q), Q, Q, 1,4-C_6H_4(Q'), Q', Q', Q'

e) 

Cyclopropyl-methyl-(thio)-acid amides.

R = (un)substituted alkyl;

X = O,S.

f) 

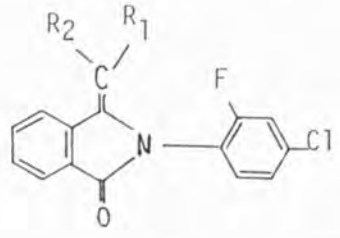
Benzofuran derivatives

R = H, Ac, R_1 = H, F, Cl;

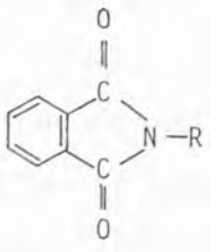
X = O, CH_2; X' = CH_2 , O ;

Z = O, CH_2.

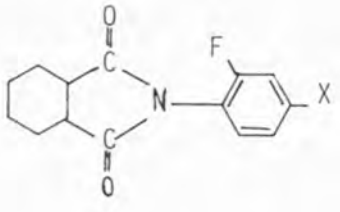
Fig. I.2

a) 

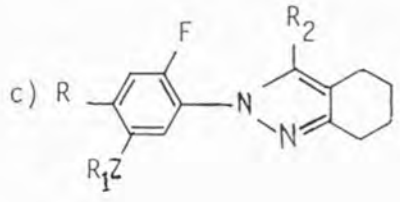
Herbicidal isoindole-1-one derivatives.
R_1 = H, Me; R_2 = H, alkyl of 1 to 4 carbons.



Isoindole-1,3-diones.

b) 

Herbicidal 2-(substituted aryl) -3A, 4,5,6,7,7A-hexahydro-1H-isoindole-1,3 (2H)-diones
X = Cl, Br.

c) 

Herbicidal 2-substituted phenyl-4,5,6,7-tetrahydro-2H-indazoles
R = Cl, Br; R_1 = alkyl, alkenyl, cycloalkoxycarbonylmethyl, (halo)alkoxycarbonylmethyl;
R_2 = Cl, Me; Z = O, NH.

I.B Aim of Work

Halogenated phenols and anilines are widely used in industry and agriculture, they have extensive use as herbicides, fungicides, and insecticides. Because of the toxicity of these substances which resist degradation and tend to persist in the environment these halogenated compounds form a special group among the numerous micropollutants found in surface water, they can be hazardous to public health. The identification of these halogenated compounds in environmental samples is therefore of interest.

In this work the bromination of fluorophenols and fluoroanilines was carried out using bromate/bromide in acidic medium as a source of bromine, while the chlorination of these compounds was made with sulphuryl chloride as a source of chlorine. The reaction mixtures were analyzed by three techniques, high-performance liquid chromatography (HPLC), gas liquid chromatography (GLC) and fluorine-19 nuclear magnetic resonance spectroscopy (^{19}F n.m.r.).

CHAPTER II

II: EXPERIMENTAL

II. EXPERIMENTAL

II. A. Materials and Methods

2-Fluorophenol, 3-fluorophenol, 4-fluorophenol, 2-fluoroaniline, 3-fluoroaniline and 4-fluoroaniline were commercial materials. Most of these samples were liquid and they were purified by redistillation under atmospheric pressure.

Bromine, potassium bromide (Reagent grade) and potassium bromate (Analar), were used as supplied (B.D.H.). Sulphuryl chloride (B.D.H.) was redistilled (b.p. 69°C, lit.[62] 69.1°C).

The fluoroacetanilides were obtained from the treatment of corresponding fluoroanilines with acetic anhydride and glacial acetic acid.[32] The fluoroacetanilides were recrystallized from aqueous acetic acid, m.p. 77° (o-), 83° (m-) and 152.5°C(p-) fluoroacetanilide. Lit. values were 77 -80°C [25], 84.6°C [49] and 148-152°C [32] respectively.

II.A.1 Preparation of Some Halogenated Fluorophenols

II.A.1a 4-Bromo-2-fluorophenol

2-Fluorophenol (4.7 g, 0.042 mol) was dissolved in dichloromethane (20 cm^3), cooled in ice and salt to $\simeq$20°C, treated dropwise (with caution) with bromine (2.5 cm^3, 0.049 mol) in dichloromethane (10 cm^3) within a period of 15 min., with vigorous stirring[63], the reaction product was kept at room temperature with constant stirring for a further 15 min. The solvent was removed by rotary evaporator and the residue was distilled under reduced pressure. The bromo-fluorophenol was collected at 90°C/ 15 mm Hg (2.45 g, 31%) lit.[1] 79°C/7 mm Hg. The purity of the compound was checked by high-performance liquid chromatography (HPLC) and

gas liquid chromatography (GLC). ^{19}F Nuclear Magnetic Resonance Spectroscopy (^{19}F n.m.r. spectroscopy) was used to investigate the bromo-fluorophenol; the spectrum gave a coupling constant (9.76 Hz) which is chacteristic of o-hydrogen-fluorine coupling. (Chemical shift δF = -137.8 ppm).

II.A.1b 6-Bromo-2-fluorophenol

A mixture of 2-fluorophenol (6.2 g, 0.055 mol) and concentrated sulphuric acid (23.2 g, 12.6 cm^3), was heated in a boiling water bath for 3 h with vigorous stirring, cooled to room temperature and treated with a solution of sodium hydroxide (19.0 g) in water (47 cm^3), whilst stirring constantly. The alkaline solution was cooled to room temperature and bromine (3.4 cm^3, 0.0666 mol) was added from a dropping funnel down the condenser within 20 min. The reaction mixture was heated to $\simeq 50^oC$ and maintained at this temperature, with stirring, for 30 min. The flask and contents were heated in an oil bath at 150-155^oC for 30 min.[63] The reaction mixture was steam distilled and the organic product was extracted with ether and dried over magnesium sulphate, and the solvent was removed by rotary evaporator. HPLC and GLC analysis showed that the product consists of three components which were identified by ^{19}F n.m.r. spectroscopy as: 6-bromo-2-fluorophenol (quartet; δF = -134.0 ppm, (71%); $^oJ_{HF}$ = 9.76 Hz, $^mJ_{HF}$ = 4.88 Hz),4-bromo-2-fluorophenol (triplet; δF = -137.4 ppm (17%); $^oJ_{HF}$ = 9.77 Hz, $^mJ_{HF}$ = 8.79 Hz) and 4,6-dibromo-2-fluorophenol (doublet: δF = -131.2 ppm, (12%); $^oJ_{HF}$ = 9.76 Hz).

II.A.1c 4,6-Dibromo-2-fluorophenol

2-Fluorophenol (2.24 g, 0.02 mol), was dissolved in glacial acetic acid (4.0 cm^3) with stirring at room temperature, and treated dropwise with bromine (2.4 cm^3, 0.047 mol). After an hour the reaction was poured into water giving an oil. The product was washed with sodium bisulphite solution in order to remove the excess of bromine; this treatment caused the oil to solidify. The crude substance was purified by treating its solution in sodium hydroxide (1M) with charcoal and filtering. When the filtrate was acidified with sulphuric acid (2.5M) the brominated fluorophenol precipitated. The product was recrystallized three times from petroleum ether (b.p. 40 - 60°C), filtered off with a sintered glass funnel (G4), air dried and finally stored in a desiccator over silica-gel. The crystals obtained were white needles, m.p. 33°C (17%), lit.[3] m.p. 35°C. ^{19}F n.m.r. spectroscopy showed it is a pure compound (doublet; δF = -131.46 ppm), as did HPLC and GLC analysis.

II.A.1d 6-Bromo-3-fluorophenol

A solution of 3-fluorophenol (1.12 g, 0.01 mol) in chloroform (10 cm^3), was treated dropwise with bromine (0.6 cm^3, 0.011 mol) dissolved in chloroform (3.0 cm^3) over a period of 15 min. The reaction mixture was allowed to stand for 30 min. with constant stirring at room temperature. The solvent was removed using a rotary evaporator. According to HPLC and GLC analysis the brominated fluorophenol is a mixture of four components

which were identified by ^{19}F n.m.r. as 3-fluorophenol, 6-bromo-3-fluorophenol (δF = -112.3 ppm; (85%)), 4-bromo-3-fluorophenol (triplet; δF = -105.5 ppm; (11.6%)) and 4,6-dibromo-3-fluorophenol (quartet; δF = -105.9 ppm; (3.3%)); these results agree with that obtained from GLC (3-fluorophenol (23%), 6-bromo-3-fluorophenol (63%), 4-bromo-3-fluorophenol (11%) and 4,6-dibromo-3-fluorophenol (3%).

II.A.1e 4,6-Dibromo-3-fluorophenol

3-Fluorophenol (1.12 g, 0.01 mol) was dissolved in chloroform (10 cm^3) and treated dropwise with bromine (1.0 cm^3, 0.02 mol) dissolved in chloroform (3.0 cm^3). The reaction was allowed to stand with constant stirring at room temperature for 30 min. The chloroform was then removed by rotary evaporator to leave an oil which cooled in ice to precipitate 4,6-dibromo-3-fluorophenol. The white precipitate was recrystallized from petroleum ether (b.p. 60 - 80°C) to give a white needles (1.5 g, 56%) m.p. 45 - 46°C, lit.[4] m.p. 45°. The purity of the compound was checked by HPLC, GLC and ^{19}F n.m.r. spectroscopy (quartet, δF = -105.6 ppm; $^{o}J_{HF}$ = 9.52 Hz, $^{m}J_{HF}$ = 7.32 Hz).

II.A.1f 2,4,6-Tribromo-3-fluorophenol

3-Fluorophenol (1.12 g, 0.01 mol) was dissolved in water (100 cm^3) with vigorous stirring for 20 min then brominated by portionwise addition of a mixture of bromine (1.5 cm^3, 0.030 mol) in water (10 cm^3) containing potassium bromide (5.0 g). The white

precipitate of 2,4,6-tribromo-3-fluorophenol formed over 30 min[4], and was filtered off and recrystallized from dilute ethanol to give white needles (2.0 g, 57%), m.p. 90 - 92°C, lit.[4] m.p. 90°C. The product was pure according to HPLC and GLC analysis as well as ^{19}F n.m.r. spectroscopy (doublet, δF = -96.6 ppm; $^{m}J_{HF}$ = 7.37 Hz). Found: C, 20.63; H, 0.57; $C_6H_2Br_3FO$ requires C, 20.68; H, 0.57%.

II.A.1g 2-Bromo-4-fluorophenol

4-Fluorophenol (5.72 g, 0.051 mol), was dissolved in carbon disulphide (15 cm^3), and treated dropwise with vigorous stirring with a solution of bromine (3.0 cm^3, 0.057 mol) in carbon disulphide; the total volume of solvent was 25 cm^3.[1] The brominated product was kept in a refrigerator (-20°C) for a month, when the white precipitate of 2-bromo-4-fluorophenol was filtered off and recrystallized from petroleum ether (b.p. 30-40°C) to give white needles (1.0 g, 10%), m.p. 42°C, lit.[1] m.p. 43°C. The purity of the compound was checked by HPLC, GLC and ^{19}F n.m.r. (quartet, δF = -122.3 ppm; $^{o}J_{HF}$ = 7.81 Hz, $^{o'}J_{HF}$ = 7.82 Hz, $^{m}J_{HF}$ = 5.85 Hz).

II.A.1h 2,6-Dibromo-4-fluorophenol

4-Fluorophenol (2.24 g, 0.02 mol) was dissolved in glacial acetic acid (8.0 cm^3) and treated dropwise with bromine (2.12 cm^3, 0.041 mol). The mixture was poured into water after standing for a short time. The product was recrystallized from petroleum ether (b.p. 60 - 80°C) in white crystals (0.77 g, 14.2%) m.p. 49°C lit.[3] 48 - 56°C. The purity of the compound was

checked by HPLC and GLC as well as ^{19}F n.m.r. spectroscopy (triplet δF = -120.7 ppm; $^{o}J_{HF}$ = 7.33 Hz, $^{o'}J_{HF}$ = 7.81 Hz).

II.A.2 Preparation of Some Halogenated Fluoroanilines

II.A.2a 2-Fluoroacetanilide

2-Fluoroaniline (20.0 g, 0.18 mol) was cooled in an ice bath and treated dropwise with acetic anhydride (20 cm^3, 0.21 mol) with constant stirring over a period of 1 h, then glacial acetic acid (10 cm^3) was added, and the reaction kept with stirring at room temperature for further 15 min. The precipitate was filtered off and recrystallized from dilute acetic acid and air dried (20.5 g, 74.3%) m.p. 77°C, lit.[25] 77 - 80°C; the purity of the compound was checked by HPLC and GLC.

II.A.2b 3-Fluoroacetanilide

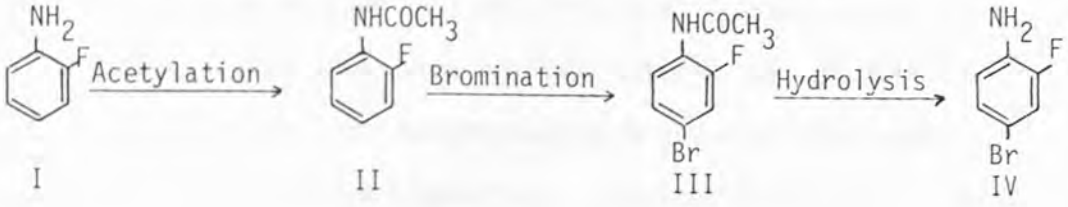
3-Fluoroaniline (11.0 g, 0.099 mol) was cooled in an ice bath and treated dropwise with acetic anhydride (10 cm^3) with stirring over a period of 1 h, then glacial acetic acid (10 cm^3) was added. The white precipitate was filtered off and recrystallized from dilute acetic acid, and the white crystals were filtered off, washed with distilled water, drained and air dried (8.0 g, 53.3%) m.p. 83°C lit.[49] 84.6°C. The purity of the compound was checked by HPLC and GLC.

II.A.2c 4-Fluoroacetanilide

4-Fluoroaniline (20.0 g, 0.18 mol), was treated with acetic anhydride by the method described for 3-fluoroaniline (II.A.2b) when pure white needles of 4-fluoroacetanilide were obtained (22.0 g, 81%) m.p. 152.5°C lit.[32] 148 - 152°C.

II.A.2d 4-Bromo-2-fluoroaniline

The preparation of 4-bromo-2-fluoroaniline was carried out using the method of preparation of 4-bromoaniline.



I II III IV

I: 2-Fluoroaniline; II: 2-Fluoroacetanilide;

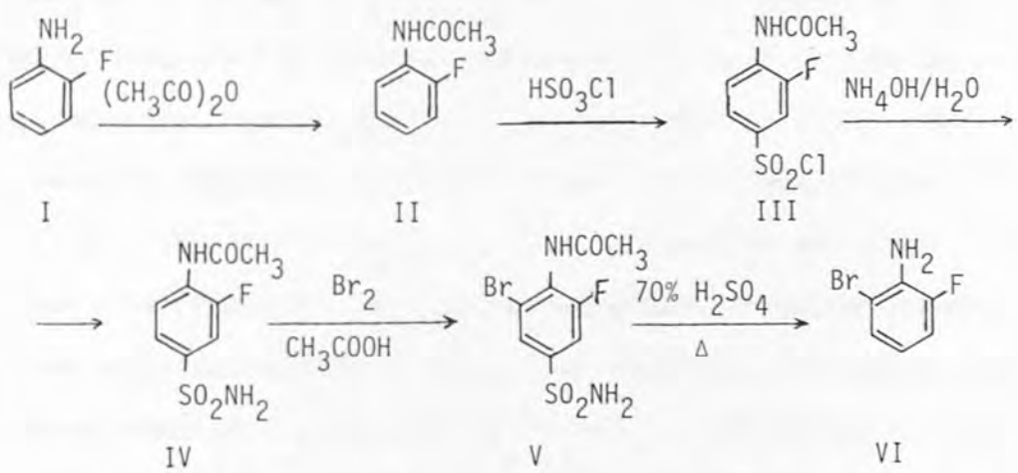
III: 4-Bromo-2-fluoroacetanilide; IV: 4-Bromo-2-fluoroaniline.

2-Fluoroacetanilide (6.19 g, 0.04 mol) was dissolved in glacial acetic acid (18 cm^3, 0.3 mol) in a conical flask. A solution of bromine (2.0 cm^3, 0.04 mol) in glacial acetic acid (10 cm^3, 0.166 mol), was transferred to a separatory funnel supported over the conical flask. While the flask contents were stirring the bromine solution was added very slowly. (The preparation was conducted in a fume cupboard). When all the bromine was added, the reaction was allowed to stand at room temperature with stirring for 2 h. The product was poured into 400 cm^3 of distilled water with vigorous stirring and the flask rinsed with ≃100 cm^3 of distilled water and added to the stock. The precipitate was filtered off and recrystallized from dilute methanol (5.44 g, 58%) m.p. 153 - 154°C. Found; C, 42.41, H, 3.1; C_8H_7BrFNO requires, C, 41.4, H, 3.04%. ^{19}F n.m.r. spectroscopy confirmed the structure (triplet; δF = -128.9 ppm; $^{o}J_{HF}$ = 8.79 Hz).

4-Bromo-2-fluoroacetanilide (3.2 g, 0.138 mol) was dissolved in ethanol (15.7 cm^3) and concentrated hydrochloric acid (3.4 cm^3, 0.04 mol) was added. The mixture was heated at 85°C for 1 h, diluted with water (100 cm^3) and distilled. After collecting $\simeq$100 cm^3 of distillate, the residual solution was poured into ice-water (100 cm^3) and sodium hydroxide solution (5%) added with stirring until just alkaline. The precipitate was filtered off and recrystallized from dilute methanol to give white crystals of 4-bromo-2-fluoroaniline (0.8 g, 31%), m.p. 37 - 38°C.

The purity of the compound was checked by HPLC and GLC, while ^{19}F n.m.r. spectroscopy was used to confirm the structure (triplet, δF = -132.63 ppm; $^{o}J_{HF}$ = 8.79 Hz, $^{m}J_{Hf}$ = 7.33 Hz, $^{p}J_{HF}$ 1.47 Hz).

II.A.2e 6-Bromo-2-fluoroaniline

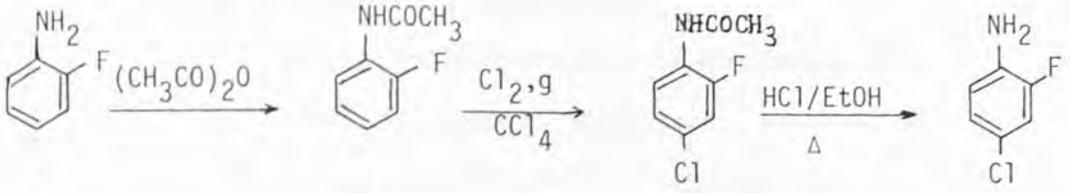


I: 2-Fluoroaniline; II: 2-Fluoroacetanilide; III: 4-Chlorosulphonyl-2-fluoroacetanilide; IV: 4-sulphonamido-2-fluoroacetanilide; V: 6-Bromo-4-sulphonamido-2-fluoroacetanilide; VI: 6-Bromo-2-fluoroaniline.

In a two-necked flask, 2-fluoroacetanilide (15.0 g, 0.098 mol) was treated dropwise with chlorosulphonic acid (33 cm^3, 14.6 M). After the addition the flask was heated in a water bath for 1 h, cooled and the contents poured with care into ice, the solid was filtered and washed with a little water, and then treated with a mixture of ammonia (75 cm^3, 17 M) and water (75 cm^3). The mixture was heated with occasional swirling to just below the boiling point for 15 min. cooled and treated with sulphuric acid (5 M) until acid to Congo Red. The resultant precipitate was filtered, drained well, washed with cold water and left to dry overnight.[63] The dry 4-sulphonamido-2-fluoroacetanilide (7.2 g, 32%) had m.p. 162 - 170°C, lit.[32] 162 - 165°C.

4-Sulphonamido-2-fluoroacetanilide (5.2 g) was dissolved in glacial acetic acid (27 cm^3) and treated with bromine (1.1 cm^3) in glacial acetic acid (5 cm^3). After the addition of bromine, the reaction was heated in a water bath for 1 h, was stirred at room temperature for 7 h, filtered and washed with water to give the bromo-sulphonamido-fluoroacetanilide , (2.33 g, 33%) m.p. 194°C. The brominated product was boiled for 30 min with sulphuric acid (40 cm^3, 70%), cooled and neutralized with ammonium hydroxide. After steam distillation the product was extracted with dichloromethane, dried (anhydrous sodium sulphate), and the solvent was removed under reduced pressure (rotary evaporator) to leave the 6-bromo-2-fluoro-aniline (0.09 g, 6.8%). The structure was confirmed using ^{19}F n.m.r. spectroscopy (octet; δF = -131.1 ppm); according to the ^{19}F n.m.r. spectroscopy analysis it was 95% pure in agreement with GLC analysis.

II.A.2f 4-Chloro-2-fluoroaniline



I II III IV

I: 2-Fluoroaniline; II: 2-Fluoroacetanilide; III: 4-Chloro-2-fluoroacetanilide; IV: 4-Chloro-2-fluoroaniline.

2-Fluoroacetanilide (7.0 g, 0.046 mol) in carbon tetrachloride (20 cm^3) was treated dropwise with carbon tetrachloride (68.3 g) containing chlorine gas (3.33 g, 0.047 mol). The addition was carried out in an ice bath. The reaction was left at room temperature with constant stirring for 17 h, treated with a mixture of concentrated hydrochloric acid (22 cm^3) and ethyl alcohol (22 cm^3) and heated at 80 - 90°C under reflux for 5 h, after which it was treated with potassium hydrogen carbonate until neutral to litmus paper. The organic product was extracted with diethyl ether and dried with anhydrous sodium sulphate, and the solvent was removed under reduced pressure (rotary evaporator was used). The crude material (5.37 g) was distilled under vacuum, the 4-chloro-2-fluoroaniline being obtained as a fraction b.p. 70°C/18 mm Hg (0.3 g, 3.5%), n_D^{22} = 1.5597, lit.[22] n_D^{25} = 1.5541. The purity and structure was confirmed by ^{19}F n.m.r. spectroscopy (triplet; δF = -132.8 ppm; $^{o}J_{HF}$ = 9.76 Hz, $^{m}J_{HF}$ = 8.78 Hz).

II.A.2g 2-Chloro-6-fluoroaniline

A solution of 2-chloro-6-fluorobenzoic acid (11.5 g, 0.065 mol) in concentrated sulphuric acid (50 cm^3) was prepared by stirring at 70°C for 1 h. Sodium azide (5.0 g, 0.075 mol) was added in small portions to the solution at 60°C over a period of 1.5 h. The mixture was allowed to stand overnight, after which it was made basic with ammonium hydroxide and steam distilled. The product was extracted from the steam distillate with ether and dried over magnesium sulphate; the solvent being removed by a rotary evaporator. The 2-chloro-6-fluoroaniline was distilled under reduced pressure b.p. 71°/ 20 mm Hg, lit.[28] 91°C/30 mm Hg (5.0 g, 52%). The structure of the compound was confirmed by ^{19}F n.m.r. spectroscopy (δF = -132.0 ppm; $^{o}J_{HF}$ = 9.77 Hz), and by micro-analysis. Found: C, 49.52; H, 3.41; N, 10.38; C_6H_5ClFN requires; C, 49.48; H, 3.43; N, 9.62%.

II.A.2h 4,6-Dichloro-2-fluoroaniline[64]

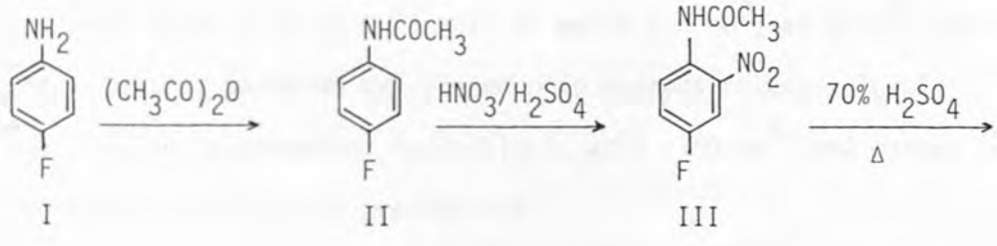
2-Fluoroaniline (11.1 g, 0.10 mol) was dissolved in a mixture of petroleum ether (b.p. 40 - 60°C, 200 cm^3) with sufficient dichloromethane (18 cm^3) to give a one-phase system with no undissolved oil. This solution was treated with chlorine gas (keeping air and moisture out as much as possible) until no more chlorine gas was absorbed. The precipitate was filtered, washed with a little petroleum ether (b.p. 40 - 60°C) and then added to a hot solution of sodium metabisulphite (10.0 g) in water (100 cm^3)

(no flames), and the resultant dark oil was steam distilled and recrystallized from dilute ethanol to give yellow crystals of 4,6-dichloro-2-fluoroaniline (0.42 g, 2.33%), m.p. 42 - 43°C. The purity of the compound was confirmed by HPLC and GLC. The structure of the compound was confirmed using ^{19}F n.m.r. spectroscopy (doublet; δF = -130.0 ppm; $^{o}J_{HF}$ = 9.52 Hz) and micro-analysis.

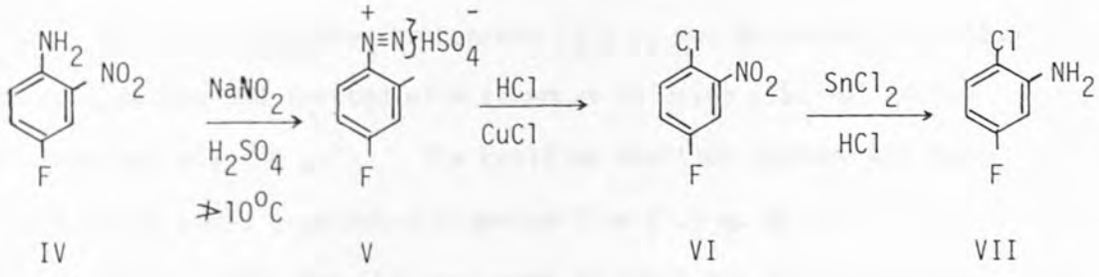
Found; C, 38.56; H, 2.17; N, 7.5; $C_6H_4NFCl_2$ requires C, 40.0; H, 2.23, N, 7.77%.

II.A.2i 6-Chloro-3-fluoroaniline[64]

6-Chloro-3-fluoroaniline was prepared from 4-fluoroaniline as follows



I II III



IV V VI VII

I: 4-Fluoroaniline; II: 4-Fluoroacetanilide; III: 2-Nitro-4-fluoroacetanilide; IV: 2-Nitro-4-fluoroaniline; V: Diazonium salt; VI: 6-Chloro-3-fluoronitrobenzene; VII: 6-Chloro-3-fluoroaniline.

4-Fluoroaniline (11.1 g, 0.01 mol) was treated with acetic anhydride (14 cm^3) to give 4-fluoroacetanilide which was dissolved in glacial acetic acid (20 cm^3). Sulphuric acid (30 cm^3, 18 M) was added, the mixture was cooled in ice and salt and a mixture of nitric acid (4.0 cm^3, 70%) and sulphuric acid (6.0 cm^3, 98%) was added at 0 - 10°C. No exotherm was seen until the mixture reached 18°C; the temperature was held below 25°C by judicial cooling. The mixture was left for 30 min at room temperature and then was thrown onto ice ($\simeq$ 200 g). The resulting yellow brown solid, after filtration, washing with water and drying overnight (28.0 g) was boiled for 30 min with sulphuric acid (70%; made by mixing sulphuric acid (80 cm^3, 98%), with water (60 cm^3)). After pouring onto ice ($\simeq$ 500 g) the solution was diazotised by the cautious addition of sodium nitrite (7.2 g, 0.11 mol) in water (15 cm^3) at $\not>$10°C and the resulting solution was poured onto cuprous chloride (CuCl) (25.0 g) in concentrated hydrochloric acid (150 cm^3) and warmed to decompose the original precipitate.

Steam distillation gave a semisolid oil (10.5 g, 60%) which was recrystallized from ethanol, m.p. 37 - 38°C, lit.[65,66] 37° - 38.5°C; 36°C. 6-Chloro-3-fluoronitrobenzene (5.0 g) was dissolved in ethanol (10 cm^3), warmed and treated with stannous chloride (15.0 g) in concentrated HCl (30 cm^3). The basified reaction mixture was steam distilled to yield 6-chloro-3-fluoroaniline (1.1 g, 27.3%), n_D^{22} = 1.5532. HPLC and GLC were used to check the purity of the compound. ^{19}F n.m.r. spectroscopy was used to confirm the structure which showed a single peak split into seven (δF = -115.1 ppm,

* The distillate was dissolved in ethanol, warmed, treated with $SnCl_2$ in conc. HCl, basified with NaOH and steam distilled.

$^{o}J_{HF}$ = 9.52 Hz; $^{m}J_{HF}$ = 8.78 Hz).
Found; C, 49.31; H, 3.42; N, 10.2; C_6H_5NClF requires C, 49.5; H, 3.46; N, 9.6%.

II.A.2j 4-Chloro-3-fluoroaniline[64]

4-Nitro-2-fluoroacetanilide (3.78 g, 0.019 mol) was suspended in sulphuric acid (20 cm^3, 50%) and boiled gently for 30 min, cooled, poured onto ice ($\simeq$ 70 g) and treated with caution with sodium nitrite (1.0 g) in water (2.0 cm^3) at $\not>$ 10°C, and left with constant stirring at room temperature for 20 min. The completeness of the diazotisation was checked, after dilution of a drop of the mixture with water, by an immediate blue coloration with potassium iodide-starch paper. This solution was poured onto CuCl (3.5 g) in concentrated HCl (21 cm^3) and steam distilled. The distillate was extracted with dichloromethane, dried with anhydrous sodium sulphate, and the solvent was removed under reduced pressure (rotary evaporator) to leave a solid which recrystallized from dilute ethanol to give pure crystals of 4-chloro-3-fluoroaniline (0.23 g) m.p. 60°C, lit.[30,49] m.p. 61°C; 61-62°C. The purity and the structure of the compound was confirmed by using ^{19}F n.m.r. spectroscopy (triplet; δF = -114.3 ppm; $^{o}J_{HF}$ = 9.76 Hz, $^{m}J_{HF}$ = 7.07 Hz). Found; C, 48.71; H, 3.33; N, 9.23; C_6H_5ClFN requires C, 49.5; H, 3.46; N, 9.6%.

II.A.2k 4,6-Dichloro-3-fluoroaniline

3-Fluoroacetanilide (6.25 g, 0.041 mol) dissolved in nitromethane (15 cm^3) was treated dropwise with sulphuryl chloride

(7.0 cm^3, 0.085 mol) in nitromethane (10 cm^3) over a period of 30 min in the presence of concentrated hydrochloric acid (1.0 cm^3, 0.01 mol) and with constant stirring at room temperature, and then stirred further for 48 h. The white precipitate was filtered and recrystallized from dilute ethanol (5.72 g, 63.4%) m.p. 124°C, lit.[30,49] m.p. 126°C, m.p. 124°C. This 4,6-dichloro-3-fluoroacetanilide (5.0 g, 0.023 mol) was heated at 80°C with hydrochloric acid (50 cm^3, 20%) for 60 h. The amine was isolated by extraction with ether, the extract dried with magnesium sulphate, and the solvent was removed (rotary evaporator). The precipitate was recrystallized from dilute ethanol (0.6 g, 15%) m.p. 65°C, lit.[49] 65 - 67°C. HPLC and GLC were used to check the purity of the compound and ^{19}F n.m.r. spectroscopy (δF = -117.6 ppm, $^{o}J_{HF}$ = 9.76 Hz), and micro-analysis were used to confirm the structure of the compound.

Found; C, 40.64; H, 2.29; N, 7.82; $C_6H_4Cl_2FN$ requires C, 40.04; H, 2.24; N, 7.78%.

II.A.21 6-Bromo-3-fluoroaniline[64]

6-Bromo-3-fluoroaniline was prepared by a method analogous to that for the preparation of 6-chloro-3-fluoroaniline but replacing HCl/CuCl with HBr/CuBr. 2-Nitro-4-fluoroacetanilide (8.0 g, 0.04 mol) was dissolved in sulphuric acid (80 cm^3, 70%) heated gently under reflux for 30 min cooled, poured into ice and diazotised with sodium nitrite (5.0 g) in water (20 cm^3) at $\not>$ 10°C. The reaction mixture was maintained at room temperature with stirring for 2 h, then was transferred into a flask containing

CuBr (12.5 g) in hydrobromic acid (70 cm^3, 60%) warmed to decompose the diazonium salt and then steam distilled to give an oil (4.7 g) was separated from the aqueous layer. $SnCl_2$ (12.0 g) was dissolved in concentrated hydrochloric acid (20 cm^3) and poured down the reflux condenser to react with the nitro-compound obtained from the steam distillation (4.0 g). The flask was shaken steadily to ensure thorough mixing and the mixture heated on a boiling water bath for 30 min until the odour of nitroarene was no longer perceptible. The reaction mixture was cooled to room temperature and gradually a solution of sodium hydroxide (50%) was added until the mixture was strongly alkaline. The resulting oil after steam distillation was extracted with dichloromethane, dried over anhydrous sodium sulphate and the solvent was removed by using the rotary evaporator to leave the halogenated aniline (1.63 g). The HPLC and GLC analysis indicated that the product was not pure but contained some 3-fluoroaniline and 6-bromo-3-fluoronitrobenzene. ^{19}F n.m.r. spectroscopy confirmed that the product was a mixture of 6-bromo-3-fluoroaniline (δF = -114.5 ppm (30%)), 6-bromo-3-fluoronitrobenzene (δF = -115.5 ppm (58%) and 3-fluoroaniline (δF = -113.4 ppm, (12%)).

II.A.2m 4-Bromo-3-fluoroaniline[64]

4-Nitro-2-fluoroacetanilide (0.88 g) was converted to 4-nitro-2-fluoroaniline by hydrolysis with sulphuric acid (20 cm^3, 70%) and this was diazotised with caution by the addition of sodium nitrite (0.67 g) in water (5.0 cm^3) at $\not>$ 10°C. The reaction left to stand at room temperature with frequent

stirring for 30 min. The reaction solution was poured onto cuprous bromide (2.5 g) in hydrobromic acid (50 cm^3, 60%), warmed and steam distilled. The bromo-compound was extracted with dichloromethane, dried over anhydrous sodium sulphate and the solvent was removed by the rotary evaporator to leave a solid (0.77 g) m.p. 87 - 90°C. The solid was dissolved in ethanol and treated with $SnCl_2$ (3.0 g) in concentrated hydrochloric acid (20 cm^3), heated for 20 min in a water bath, cooled, basified with sodium hydroxide solution and steam distilled. The distillate was extracted with dichloromethane and dried over anhydrous sodium sulphate. After removing solvent the solid of bromo-fluoroaniline was recrystallized from dilute ethanol (0.3 g, 45%) m.p. 67°C. HPLC and GLC were used to check the purity of the product. ^{19}F n.m.r. spectroscopy was used to confirm the structure (triplet; δF = -107.8 ppm; $^{o}J_{HF}$ = 9.77 Hz; $^{m}J_{HF}$ = 6.84 Hz) as well as micro-analysis. Found; C, 37.94; H, 2.59; N, 7.34; C_6H_5BrFN requires C, 37.92; H, 2.65; N, 7.37%.

II.A.2n <u>2,4,6-Tribromo-3-fluoroaniline</u>

3-Fluoroaniline 2,4,6-Tribromo-3-fluoroaniline

3-Fluoroaniline (6.11 g, 0.055 mol) dissolved in glacial acetic acid (24.5 cm^3) was treated dropwise with caution with bromine (9.5 cm^3, 0.185 mol) in glacial acetic acid (19 cm^3), while the

solution was well stirred by a magnetic stirrer. The reaction mixture was allowed to stand for 1.5 h at room temperature with frequent stirring and was then treated with a solution of sodium metabisulphite to remove the extra bromine, after which the resulting precipitate was filtered, washed with water and recrystallized from methanol (12.8 g, 67%), m.p. 91°C. The purity of the compound was checked by HPLC and GLC. ^{19}F n.m.r. spectroscopy was used to confirm the structure of the product (doublet; δF = -98.0 ppm; $^{m}J_{HF}$ = 7.32 Hz) as well as the micro-analysis. Found; C, 20.83; H, 0.88; N, 3.99; $C_6H_3Br_3NF$ requires C, 20.71; H, 0.87; N, 4.02%.

II.A.2o 2-Bromo-4-fluoroaniline

4-Fluoroaniline (5.5 g, 0.05 mol) in dichloromethane (50 cm^3), was cooled to 0°C and treated dropwise with N-bromosuccinimide (9.0 g, 0.051 mol) in dichloromethane (50 cm^3), the reaction mixture was allowed to stand at 25°C with stirring for 10 min. 2-Bromo-4-fluoroaniline was obtained from the fractional distillation of the reaction mixture (1.4 g, 23%) b.p. 60 - 64°C/0.7 mm Hg, m.p. 23°C, lit.[36] m.p. 22 - 23°C, b.p. 46 - 47°C/0.05 mm Hg. The purity and structure of the compound were checked by using ^{19}F n.m.r. spectroscopy (quartet; δF = -125.6 ppm (91%); $^{o}J_{HF}$ = 7.8 Hz, $^{m}J_{HF}$ = 4.9 Hz), the impurities were identified as 4-fluoroaniline (6%) and 2,6-dibromo-4-fluoroaniline (3%).

II.A.2p 2,6-Dibromo-4-fluoroaniline

A solution of bromine (1.6 cm^3, 0.03 mol) in glacial acetic acid (1.2 cm^3, 0.02 mol) was added dropwise to a solution of 4-fluoroaniline (1.11 g, 0.01 mol) in glacial acetic acid (1.2cm^3,0.02 mol).The mixture was heated on the water bath under reflux for 1 h, allowed to cool to room temperature and the precipitated product was filtered and recrystallized from dilute acetic acid (1.5 g, 56%) m.p. 65°C, lit.[43] 68°C. HPLC and GLC analysis showed this 2,6-dibromo-4-fluoroaniline to be pure; ^{19}F n.m.r. spectroscopy (triplet; δF = -125.1 ppm, $^{o}J_{HF}$ = 7.8 Hz), identified the product.

II.A.2q 2-Chloro-4-fluoroaniline

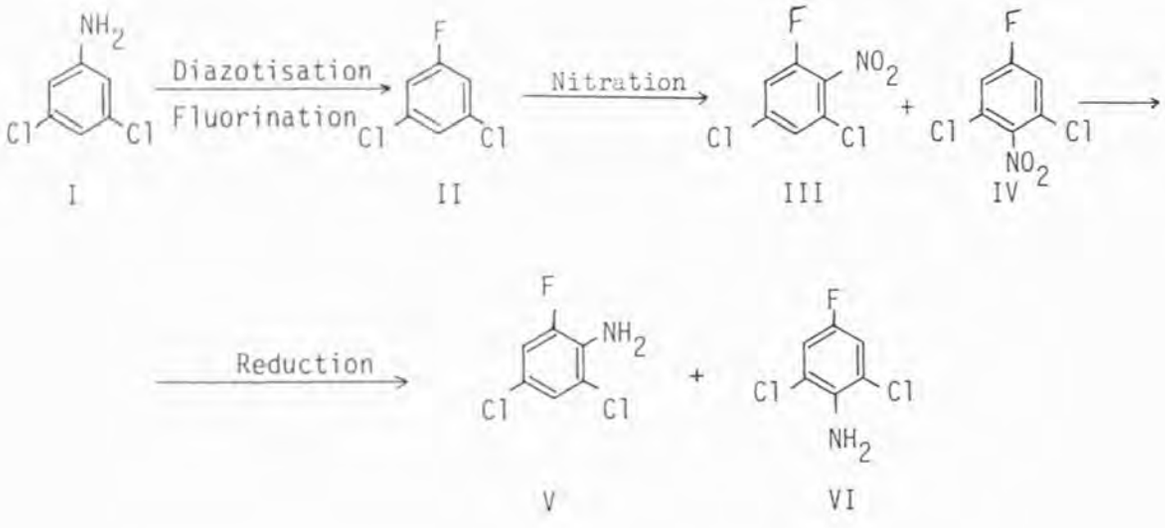
4-Fluoroacetanilide (2.76 g, 0.018 mol) was dissolved in nitromethane (30 cm^3) treated with sulphuryl chloride (3.0 cm^3, 0.036 mol) in nitromethane (20 cm^3) and the reaction mixture heated for 3.5 h at 80°C with constant stirring. The solvent was removed using the rotary evaporator. The residue was dissolved in hot ethanol, treated with charcoal, filtered through sintered glass G4 and recrystallized from dilute ethanol (0.72 g, 18%) m.p. 115°C, lit.[32] 115 - 116°C. This 2-chloro-4-fluoroacetanilide (0.65 g, 0.0035 mol) was treated with hydrochloric acid (3.5 cm^3, 6N) and the mixture was refluxed for 1 h and allowed to stand at room temperature overnight. The reaction mixture solution was treated with sodium hydroxide (4.5 cm^3, 5N) and extracted four times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and the solvent was removed using the

rotary evaporator. The brownish yellow liquid obtained (0.31 g, 62%) was identified by ^{19}F n.m.r. spectroscopy (quartet; δF = -125.6 ppm; $^{o}J_{HF}$ = 7.32 Hz; $^{m}J_{HF}$ = 5.86 Hz) and by micro-analysis.

Found; C, 49.07; H, 3.40; N, 10.55; C_6H_5ClFN requires C, 49.85; H, 3.46; N, 9.69%.

II.A.2r 2,6-Dichloro-4-fluoroaniline[64]

2,6-Dichloro-4-fluoroaniline was prepared from 3,5-dichloroaniline as follows:-



I II III IV V VI

1: 3,5-Dichloroaniline; II: 3,5-Dichlorofluorobenzene; III: 3,5-Dichloro-2-nitrofluorobenzene; IV: 3,5-Dichloro-4-nitrofluorobenzene; V: 4,6-Dichloro-2-fluoroaniline; VI: 2,6-Dichloro-4-fluoroaniline.

3,5-Dichloroaniline (16.2 g, 0.1 mol) was dissolved in a mixture of concentrated hydrochloric acid (40 cm^3) and water (40 cm^3) cooled to -5^oC in a bath of ice and salt, and a solution of sodium nitrite (7.0 g, 0.1 mol) in water (15 cm^3) was added in small portions. A cooled solution of sodium borofluoride (30 g, 0.27 mol) in water (40 cm^3) was added slowly to the diazonium salt solution. After standing for 10 min with frequent stirring, the precipitate was filtered, drained and washed with ice water ($\simeq$ 30 cm^3), methanol (30 cm^3) and ether (30 cm^3); the solid was sucked as free as possible from liquid after each washing. The salt was spread upon absorbent filter paper and dried overnight in air. The dry dichloro-benzenediazonium fluoroborate was heated gently with a small luminous flame at one point near its surface until decomposition began. The cautious heating was continued from time to time until the decomposition appeared complete and no more fumes were evolved when the flask was heated strongly. The distillate was washed with water, and the oil was steam distilled from dilute sodium hydroxide. Redistillation gave 3,5-dichloro-fluorobenzene (10.05 g, 61%) b.p. 160 - 162^oC/760 mm Hg, lit.[43] b.p. 160^oC.

The product 3,5-dichlorofluorobenzene (1.0 g) was dissolved in fuming nitric acid (5.0 cm^3, 95%) at room temperature. When the reaction product was poured into water, it gave a precipitate which was filtered and dried, ^{19}F n.m.r. spectroscopy was used to identify the product, which showed it was a mixture of 3,5-dichloro-4-nitrofluoro-benzene (triplet; δF =-102.4 ppm (62%); $^oJ_{HF}$ = 7.81 Hz), and 3,5-dichloro-2-nitro-fluorobenzene (doublet; δF = -116.2 ppm (38%), $^oJ_{HF}$ = 8.79 Hz).

The mixed nitrocompound was dissolved in ethanol (2 cm^3) and treated with $SnCl_2$ (3.0 g) in concentrated HCl (20 cm^3), heated on a water bath for 20 min, cooled, basified and steam distilled to give the dichlorofluoroaniline (0.65 g) which was extracted with dichloromethane, dried (Na_2SO_4), and the solvent was removed by rotary evaporator to leave an oil. ^{19}F N.m.r. spectroscopy was used to show that the oil was a mixture of 2,6-dichloro-4-fluoroaniline (triplet, δ F = -123.8 ppm, (63%); $^{o}J_{HF}$ = 8.05 Hz, $^{o'}J_{HF}$ = 8.05 Hz),4,6-dichloro-2-fluoroaniline (doublet; δF = -128.4 ppm (36%); $^{o}J_{HF}$ = 8.79 Hz, $^{p}J_{HF}$ = 1.46 Hz) and 3,5-dichloro-4-nitrofluorobenzene (triplet; δ F =-103.2 ppm, (1%); $^{o}J_{HF}$ = 7.3 Hz).

II.A.3 Bromination of Fluorophenols using Potassium Bromate/ Potassium Bromide as Source of Bromine

Throughout this section, bromine (0.01 mol) was obtained by dissolving potassium bromate (0.556 g, 0.0033 mol) in water (25 cm^3), and adding potassium bromide (1.0 g) and then concentrated hydrochloric acid (1.0 cm^3). Other quantities of bromine were obtaining by changing these amounts in proportion.

II.A.3a Bromination of 2-fluorophenol

2-Fluorophenol (1.12 g, 0.01 mol) was suspended in distilled water (50 cm^3) with vigorous stirring and was treated dropwise with bromine (0.01 mol). The reaction product was extracted by shaking with ether (25 cm^3). The extract was dried with anhydrous sodium sulphate and the solvent was removed by rotary evaporator to leave a brownish yellow oil.

In the same way 2-fluorophenol (1.12 g, 0.01 mol) was treated dropwise with bromine (0.02 mol).

The reaction products were analysed by HPLC, GLC and ^{19}F n.m.r. spectroscopy; the results obtained are recorded in Table II.1.

II.A.3b Bromination of 3-fluorophenol

3-Fluorophenol (1.12 g, 0.01 mol), suspended in water (50 cm^3) with stirring, was treated dropwise with bromine (0.01 mol) within a period of 30 min, the reaction mixture remained at room temperature for further 30 min with constant stirring. The product was extracted with ether for three times and the combined extracted were dried with anhydrous sodium sulphate. The solvent was removed by using rotary evaporator.

In another flask 3-fluorophenol was brominated by the same method using two molecular proportions of bromine.

The resultant product in both cases was analysed by using HPLC, GLC and ^{19}F n.m.r. spectroscopy. The results obtained are recorded in Table II.2.

II.A.3c Bromination of 4-fluorophenol

An aqueous solution of 4-fluorophenol (1.12 g, 0.01 mol) was treated with bromine (0.01 mol) in water (25 cm^3) over a period of 1 h. The mixture was extracted with ether and the combined organic layers were dried with anhydrous sodium sulphate.

At the same time 4-fluorophenol (1.12 g, 0.01 mol) in water (50 cm^3) was treated with bromine (0.02 mol). The resultant product was extracted with ether, dried with anhydrous sodium sulphate and the solvent was removed with rotary evaporator.

The product obtained in both cases was analysed by HPLC, GLC and ^{19}F n.m.r. spectroscopy. The results obtained are recorded in Table II.3.

II.A.4 Chlorination of Fluorophenols using Sulphuryl Chloride as Source of Chlorine

II.A.4a Chlorination of 2-fluorophenol

2-Fluorophenol (1.53 g, 0.0136 mol) dissolved in chloroform (15 cm^3) was cooled in ice and treated dropwise with sulphuryl chloride(1.12 cm^3, 0.0136 mol)in chloroform (10 cm^3). The reaction mixture was heated in an oil bath at 74°C for 1 h, and left to cool to room temperature. The solvent was removed under reduced pressure (rotary evaporator).

In the same way 2-fluorophenol (1.4 g, 0.0125 mol) was treated with sulphuryl chloride (2.06 cm^3, 0.025 mol) in a total volume of chloroform of 25 cm^3.

These reaction products were analysed by HPLC, GLC and ^{19}F n.m.r. spectroscopy. The analyses obtained are given in Table II.1.

II.A.4b Chlorination of 3-fluorophenol

Two round-bottomed 100 cm^3 flasks were used for the reaction between 3-fluorophenol and sulphuryl chloride. In the first flask the chlorination of 3-fluorophenol was carried out by treating 3-fluorophenol dropwise with one molecular portion of sulphuryl chloride in chloroform. In the second flask 3-fluorophenol (1.43 g, 0.0128 mol) dissolved in chloroform (15 cm^3) was cooled in an

ice bath and treated with sulphuryl chloride (2.1 cm^3, 0.0256 mol) in chloroform (10 cm^3). The two flasks with their contents were heated under reflux for 45 min in an oil bath at 84°C. They were allowed to cool and the solvent was removed by using rotary evaporator. The products were analysed by using HPLC, GLC and ^{19}F n.m.r. spectroscopy. The results obtained are recorded in Table II.2.

II.A.4c Chlorination of 4-fluorophenol

In a round-bottomed flask, 4-fluorophenol (1.12 g, 0.01 mol) in chloroform (15 cm^3) was treated dropwise with sulphuryl chloride (0.88 cm^3, 0.01 mol) in chloroform (10 cm^3).

In another round-bottomed flask, 4-fluorophenol (1.12 g, 0.01 mol) in chloroform (15 cm^3) was treated dropwise with sulphuryl chloride (1.64 cm^3, 0.02 mol) in chloroform (10 cm^3). The reaction mixtures were maintained under reflux for 7 h. in an oil bath at 74°C. They were cooled and the resultant products were analysed by using HPLC, GLC and ^{19}F n.m.r. spectroscopy. The results are recorded in Table II.3.

II.A.5 Bromination of Fluoroanilines using Potassium Bromate/ Potassium Bromide as Source of Bromine

Throughout this section, bromine (0.01 mol) was obtained by dissolving potassium bromate (0.556 g, 0.0033 mol) in water (25 cm^3) and adding potassium bromide (1.0 g) and then concentrated hydrochloric acid (1.0 cm^3). Other quantities of bromine were obtained by changing these amounts in proportion.

II.A.5a Bromination of 2-fluoroaniline

2-Fluoroaniline (1.11 g, 0.01 mol) suspended in distilled water (50 cm^3) was treated dropwise with bromine (0.01 mol). The reaction product was extracted by shaking with ether (25 cm^3). The organic layer was dried with anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure (rotary evaporator). The resultant reaction mixture was analysed by using HPLC, GLC and ^{19}F n.m.r. spectroscopy. The results obtained are shown in Table II.4.

In the same way, 2-fluoroaniline (1.11 g, 0.01 mol) was treated with bromine (0.02 mol). After work up the reaction product was analysed; HPLC, GLC and ^{19}F n.m.r. spectroscopy; data are shown in Table II.4.

II.A.5b Bromination of 3-fluoroaniline

In a round-bottomed flask, 3-fluoroaniline (1.11 g, 0.01 mol), suspended in distilled water (50 cm^3) was treated with bromine solution (0.01 mol). In another round-bottomed flask, 3-fluoroaniline (1.11 g, 0.01 mol), suspended in distilled water (50 cm^3) was treated with bromine solution (0.02 mol). The brominated product was extracted with ether, the aqueous layer washed with ether, the combined organic layers were dried with anhydrous sodium sulphate and the solvent was removed. The results were obtained from analysing the reaction product by HPLC, GLC and ^{19}F n.m.r. spectroscopy techniques are recorded in Table II.5.

II.A.5c Bromination of 4-fluoroaniline

The bromination of 4-fluoroaniline was carried out in the same way as the bromination of 2-fluoroaniline and 3-fluoroaniline. One product was obtained from the reaction between 4-fluoroaniline (1.11 g, 0.01 mol) with bromine (0.01 mol). The other was obtained from the reaction between 4-fluoroaniline (1.11 g, 0.01 mol) with bromine (0.02 mol).

The results were obtained from using HPLC, GLC and ^{19}F n.m.r. spectroscopy techniques for analysing the reaction products are recorded in Table II.6.

II.A.6 Chlorination of Fluoroaniline using Sulphuryl Chloride as Source of Chlorine

Sulphuryl chloride was used as a source of chlorine in the presence of aluminium chloride as a catalyst:-

$$SO_2Cl_2 \rightleftharpoons SO_2 + Cl_2$$

$$AlCl_3 + SO_2Cl_2 \rightleftharpoons AlCl_3.SO_2 + Cl_2$$

The effect of aluminium chloride is attributed to the formation of aluminium sulphurylchloride $AlCl_3.SO_2$ as an intermediate.[67]

II.A.6a Chlorination of 2-fluoroaniline

1. 2-Fluoroaniline (1.94 g, 0.0175 mol) was dissolved in dry diethyl ether (20 cm^3) and treated dropwise with sulphuryl chloride (1.5 cm^3, 0.0183 mol) in dry diethyl ether (30 cm^3) in the

presence of aluminium chloride (2.33 g) as a catalyst. After adding the calculated amount of sulphuryl chloride, the reaction mixture was stirred for 45 min at room temperature.

2. 2-Fluoroaniline (1.18 g, 0.0106 mol) was dissolved in dry diethyl ether (20 cm^3) with stirring and treated dropwise with sulphuryl chloride (1.7 cm^3, 0.0208 mol) dissolved in dry diethyl ether (30 cm^3) in the presence of aluminium chloride (2.66 g) as catalyst. The reaction mixture was maintained with constant stirring for 45 min at room temperature.

The reaction mixtures obtained from 1. and 2. were each treated with potassium hydrogen carbonate until the medium became alkaline. The organic and aqueous layers were separated. The aqueous layer was washed with dry diethyl ether twice and the organic layers were combined and dried with magnesium sulphate. The solvent was removed under reduced pressure (rotary evaporator).

The resultant reaction mixtures were analysed by using HPLC, GLC and ^{19}F n.m.r. spectroscopy and the results obtained are recorded in Table II.4.

II.A.6b Chlorination of 3-fluoroaniline

3-Fluoroaniline (0.9 g, 0.008 mol) dissolved in dry diethyl ether (20 cm^3) was treated dropwise with constant stirring with sulphuryl chloride (0.67 cm^3, 0.008 mol) in dry diethyl ether (30 cm^3) in the presence of aluminium chloride (1.09 g) as catalyst. The reaction mixture was allowed to stand at room temperature for 45 min with constant stirring. Afterwards, a solution of potassium

hydrogen carbonate was added to the reaction mixture until the medium became alkaline. The organic layer was separated and the aqueous layer was washed with ether, the combined organic layers were dried with dry magnesium sulphate. The solvent was removed by using rotary evaporator.

The components of the resultant reaction mixture were separated chromatographically by HPLC and by GLC. They could also be distinguished by ^{19}F n.m.r. spectroscopy. The results obtained are shown in Table II.5.

In the same way the reaction was carried out between 3-fluoroaniline (1.11 g, 0.01 mol) and sulphuryl chloride (1.64 cm^3, 0.02 mol). By the same technique the resultant product was identified and the results are recorded in Table II.5.

II.A.6c Chlorination of 4-fluoroaniline

Chlorination of 4-fluoroaniline using sulphuryl chloride was carried out in the same way as the chlorination of 2-fluoroaniline and 3-fluoroaniline.

HPLC, GLC and ^{19}F n.m.r. spectroscopy data, shown in Table II.6, refer to the components in the mixtures obtained from the reaction of 4-fluoroaniline (1.49 g, 0.0134 mol) with sulphuryl chloride (1.1 cm^3, 0.0134 mol), and the reaction product of 4-fluoroaniline (1.6 g, 0.0144 mol) with sulphuryl chloride (2.36 cm^3, 0.0288 mol) in the presence of $AlCl_3$ as catalyst.

II.B Analytical Measurements and Working Procedure

II.B.1 ^{19}F Nuclear Magnetic Resonance Spectroscopy (^{19}F n.m.r. Spectroscopy).

It is fortunate that the fluorine-19-isotope has 100% natural abundance and like $^{1}H_{1}$ has spin $\frac{1}{2}$, but the signal response for a given number of nuclei is however, about 20% weaker than for the same number of hydrogen nuclei. The range of fluorine-19-chemical shifts is many times greater than the range of proton chemical shifts. The larger range of the ^{19}F chemical shifts is attributed to the large paramagnetic contributions to the shielding constants arising from the fluorine atoms.[68] Trichlorofluoromethane has been used as reference standard because it has the advantage of being volatile and the fluorine resonances occurs at low field, well away from other ^{19}F resonance signals of fluorocarbons.[68]

The ^{19}F n.m.r. spectra of organic fluorine compounds are characterized by large chemical shift and strong spin-spin interaction between ^{1}H, ^{19}F and ^{19}F, ^{19}F nuclei. The relative magnitude of the proton-fluorine coupling constants in partially fluorinated aromatics are[69]:

	ortho H-F	6 to 10 Hz
	meta H-F	6 to 8 Hz
	para H-F	~2 Hz
elsewhere[68]	ortho H-F	8 to 12 Hz
	meta H-F	5 to 8 Hz
	para H-F	1.5 to 2.5 Hz

In fluorinated aromatics extensive coupling of fluorine atoms to the other fluorine substituents also occurs although the magnitude

of the coupling constants tends to be rather variable. Representative values of F-F aromatic coupling constants are [69] :

ortho F-F	20 Hz
meta F-F	-20 to +20 Hz
para F-F	5 to 18 Hz

^{19}F N.m.r. spectroscopy was used to identify the structures of the halogenated products of fluorophenols and fluoroanilines. In this work a Jeol FX-90Q spectrometer operating at 84.26 MHz was used and trichlorofluoromethane ($CFCl_3$) was used as internal standard for all samples.

II.B.2 Chromatography

Chromatography is a method of separation of the components of a mixture which depends upon the relative affinities of the various solute molecules for the stationary phase and the mobile phase, whatever they may be. The chromatographic methods are classified according to the type of stationary and mobile phases used and the form in which they are present, and by the different mechanisms which control separation, e.g. Thin Layer Chromatography (TLC), Gas Chromatography (GC) which its sub-divisions Gas-Liquid Chromatography (GLC) and Gas-Solid Chromatography (GSC), Liquid-Solid (Adsorption) Chromatography (LSC) and Liquid-Liquid (Partition) Chromatography (LLC). The modernization and the development of liquid chromatography is called High-Performance Liquid Chromatography (HPLC).

In this work HPLC and GLC were used to investigate the halogenated products of fluorophenols and fluoroanilines.

(a) HPLC: A Varian model 5000 Liquid Chromatography machine was used to separate the resultant reaction mixtures. Halogenated products of fluorophenols were separated by using Partisil 10-ODS Column, degassed acetonitrile (40%)/deionised water (60%) as eluent, flow rate 1 cm^3/min., UV detector at wavelength 254 nm, the appropriate dilutions were made from the stock solutions of samples in methanol, the injection volume was 10 μdm^3 and the temperature was 25.0^oC. All sample solutions were filtered before use.

Halogenated products of fluoroanilines were separated by the same way using a Spherisorb S5-ODS column, and methanol (70%)/ deionised water (30%) as eluent.

(b) GLC: A Pye Unicam series 104 Chromatography machine was used to analyse the halogenated products of fluorophenols and fluoroanilines qualitatively and quantitatively. A Carbowax 1500 (20%),Gas Chrom P column was used with a flame ionisation detector, and nitrogen gas as carrier gas at flow rate 40 cm^3/min.

The appropriate dilutions were made from the stock solutions of samples in methanol, the injection volume was 2μ dm^3. The separation of some reaction products were carried out at 190^oC and the others were carried out at 150^oC.

Table II.1

Analytical Results of Halogenated Products of 2-Fluorophenol

Compound	HPLC analysis at 25°C		GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
					Chemical shift			
	Retention time (min)	Area (cm^2)	Retention time (min)	Yield (%)	Expected[+] (ppm)	Found (ppm)	Yield (%)	
2-Fluorophenol	4.5	-	1.3	100	-138.10	-141.5	100	2-Fluorophenol.
6-Bromo-2-fluorophenol	5.8	-	3.3	69	-138.78	-134.0	71	6-Bromo-2-fluorophenol.
4-Bromo-2-fluorophenol	6.7	-	5.0	100	-138.78	-137.8	100	4-Bromo-2-fluorophenol.
4,6-Dibromo-2-fluoro-phenol	8.2	-	11.0	100	-137.04	-131.4	100	4,6-Dibromo-2-fluoro-phenol.
2-Fluorophenol and	4.5	0.93	1.3	12	-138.10	-141.0	12	2-Fluorophenol.
Br_2 (BrO_3^-/Br^-)	5.8	0.74	3.4	9	-138.78	-133.7	8	6-Bromo-2-fluorophenol.
(1:1; 0.01 mol)	6.5	5.69	5.0	66	-138.78	-137.2	65	4-Bromo-2-fluorophenol.
	8.3	4.00	11.0	13	-137.04	-131.1	15	4,6-Dibromo-2-fluorophenol.
2-Fluorophenol and	4.5	0.42	1.3	8	-138.10	-141.7	6	2-Fluorophenol.
Br_2 (BrO_3^-/Br^-)	5.8	0.32	3.4	6	-138.78	-134.3	7	6-Bromo-2-fluorophenol.
(0.01 mol phenol,	6.5	3.75	4.7	63	-138.78	-138.0	64	4-Bromo-2-fluorophenol.
0.02 mol Br_2)	8.4	4.51	11.0	23	-137.04	-131.6	23	4,6-Dibromo-2-fluorophenol.
2-Fluorophenol and	5.8*	2.96	1.4	23	-138.10	-141.5	22	2-Fluorophenol.
SO_2Cl_2 (1:1; 0.01 mol)	7.9	2.54	2.5	23	-139.06	-134.8	24	6-Chloro-2-fluorophenol.
	9.6	3.75	3.4	54	-139.06	-137.7	54	4-Chloro-2-fluorophenol.
2-Fluorophenol and	5.8*	1.32	1.4	15	-138.10	-141.3	8	2-Fluorophenol.
SO_2Cl_2 (0.01 mol phenol,	8.0	3.13	2.5	29	-139.06	-134.9	31	6-Chloro-2-fluorophenol.
0.02 mol SO_2Cl_2)	9.7	4.46	3.5	56	-139.06	-137.8	61	4-Chloro-2-fluorophenol.

[+] Appendix I.

* Eluent of 30% Acetonitrile/de-ionised water.

Table II.2

Analytical Results of Halogenated Products of 3-Fluorophenol

Compound	HPLC analysis at 25°C		GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
					Chemical shift		Yield (%)	
	Retention time (min)	Area (cm^2)	Retention time (min)	Yield (%)	Expected+ (ppm)	Found (ppm)		
3-Fluorophenol	4.7	-	3.1	100	-111.57	-112.3	100	3-Fluorophenol.
4,6-Dibromo-3-fluoro-phenol	9.3	-	9.7	100	-107.76	-105.6	100	4,6-Dibromo-3-fluoro-phenol.
2,4,6-Tribromo-3-fluoro-phenol.	3.8	-	-	-	-100.69	-96.6	100	2,4,6-Tribromo-3-fluoro-phenol.
3-Fluorophenol and	4.9	0.82	3.1	23	-111.57	112.3	83	3-Fluorophenol.
Br_2 (1:1; 0.01 mol)	6.4	2.10	2.4	23	-114.83			6-Bromo-3-fluorophenol.
	6.8	0.85	17.3	11	-105.03	105.7	17	4-Bromo-3-fluorophenol.
	9.0	0.34	9.6	3	-107.76			4,6-Dibromo-3-fluorophenol.
3-Fluorophenol and	4.8	1.05	3.3	29	-111.57	-112.0	48	3-Fluorophenol.
Br_2 (BrO_3^-/Br^-)	6.3	1.95	2.4	33	-114.83	-112.2		6-Bromo-3-fluorophenol.
(1:1; 0.01 mol)	6.8	1.45	17.2	32	-105.03	-105.5		4-Bromo-3-fluorophenol.
	9.2	0.75	9.7	6	-107.76	-105.8	50	4,6-Dibromo-3-fluorophenol.
	-	-	-	-	-100.69	-96.8	2	2,4,6-Tribromo-3-fluoro-phenol.
3-Fluorophenol and	4.9	1.35	3.1	25	-111.57	-112.0	22	3-Fluorophenol.
Br_2 (BrO_3^-/Br^-)	6.3	2.60	2.4	37	-114.83	-112.2	35	6-Bromo-3-fluorophenol.
(0.01 mol phenol;	6.7	1.60	17.2	32	-105.03	-105.4	34	4-Bromo-3-fluorophenol.
0.02 mol Br_2)	9.0	1.20	9.9	6	-107.76	-105.6	7	4,6-Dibromo-3-fluorophenol.
	3.8	5.75	-	-	-100.69	-96.8	2	2,4,6-Tribromo-3-fluoro-phenol.
3-Fluorophenol and	8.7*	3.22	2.7	6	-111.57	-112.0	15	3-Fluorophenol.
SO_2Cl_2 (1:1; 0.01 mol)	14.5	9.14	2.1	76	-115.40	-113.5	60	6-Chloro-3-fluorophenol.
	19.2	2.43	4.4	18	-113.28	-114.9	22	4-Chloro-3-fluorophenol.
3-Fluorophenol and	5.9	3.37	2.1	63	-115.40	-113.0	63	6-Chloro-3-fluorophenol.
SO_2Cl_2 (0.01 mol phenol,	8.2	1.97	4.4	37	-113.28	-114.7	37	4-Chloro-3-fluorophenol.
0.02 SO_2Cl_2)								

+ Appendix I.

* Eluent of 20% Acetonitrile/de-ionised water.

Table II.3

Analytical Results of Halogenated Products of 4-Fluorophenol

Compound	HPLC analysis at 25°C		GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
					Chemical shift		Yield (%)	
	Retention time (min)	Yield (%)	Retention time (min)	Yield (%)	Expected* (ppm)	Found (ppm)		
4-Fluorophenol	4.7	100	3.5	100	-123.54	-124.5	100	4-Fluorophenol.
2-Bromo-4-fluoro-phenol	6.1	100	2.3	100	-121.68	-122.2	100	2-Bromo-4-fluorophenol.
2,6-Dibromo-4-fluoro-phenol	7.2	100	5.9	100	-119.94	-120.6	100	2,6-Dibromo-4-fluorophenol.
4-Fluorophenol and	4.6	14	3.3	16	-123.54	-124.2	15	4-Fluorophenol.
Br_2 (BrO_3^-/Br^-)	5.9	69	2.5	69	-121.68	-122.0	69	2-Bromo-4-fluorophenol.
(1:1; 0.01 mol)	7.2	17	5.9	15	-119.94	-120.7	16	2,6-Dibromo-4-fluorophenol.
4-Fluorophenol and	4.6	16	3.2	19	-123.54	-124.1	24	4-Fluorophenol.
Br_2(BrO_3^-/Br^-)	6.0	59	2.4	55	-121.68	-122.0	54	2-Bromo-4-fluorophenol.
(0.01 mol phenol, 0.02 mol Br_2)	7.4	25	5.9	26	-119.94	-120.6	22	2,6-Dibromo-4-fluorophenol.
4-Fluorophenol and	4.7	-	3.5	28	-123.54	-124.4	27	4-Fluorophenol.
SO_2Cl_2 (1:1; 0.01 mol)	5.9	-	1.9	72	-121.96	-122.2	73	2-Chloro-4-fluorophenol.
4-Fluorophenol and SO_2Cl_2 (0.01 mol phenol, 0.02 mol SO_2Cl_2)	5.8	100	1.9	100	-121.96	-122.9	100	2-Chloro-4-fluorophenol.

* Appendix I.

Table II.4

Analytical Results of Halogenated Products of 2-Fluoroaniline

Compound	HPLC analysis at 25°C	GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
	Retention time (min)	Retention time (min)	Yield (%)	Chemical shift Expected* (ppm)	Chemical shift Found (ppm)	Yield (%)	
2-Fluoroaniline	4.1	1.0	100	-136.20	-135.9	100	2-Fluoroaniline.
4-Bromo-2-fluoro-aniline	5.9	3.2	100	-133.08	-132.6	100	4-Bromo-2-fluoroaniline.
6-Bromo-2-fluoro-aniline	5.9	1.6	95	-133.08	-131.1	95	6-Bromo-2-fluoroaniline.
2-Fluoroaniline and	4.1	1.0	50	-136.20	-135.6	48	2-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	5.9	1.6	2	-133.08	-130.6	2	6-Bromo-2-fluoroaniline.
(1:1; 0.01 mol)	5.9	3.2	7	-133.08	-132.5	9	4-Bromo-2-fluoroaniline.
	10.4	4.3	41	-131.34	-128.4	41	4,6-Dibromo-2-fluoroaniline.
2-Fluoroaniline and	4.1	1.0	67	-136.20	-135.4	65	2-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	5.9	1.6	2	-133.08	-130.4	2	6-Bromo-2-fluoroaniline.
(0.01 mol phenol,	5.9	3.2	8	-133.08	-132.3	9	4-Bromo-2-fluoroaniline.
0.02 mol Br_2)	10.4	4.4	23	-131.34	-128.2	24	4,6-Dibromo-2-fluoroaniline.
6-Chloro-2-fluoro-aniline	5.4	2.0**	100	-133.36	-132.0	100	6-Chloro-2-fluoroaniline.
4-Chloro-2-fluoroaniline	5.4	5.0**	100	-133.36	-132.8	100	4-Chloro-2-fluoroaniline.
4,6-Dichloro-2-fluoro-aniline.	8.5	4.4**	100	-131.02	-130.0	100	4,6-Dichloro-2-fluoroaniline.
2-Fluoroaniline and	4.1	1.7**	42	-136.20	-135.8	40	2-Fluoroaniline.
SO_2Cl_2 (1:1; 0.01 mol)	5.4	2.1	3				6-Chloro-2-fluoroaniline.
	5.4	5.2	34	-133.36	-133.0	42	4-Chloro-2-fluoroaniline.
	8.5	4.6	21	-131.02	-129.9	18	4,6-Dichloro-2-fluoroaniline.
2-Fluoroaniline and	4.1	1.6**	45	-136.20	-135.8	42	2-Fluoroaniline.
SO_2Cl_2 (0.01 mol	5.4	2.0	3				6-Chloro-2-fluoroaniline.
phenol, 0.02 mol	5.4	5.0	37	-133.36	-132.9	43	4-Chloro-2-fluoroaniline.
SO_2Cl_2)	8.5	4.4	15	-131.02	-129.9	15	4,6-Dichloro-2-fluoroaniline.

* Appendix I

** GLC analysis at 150°C.

Table II.5

Analytical Results of Halogenated Products of 3-Fluoroaniline

Compound	HPLC analysis at 25°C	GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
	Retention time (min)	Retention time (min)	Yield (%)	Chemical shift Expected* (ppm)	Chemical shift Found (ppm)	Yield (%)	
3-Fluoroaniline	5.2	1.2	100	-113.65	-113.6	100	3-Fluoroaniline.
6-Bromo-3-fluoroaniline	4.0	2.7	27	-116.33	-114.6	30	6-Bromo-3-fluoroaniline.
4-Bromo-3-fluoroaniline	8.5	7.1	95	-106.53	-107.8	93	4-Bromo-3-fluoroaniline.
2,4,6-Tribromo-3-fluoroaniline	17.8	14.5	100	-102.19	-98.0	100	2,4,6-Tribromo-3-fluoro-aniline.
3-Fluoroaniline and	5.2	1.5	78	-113.65	-113.2	78	3-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	4.0	3.0	1	-	-	-	6-Bromo-3-fluoroaniline.
(1:1; 0.01 mol)	5.7	4.5	1	-106.33	-105.9	1	2-Bromo-3-fluoroaniline.
	8.4	7.5	1	-106.53	-107.8	2	4-Bromo-3-fluoroaniline.
	9.5	12.6	7	-109.26	-108.9	8	4,6-Dibromo-3-fluoroaniline.
	17.6	14.8	12	-102.19	-98.2	11	2,4,6-Tribromo-3-fluoro-aniline.
3-Fluoroaniline and	5.2	1.4	75	-113.65	-113.6	74	3-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	4.0	3.0	1	-116.33	-114.7	2	6-Bromo-3-fluoroaniline.
(0.01 mol phenol,	5.7	4.5	1	-106.53	-106.0	1	2-Bromo-3-fluoroaniline.
0.02 mol Br_2)	8.4	7.4	2	-106.53	-107.8	3	4-Bromo-3-fluoroaniline.
	9.6	12.5	8	-109.26	-109.0	9	4,6-Dibromo-3-fluoroaniline.
	17.6	14.8	13	-102.19	-98.1	11	2,4,6-Tribromo-3-fluoroaniline.
6-Chloro-3-fluoroaniline	6.7	1.6	100	-116.90	-115.1	100	6-Chloro-3-fluoroaniline.
4-Chloro-3-fluoroaniline	14.5	3.7	75	-114.78	-115.8	84	4-Chloro-3-fluoroaniline.
4,6-Dichloro-3-fluoro-aniline	9.8	3.9	100	-118.08	-117.6	100	4,6-Dichloro-3-fluoroaniline.
3-Fluoroaniline and	5.1	1.1	40	-113.64	-113.6	41	3-Fluoroaniline.
SO_2Cl_2 (1:1; 0.01 mol)	6.9	1.5	27	-116.90	-115.8	23	6-Chloro-3-fluoroaniline.
	14.1	3.4	22	-114.78	-115.2	29	4-Chloro-3-fluoroaniline.
	9.9	3.9	11	-118.08	-117.5	7	4,6-Dichloro-3-fluoroaniline.
3-Fluoroaniline and	5.2	1.1	47	-113.64	-113.6	44	3-Fluoroaniline.
SO_2Cl_2 (0.01 mol phenol,	6.9	1.5	8	-116.90	-115.9	2	6-Chloro-3-fluoroaniline.
0.02 mol SO_2Cl_2)	14.3	3.4	26	-114.78	-115.8	37	4-Chloro-3-fluoroaniline.
	10.0	3.9	19	-118.08	-117.4	17	4,6-Dichloro-3-fluoroaniline.

* Appendix I.

Table II.6

Analytical Results of Halogenated Products of 4-Fluoroaniline

Compound	HPLC analysis at 25°C		GLC analysis at 190°C		^{19}F n.m.r. spectroscopy			Comments
					Chemical shift			
	Retention time (min)	Yield (%)	Retention time (min)	Yield (%)	Expected [+] (ppm)	Found (ppm)	Yield (%)	
4-Fluoroaniline	4.2	100	1.4	100	-127.12	-127.3	100	4-Fluoroaniline.
2-Bromo-4-fluoroaniline	5.8	-	2.6	-	-124.95	-125.6	91	2-Bromo-4-fluoroaniline.
2,6-Dibromo-4-fluoro-aniline	9.9	100	3.6	100	-122.59	-125.1	100	2,6-Dibromo-4-fluoro-aniline.
4-Fluoroaniline and	4.0	76	1.3	77	-127.12	-127.1	78	4-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	5.7	7	2.6	5	-124.52	-125.6	5	2-Bromo-4-fluoroaniline.
(1:1; 0.01 mol)	9.6	18	3.3	18	-122.78	-124.9	17	2,6-Dibromo-4-fluoro-aniline.
4-Fluoroaniline and	4.0	71	1.3	72	-127.12	-127.1	72	4-Fluoroaniline.
$Br_2(BrO_3^-/Br^-)$	5.7	8	2.6	7	-124.52	-125.5	7	2-Bromo-4-fluoroaniline.
(0.01 mol phenol, 0.02 mol Br_2)	9.8	21	3.3	21	-122.78	-124.8	21	2,6-Dibromo-4-fluoro-aniline.
2-Chloro-4-fluoroaniline	5.2	100	4.0**	100	-125.30	-125.6	100	2-Chloro-4-fluoroaniline.
4-Fluoroaniline	4.2	100	2.7**	100	-127.12	-127.3	100	4-Fluoroaniline.
2,6-Dichloro-4-fluoro-aniline	7.7	-	3.3**	-	-123.29	-123.8	63	2,6-Dichloro-4-fluoro-aniline.
4-Fluoroaniline and	4.0	-	2.7**	63	-127.31	-127.1	63	4-Fluoroaniline.
SO_2Cl_2(1:1; 0.01 mol)	5.2	-	4.0	29	-124.80	-125.7	28	2-Chloro-4-fluoroaniline.
	7.7	-	3.4	8	-122.64	-124.3	9	2,6-Dichloro-4-fluoro-aniline.
4-Fluoroaniline and	4.0	-	2.7**	63	-127.31	-127.1	63	4-Fluoroaniline.
SO_2Cl_2 (0.01 mol phenol,	5.2	-	4.1	31	-124.80	-125.7	28	2-Chloro-4-fluoroaniline.
0.02 mol SO_2Cl_2)	7.7	-	3.4	6	-122.64	-124.4	9	2,6-Dichloro-4-fluoro-aniline.

[+] Appendix I.

** GLC analysis at 150°C.

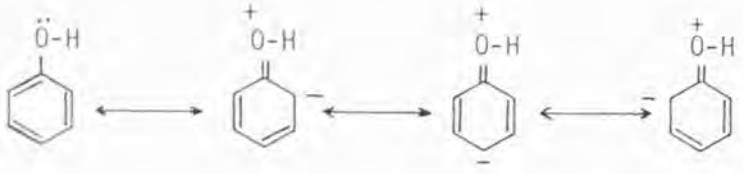
CHAPTER III

III: DISCUSSION OF THE RESULTS

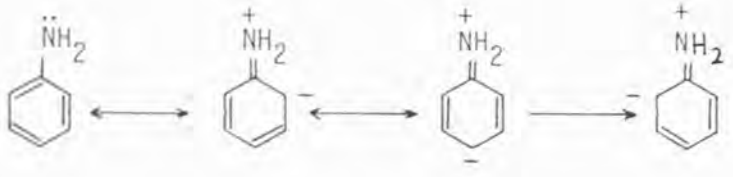
III. DISCUSSION OF THE RESULTS

The hydroxyl group in phenols and the amino group in anilines are o- and p- directing groups:[70,71]

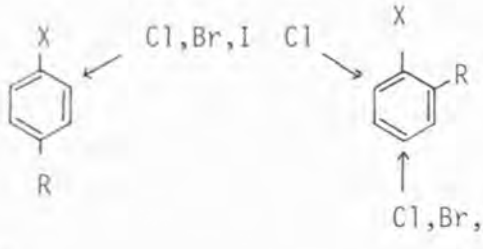
Phenol



Aniline



In the case of halogenation of disubstituted benzenes the orientation can be shown as:[72]



X = NH_2, OH, NHAc

R = Halogen

That is what was noticed throughout the results obtained from the bromination and chlorination of fluorophenols and fluoroanilines.

The bromination of fluorophenols and fluoroanilines was carried out using bromine solution produced from an acidified mixture of potassium bromate (BrO_3^-) and potassium bromide (Br^-). The solution was acidified with concentrated hydrochloric acid.

$$BrO_3^- + 5Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$$

Aqueous bromine was used because bromine dissolved in water is more reactive than in the common non-aqueous solvents. Under this condition poly-substitution often occurs.[72]

The chlorination of fluorophenols with sulphuryl chloride takes place at sites o- and p- relative to the hydroxyl group.

$$SO_2Cl_2 \rightleftharpoons SO_2 + Cl_2$$

For the halogenation of fluoroanilineswith sulphuryl chloride, no chlorination happened in the aromatic ring unless aluminium chloride was used as a catalyst. Using aluminium chloride as a catalyst with sulphuryl chloride as chlorinating agent is well known.[67,73] The anhydrous aluminium chloride reacted with sulphuryl chloride to generate chlorine; it was reported[67] that aluminium sulphurylchloride was an intermediate and this was confirmed by passing a current of carbon dioxide through a flask containing sulphuryl chloride only. Equal proportions of Cl_2 and SO_2 were found, while when an $AlCl_3$ catalyst was used, an excess of Cl_2 was evolved.

$$SO_2Cl_2 + AlCl_3 \rightleftharpoons AlCl_3 \cdot SO_2 + Cl_2$$

The catalyst can be generated by:

$$AlCl_3.SO_2 \rightleftharpoons AlCl_3 + SO_2$$

Throughout this work the halogenated products of fluorophenols and fluoroanilines were analyzed by three techniques, ^{19}F n.m.r. spectroscopy, GLC and HPLC.

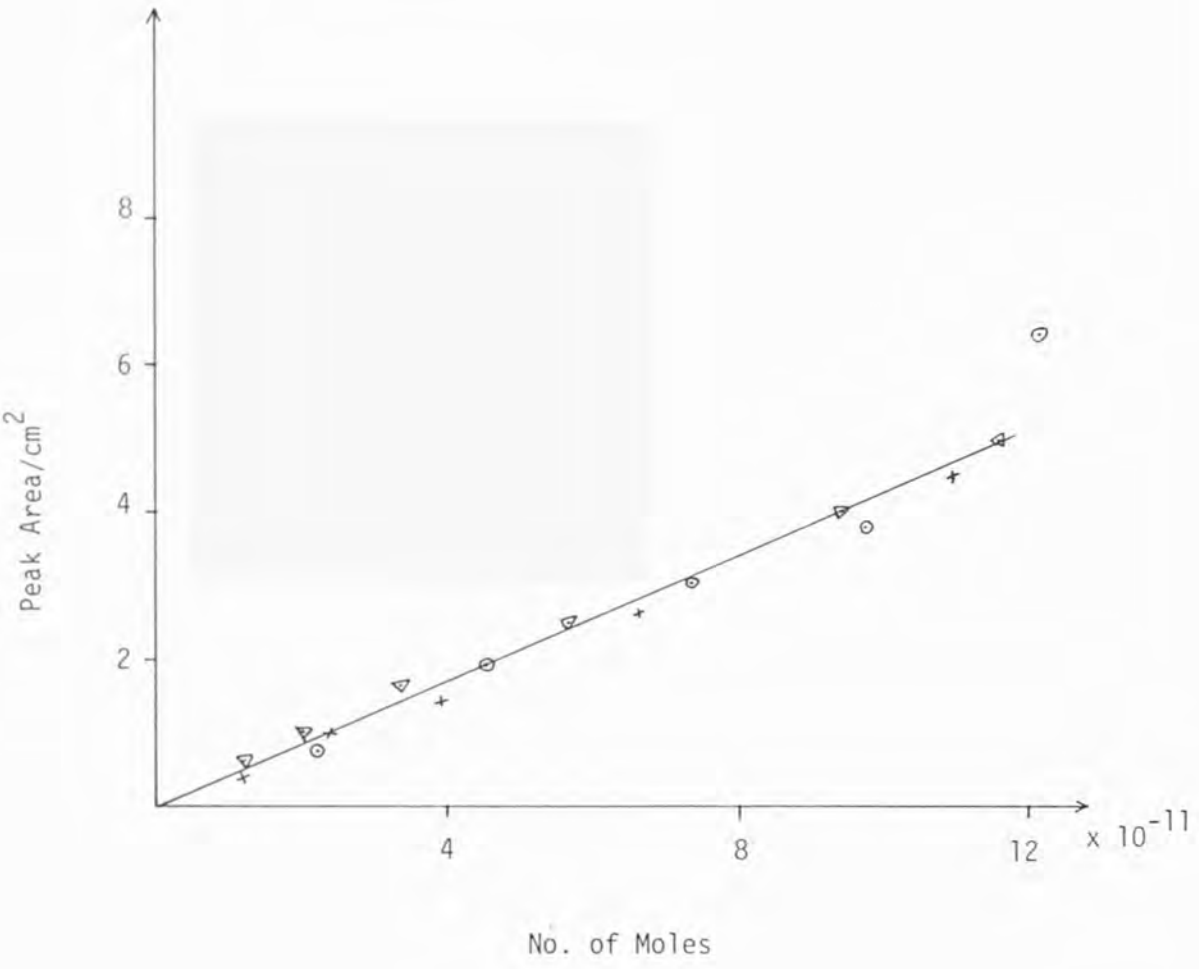
GLC was used for the separation of the components of the reaction mixtures and because it was found that the detector response for all halogenated phenols and anilines were the same (Fig. III.1), the peak areas could be related to the concentrations of the components. A Lab Data Control 308 computing integrator was used for measuring all peak areas. This technique was used to provide quantitative analysis. HPLC was often used qualitatively, separating the components at specific retention times under certain conditions, because the detector response was different for all species and because not all the reference compounds were in a highly pure state.

In a few reaction mixtures, however, HPLC was used to give quantitative analysis, such as in the brominated products of 4-fluorophenol and 4-fluoroaniline.

^{19}F n.m.r. spectroscopy was found helpful in the investigation and identification of the reaction products and at the same time it was used for quantitative analysis.

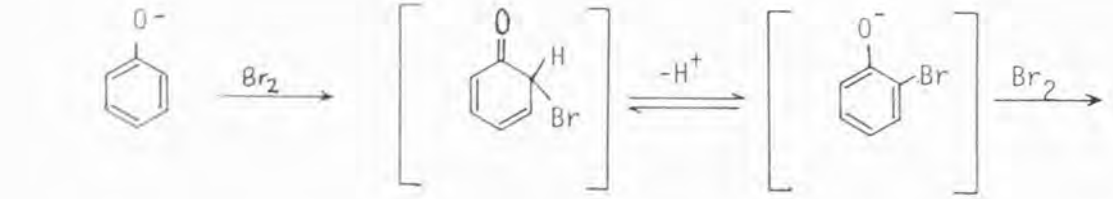
Fig. III.1 GLC Chromatogram

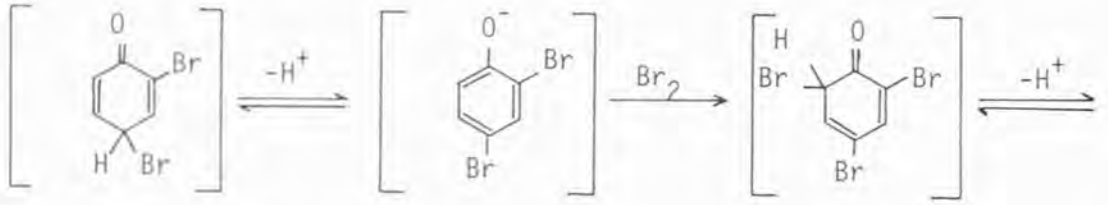
△ 2-Fluorophenol
⊙ 4-Bromo-2-fluorophenol
x 4,6-Dibromo-2-fluorophenol

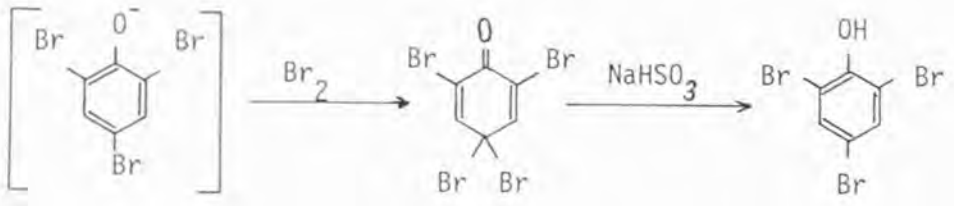


III.A Fluorophenols

The bromination of phenol with aqueous bromine is well known:-[71]







Precipitates

III.A.1 2-Fluorophenol

III.A.1a Bromination of 2-fluorophenol

Bromine was used in different proportions for brominating 2-fluorophenol preparatively, where some of the brominated 2-fluorophenols were obtained and could be used as reference compounds for analysing the reaction mixtures of 2-fluorophenol with bromine produced from acidified mixture of potassium bromate and potassium bromide. These compounds are 4-bromo-2-fluorophenol (δF = -137.8 ppm), 6-bromo-2-fluorophenol (δF = -134.0 ppm) and 4,6-dibromo-2-fluorophenol (δF = -131.4 ppm).

Attack on 2-fluorophenol by an equimolecular amount of bromine (BrO_3^-/Br^-) appeared to give a mixture of 2-fluorophenol (I) (sextet; F = -141.0 ppm), 4-bromo-2-fluorophenol (II) (triplet; δF = -137.2 ppm), 6-bromo-2-fluorophenol (III) (quartet; δF = -133.7 ppm) and 4,6-dibromo-2-fluorophenol (IV) (doublet; δF = -131.1 ppm). This reaction mixture was analysed by HPLC technique which helped in the identification of the components according to their retention times, by comparison with the retention times of the reference compounds; 4.5 min (I), 5.8 min (III) 6.5 min (II) and 8.3 min (IV). ^{19}F n.m.r. spectroscopy and GLC were used for analysing this reaction product qualitatively and quantitatively. ^{19}F N.m.r. spectroscopy suggested the presence of 12% (I), 65% (II), 8% (III) and 15% (IV) which did agree with the analysis obtained from GLC; 12% (I), 66% (II), 9% (III) and 13% (IV).

When two molecular proportions of bromine (BrO_3^-/Br^-) were used, HPLC showed it was a mixture of (I), (II), (III) and (IV). GLC and ^{19}F n.m.r. spectroscopy gave the percentage of each component in good agreement, i.e. 8% (I), 63% (II), 6% (III), 23% (IV); and 6% (I), 64% (II), 7% (III) and 23% (IV) respectively.

III.A.1b Chlorination of 2-fluorophenol

Chlorination of 2-fluorophenol using an equimolecular amount of SO_2Cl_2 as a source of chlorine appeared to give a mixture of three components. ^{19}F N.m.r. spectroscopy was used to identify this mixture which showed 22% of unreacted 2-fluorophenol (I) (δF = -141.5 ppm) , 54% of 4-chloro-2-fluorophenol (II) (δF = -137.7 ppm) and 24% of 6-chloro-2-fluorophenol (III) (δF = -134.8 ppm). This analysis did agree with the quantitative analysis of the same mixture with GLC which showed 23% (I), 54 % (II), and 23% (III). HPLC separated these components at retention times, 5.8 min. (I), 7.9 min (III) and 9.6 min. (II), eluent acetonitrile (30%) and de-ionised water (70 %).

The same components were obtained when two equimolecular proportions of SO_2Cl_2 were used for chlorination of 2-fluorophenol. HPLC separation showed the retention times 5.8 min. (I), 8.0 min (III) and 9.7 min. (II). GLC and ^{19}F n.m.r. spectroscopy analysis showed slight differences in the percentage of these components. GLC suggested the compositions 15% (I), 29% (III) and 56% (II), and ^{19}F n.m.r. showed 8% (I), 31% (III) and 61% (II).

Generally, the results obtained showed that in the bromination the product contained mono- and dibromo-derivatives but in chlorination the product was mainly the monochlorofluorophenol which means that when monobromo- takes place causing apparent activation in the ring which helps form dibromo-fluorophenol. This may occur because of a significant extent of reaction through the phenoxide ion, since this is even more reactive than the phenol is towards electrophiles and since di-halogenophenols are better acids (more dissociated) than phenol itself. Alternatively, the heterogeneous nature of the aqueous bromination system allows two distinct sets of bromination conditions, one in the organic phase and the other in the aqueous phase. The distribution of all reactants and products between these phases is expected to change with the course of the reaction and may cause the observed behaviour.

III.A.2 3-Fluorophenol

III.A.2a Bromination of 3-fluorophenol

4,6-Dibromo-3-fluorophenol and 2,4,6-tribromo-3-fluorophenol were prepared to use as reference compounds for the identification and the investigation of the brominated products of 3-fluorophenol when reacted with bromine obtained from an acidic mixture of potassium bromate and potassium bromide.

The reaction between equimolecular amounts of 3-fluorophenol and bromine gave a product consisting of five components which were identified by ^{19}F n.m.r. spectroscopy as 48% 3-fluorophenol (I) (sextet; δF = -112.0 ppm) plus 6-bromo-3-fluorophenol (II) (septet; δF = -112.2 ppm), 50% 4-bromo-3-fluorophenol (III) (triplet; δF = -105.5 ppm),

2,4-dibromo-3-fluorophenol (IV) (quartet; δF = -105.8 ppm) and 2% 2,4,6-tribromo-3-fluorophenol (V) (doublet; δF = -96.8 ppm) (Fig. III.2).

HPLC and GLC showed only four components. According to HPLC analysis, these showed retention times of 4.8 min (I), 6.3 min (II), 6.8 min (III) and 9.2 min (IV). GLC showed 29% (I), 33% (II), 32% (III) and 6% (IV), but no indication of (V) because its higher acidity (polarity) and molecular weight cause it to stay on the column.

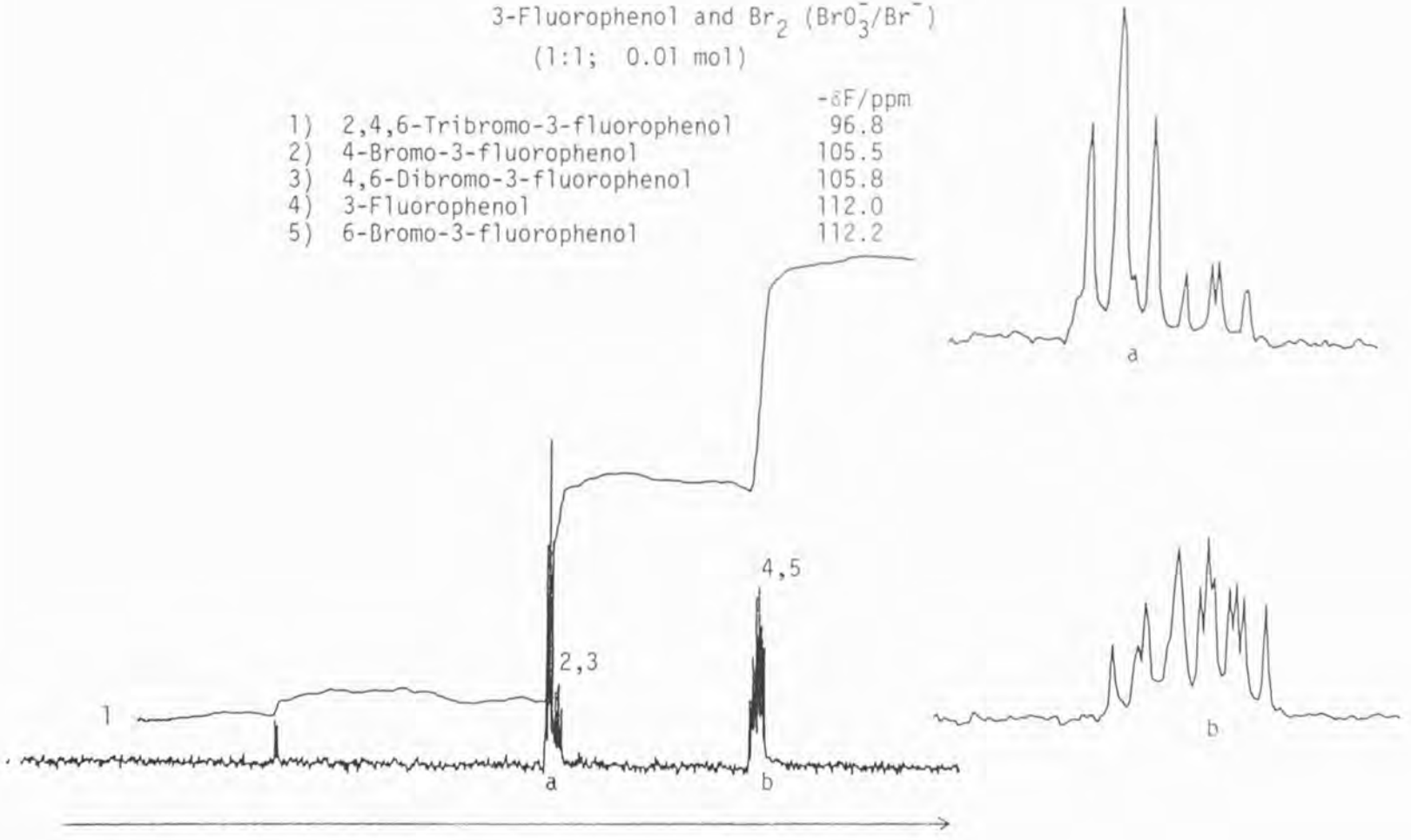
When two equimolecular proportions of brominating agent were used the final product was analysed by ^{19}F n.m.r. spectroscopy which showed five components, 22% (I), 35% (II), 34% (III), 7% (IV) and 2% (V) (Fig. III.3).

GLC analysis showed four components, 25% (I), 37% (II), 32% (III) and 6% (IV), while HPLC showed five components at retention times, 4.9 min (I), 6.3 min (II), 6.7 min (III), 9.0 min (IV) and 3.8 min (V). The sequence for these compounds was compared with the results obtained from GLC and HPLC separation of bromophenols under the same conditions. According to GLC the analysis showed 2-bromophenol eluted from the column first followed by 4-bromophenol, 2,6-dibromophenol and 4,6-dibromophenol. HPLC showed that 2,6-dibromophenol eluted from the column first followed by 2-bromophenol, 4-bromophenol and 2,4-dibromophenol. The reason for this unexpected order might be the competition in hydrogen bonding between sites on the stationary phase and substituents in the phenol. Ortho-substituted phenols would be expected to be less firmly attached to polar groups in the stationary phase, and so are more easily eluted.

Fig. III.2 ^{19}F n.m.r. Spectrum

3-Fluorophenol and Br_2 (BrO_3^-/Br^-)
(1:1; 0.01 mol)

		-δF/ppm
1)	2,4,6-Tribromo-3-fluorophenol	96.8
2)	4-Bromo-3-fluorophenol	105.5
3)	4,6-Dibromo-3-fluorophenol	105.8
4)	3-Fluorophenol	112.0
5)	6-Bromo-3-fluorophenol	112.2

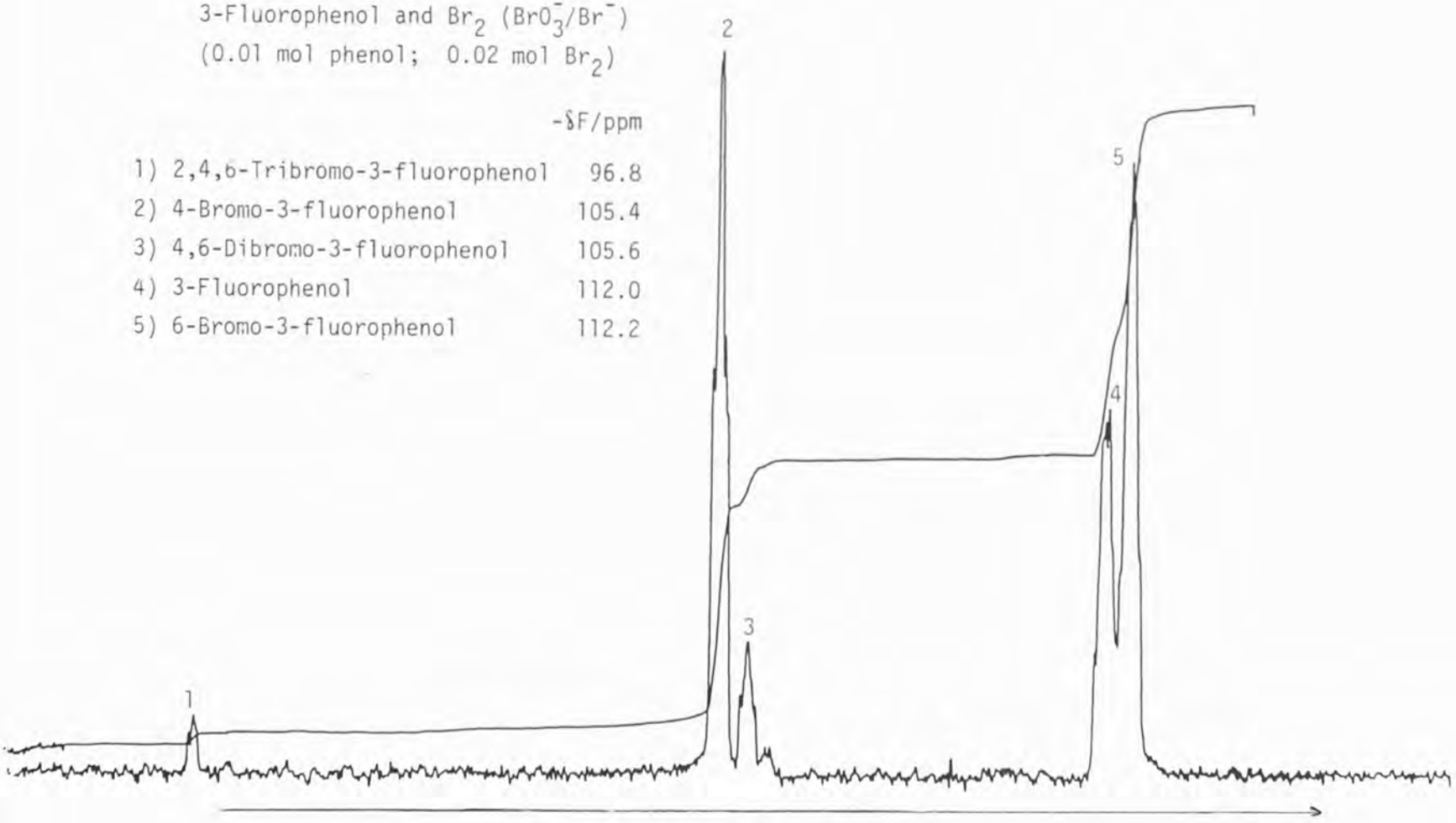


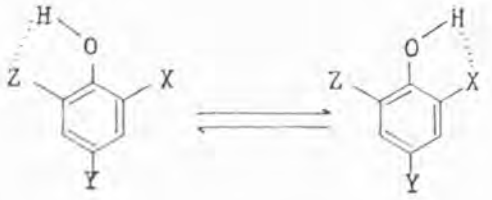
Chemical shift/ppm

Fig. III.3 ^{19}F n.m.r. Spectrum

3-Fluorophenol and Br_2 (BrO_3^-/Br^-)
(0.01 mol phenol; 0.02 mol Br_2)

	-δF/ppm
1) 2,4,6-Tribromo-3-fluorophenol	96.8
2) 4-Bromo-3-fluorophenol	105.4
3) 4,6-Dibromo-3-fluorophenol	105.6
4) 3-Fluorophenol	112.0
5) 6-Bromo-3-fluorophenol	112.2





X, Y, Z = F, Cl, Br, I.

III.A.2b Chlorination of 3-fluorophenol

Chlorinated products obtained from a reaction of equimolecular amounts of 3-fluorophenol and sulphuryl chloride (SO_2Cl_2) were analysed by ^{19}F n.m.r. spectroscopy, which showed the composition of the halogenated mixture as 15% unreacted 3-fluorophenol (I), (δF =-112.4 ppm), 60% 6-chloro-3-fluorophenol (II) (quartet; δF = -113.5 ppm) and 22% 4-chloro-3-fluorophenol (III) (triplet; δF = -114.9 ppm). GLC suggested the composition 6% (I), 76% (II) and 18% (III). HPLC showed the separation of these three compounds as well.

When two equimolecular proportions of SO_2Cl_2 were used the product was identified by ^{19}F n.m.r. spectroscopy as 63% (II) and 37% (III), which did agree with the analysis obtained from GLC 63% (II) and 37% (III). HPLC showed the presence of the same two compounds.

In comparing the results obtained from the bromination of 3-fluorophenol and the results obtained from the chlorination of the compound, bromination takes place with the formation of the polybrominated products while in the chlorination the main products are the monochlorofluorophenol.

III.A.3 4-Fluorophenol

III.A.3a Bromination of 4-fluorophenol

2-Bromo-4-fluorophenol and 2,6-dibromo-4-fluorophenol were prepared to use as references to identify the components obtained from the bromination of 4-fluorophenol using bromine (BrO_3^-/Br^-). When equimolecular amounts were used, there appeared a mixture of three compounds, which were identified from ^{19}F n.m.r. spectroscopy as 15% unreacted 4-fluorophenol (I) (septet δF = -124.2 ppm); 69% 2-bromo-4-fluorophenol (II) (quartet; δF = -122.0 ppm) and 16% 2,6-dibromo-4-fluorophenol (III),(triplet; δF = -120.7 ppm) (Fig. III.4).

HPLC analysis showed the composition of the reaction product as 14% (I), 69% (II) and 17% (III) (Fig. III.5a). This time HPLC was possible to use as quantitative analysis because all the product species were prepared separately beforehand in a pure state and the calibration curve for each component was made under the same conditions. By the aid of calibration curves the concentration of each component in the reaction mixture was determined (Fig. III.5b).

These analyses are in good agreement with that obtained from GLC separation which suggests the compositions 16% (I), 69% (II) and 15% (III) (Fig. III.6a,b).

The same components were obtained when two molecular proportions of bromine were used. ^{19}F N.m.r. spectroscopy showed 24% (I), 54% (II) and 22% (III). HPLC and GLC analysis showed 16% (I), 59% (II), 25% (III), 19% (I), 55% (II) and 26% (III) respectively.

Fig. III.4 ^{19}F n.m.r. Spectrum

4-Fluorophenol and Br_2 (BrO_3^-/Br^-)

(1 : 1 ; 0·01 mol)

		-δF/ppm
1)	2,6-Dibromo-4-fluorophenol	120.6
2)	2-Bromo-4-fluorophenol	122.0
3)	4-Fluorophenol	124.1

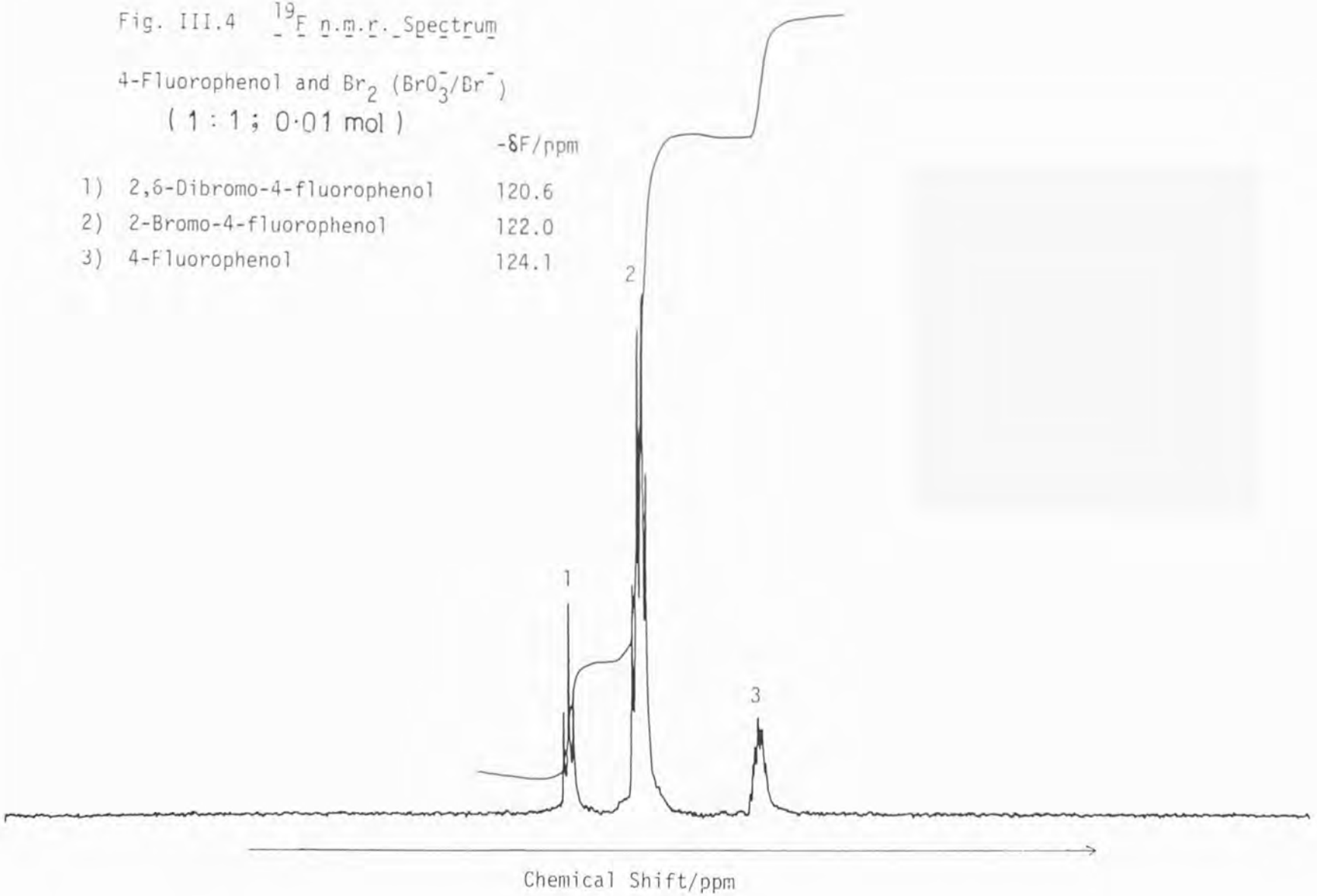


Fig. III.5 HPLC Chromatogram

4-Fluorophenol and Br_2 (BrO_3^-/Br^-) (1:1 ; 0.01 mol)

a) Calibration

b) Reaction

a)

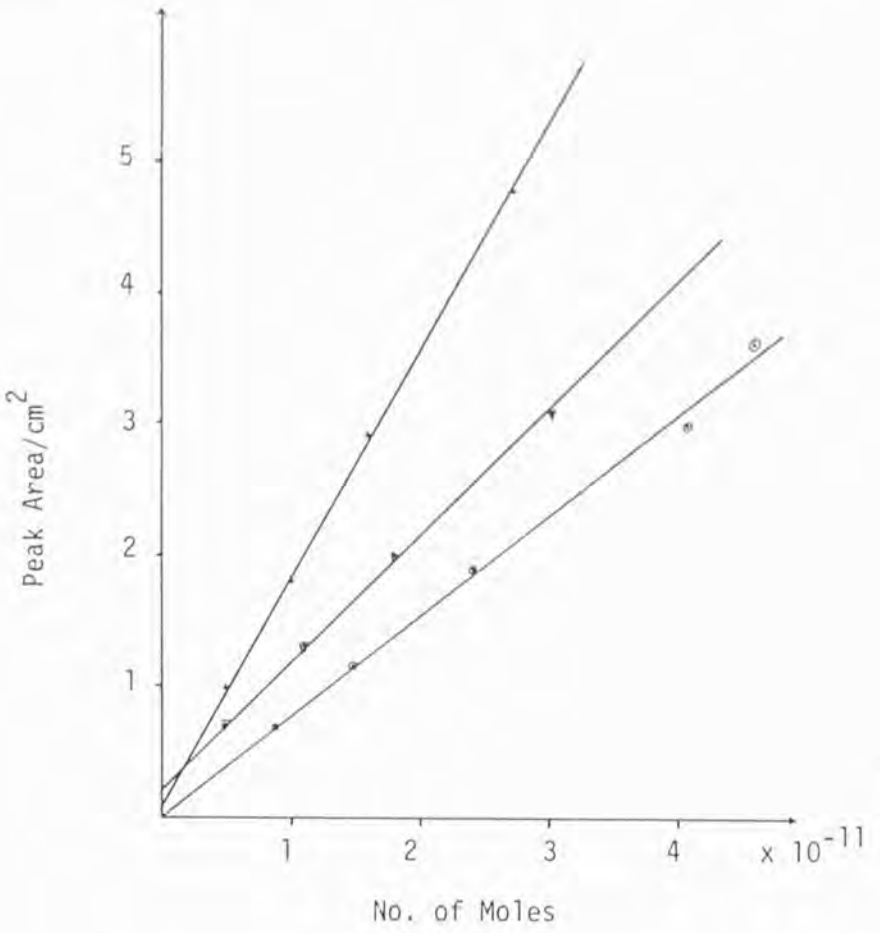
x 2,6-Dibromo-4-fluorophenol

Δ 4-Fluorophenol

⊙ 2-Bromo-4-fluorophenol

b)

1)	4-Fluorophenol	14
2)	2-Bromo-4-fluorophenol	69
3)	2,6-Dibromo-4-fluoro-phenol	17



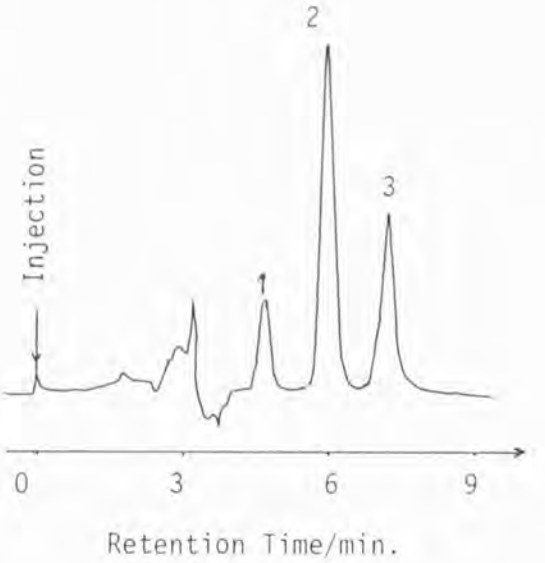
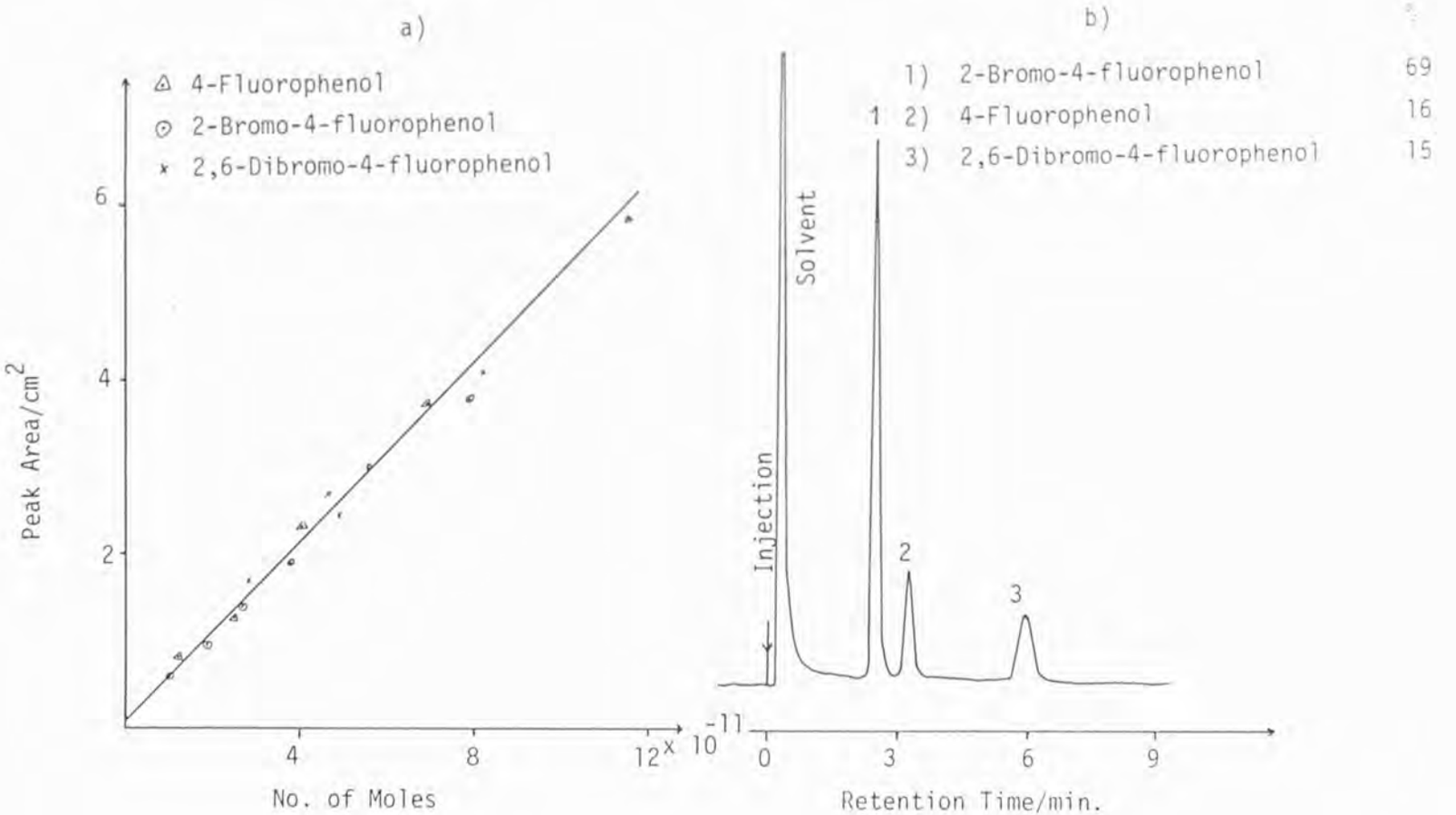


Fig. III.6 GLC Chromatogram

4-Fluorophenol and Br_2 (BrO_3^-/Br^-) (1:1; 0.01 mol)

a) Calibration
b) Reaction



Generally there is agreement between the analysis obtained from the three techniques for the brominated product. When an excess of bromine, more than equimolecular amount was used the percentage of dibromo-4-fluorophenol increased while the percentage of the monobromo-4-fluorophenol decreased which showed that the monobromo-4-fluorophenol was more active than the 4-fluorophenol and part of it was consumed in forming dibromo-4-fluorophenol.

III.A.3b Chlorination of 4-fluorophenol

Sulphuryl chloride was used as chlorinating agent for chlorinating 4-fluorophenol. When it was used in equimolecular amounts the chlorinated product was identified by ^{19}F n.m.r. spectroscopy as 27% unreacted 4-fluorophenol (I) (δF = -124.4 ppm) and 73% 2-chloro-4-fluorophenol (II) (quartet; δF = -122.2 ppm) while the chromatographic analysis showed according to GLC 28% (I) and 72% (II); HPLC showed the retention times 4.7 min (I) and 5.9 min (II).

When sulphuryl chloride was used in excess (two molecular proportions), the chlorinated product according to the analysis from the three techniques was mainly 2-chloro-4-fluorophenol.

The results obtained from the analysis of the reaction products by the three techniques were in good agreement.

III.B.1 2-Fluoroaniline

III.B.1a Bromination of 2-fluoroaniline

Some of the brominated 2-fluoroanilines were prepared and identified by ^{19}F n.m.r. spectroscopy, such as 4-bromo-2-fluoroaniline (triplet; δF = -132.6 ppm) and 6-bromo-2-fluoroaniline (octet; δF=-131.1 ppm)

The halogenated product obtained from the reaction of equimolar amounts of 2-fluoroaniline and aqueous bromine (BrO_3^-/Br^-) was analysed by ^{19}F n.m.r. spectroscopy, GLC and HPLC. From ^{19}F n.m.r. spectra the product seemed to be 48% unreacted 2-fluoroaniline (I) (septet; δF = -135.6 ppm), 2% 6-bromo-2-fluoroaniline (II) (octet; δF = -130.6 ppm), 9% 4-bromo-2-fluoroaniline (III) (triplet; δF = -132.5 ppm) and 41% 4,6-dibromo-2-fluoroaniline (IV) (doublet; δF = -128.4 ppm). GLC agreed with these results, showing 50% (I), 2% (II), 7% (III) and 41% (IV), while HPLC separation showed three peaks which were identified according to the retention times of 4.1 min (I), 5.9 min (II) and (III) and 10.4 min (IV). The same components were obtained when two molecular proportions of bromine were used. The analysis of this product according to ^{19}F n.m.r. spectroscopy showed 65% (I), 2% (II), 9% (III) and 24% (IV). GLC showed 67% (I), 2% (II), 8% (III) and 23% (IV), but HPLC still showed three peaks at the same retention times as reported above for equimolecular bromination mixtures.

Authentic 4-bromo-2-fluoroaniline and 6-bromo-2-fluoroaniline were eluted together in HPLC analysis, and could not therefore be separately identified.

The above analysis showed that a higher percentage of unreacted 2-fluoroaniline was left when two molecular proportions of bromine were used, than from the equimolecular reaction. This is attributed to the low basicity of 2-fluoroaniline in comparison with aniline. In this case the addition of bromine forms the aniline salt, which dissolved in the aqueous medium and was removed from reaction.

Bromine could now only attack the initially formed reaction products to form even further brominated amines. This was confirmed by preparing two reaction mixtures and in one the product was separated without treating with potassium hydrogen carbonate. ^{19}F N.m.r. spectroscopy showed no indication of 2-fluoroaniline. When the product was treated with potassium hydrogen carbonate before extraction, ^{19}F n.m.r. showed the unreacted 2-fluoroaniline.

III.B.1b Chlorination of 2-fluoroaniline

Some chlorinated products of 2-fluoroaniline were prepared by different methods which are described earlier (II.A.2f,g,h) for use as reference compounds in the analysis of the chlorinated products of 2-fluoroaniline when SO_2Cl_2 was used as chlorinating agent. ^{19}F N.m.r. spectra confirmed their structure. These compounds are 6-chloro-2-fluoroaniline (δF = -132.0 ppm), 4-chloro-2-fluoroaniline (triplet; δF = -132.8 ppm) and 4,6-dichloro-2-fluoroaniline (doublet; δF = -130.0 ppm).

2-Fluoroaniline reacted with equimolecular amounts of SO_2Cl_2 as a source of chlorine in the presence of anhydrous $AlCl_3$ as a catalyst. The reaction product was analysed by ^{19}F n.m.r. spectroscopy which suggested 40% unreacted 2-fluoroaniline (I) (δF = -135.8 ppm), no indication of 6-chloro-2-fluoroaniline (II), 42% 4-chloro-2-fluoroaniline (III), (δF = -133.0 ppm) and 18% 4,6-dichloro-2-fluoroaniline (IV) (δF = -129.9 ppm). This agreed with the HPLC qualitative analysis; there are only three components at retention times 4.1 min (I), 5.4 min (III) and 8.5 min (IV). In the HPLC analysis the peak at retention time

5.4 min could contain both 6-chloro-2-fluoroaniline and 4-chloro-2-fluoroaniline, because the retention time for each compound separately is 5.4 min. GLC analysis suggested the composition 42% (I), 3% (II), 34% (III) and 21% (IV).

The reaction product gave more or less the same components when two molecular proportions of SO_2Cl_2 were used. ^{19}F N.m.r. spectroscopy indicated 42% (I), 43% (III) and 15% (IV). GLC showed 45% (I), 3% (II), 37% (III) and 15% (IV), and HPLC analysis showed the three peaks at the same retention times as those mentioned above.

Generally, in comparing the types of products of bromination and of chlorination of 2-fluoroaniline, it appeared that when the mono-bromo-2-fluoroaniline is formed the ring became active which made it easy to form dibromo-compound even when an equimolecular amount of bromine was used. On the other hand in the chlorination of 2-fluoroaniline the monochloro-2-fluoroaniline was the major product even when excess of the halogenated agent was used.

III.B.2 3-Fluoroaniline

III.B.2a Bromination of 3-fluoroaniline

^{19}F N.m.r. spectroscopy was found helpful for identification of the brominated products obtained from the bromination of 3-fluoroaniline using acidic mixtures of potassium bromate and potassium bromide. When the bromination was carried out using equimolecular amounts of 3-fluoroaniline and bromine, the reaction product was identified by ^{19}F n.m.r. as 78% unreacted 3-fluoroaniline (I) (δF = -113.2 ppm), no 6-bromo-3-fluoroaniline (II), 1% 2-bromo-3-fluoroaniline (III) (triplet; δF = -105.9 ppm), 2% 4-bromo-3-fluoroaniline

(IV) (triplet; δF = -107.8 ppm), 8% 4,6-dibromo-3-fluoroaniline (V) (triplet; δF = -108.9 ppm) and 11% 2,4,6-tribromo-3-fluoroaniline (VI) (doublet; δF = - 98.2 ppm). The data obtained from GLC and HPLC showed six components, which were (according to GLC analysis) 78% (I), 1% (II), 1% (III), 1% (IV), 7% (V) and 12% (VI). HPLC showed the retention times as 5.2 min (I), 4.0 min (II), 5.7 min (III), 8.4 min (IV), 9.5 min (V) and 17.6 min (VI).When two molecular proportions of bromine were used the reaction product contained the same components which were shown from ^{19}F n.m.r. spectra to be 74% (I), 2% (II), 7% (III), 3% (IV), 9% (V) and 11% (VI) (Fig. III.7). GLC showed the composition 75% (I), 1% (II), 1% (III), 2% (IV), 8% (V), 13% (VI) (Fig. III.8). HPLC showed the retention time for each component as mentioned above (Fig. III. 9).

III.B.2b Chlorination of 3-fluoroaniline

Some chloro-3-fluoroanilines were prepared as references to identify the products obtained from chlorination of 3-fluoroaniline. These compounds were identified from ^{19}F n.m.r. spectroscopy as 6-chloro-3-fluoroaniline (septet; δF = -115.1 ppm) 4-chloro-3-fluoroaniline (triplet; δF = -115.8 ppm) and 4,6-dichloro-3-fluoroaniline (triplet; δF = -117.6 ppm).

The chlorinated product obtained from equimolecular amounts of 3-fluoroaniline and SO_2Cl_2 was identified by ^{19}F n.m.r. spectroscopy as 41% 3-fluoroaniline (I) (δF = -113.6 ppm), 23% 6-chloro-3-fluoroaniline (II) (δF = -115.8 ppm), 29% 4-chloro-3-fluoroaniline (III) (δF = -115.2 ppm) and 7% 4,6-dichloro-3-fluoroaniline (IV)

Fig. III.7 ^{19}F n.m.r. Spectrum

3-Fluoroaniline and Br_2 (BrO_3^-/Br^-)
(0.01 mol aniline; 0.02 mol Br_2)

		-δF/ppm
1)	2,4,6-Tribromo-3-fluoroaniline	98.1
2)	2-Bromo-3-fluoroaniline	106.0
3)	4-Bromo-3-fluoroaniline	107.8
4)	4,6-Dibromo-3-fluoroaniline	109.0
5)	3-Fluoroaniline	113.6
6)	6-Bromo-3-fluoroaniline	114.7

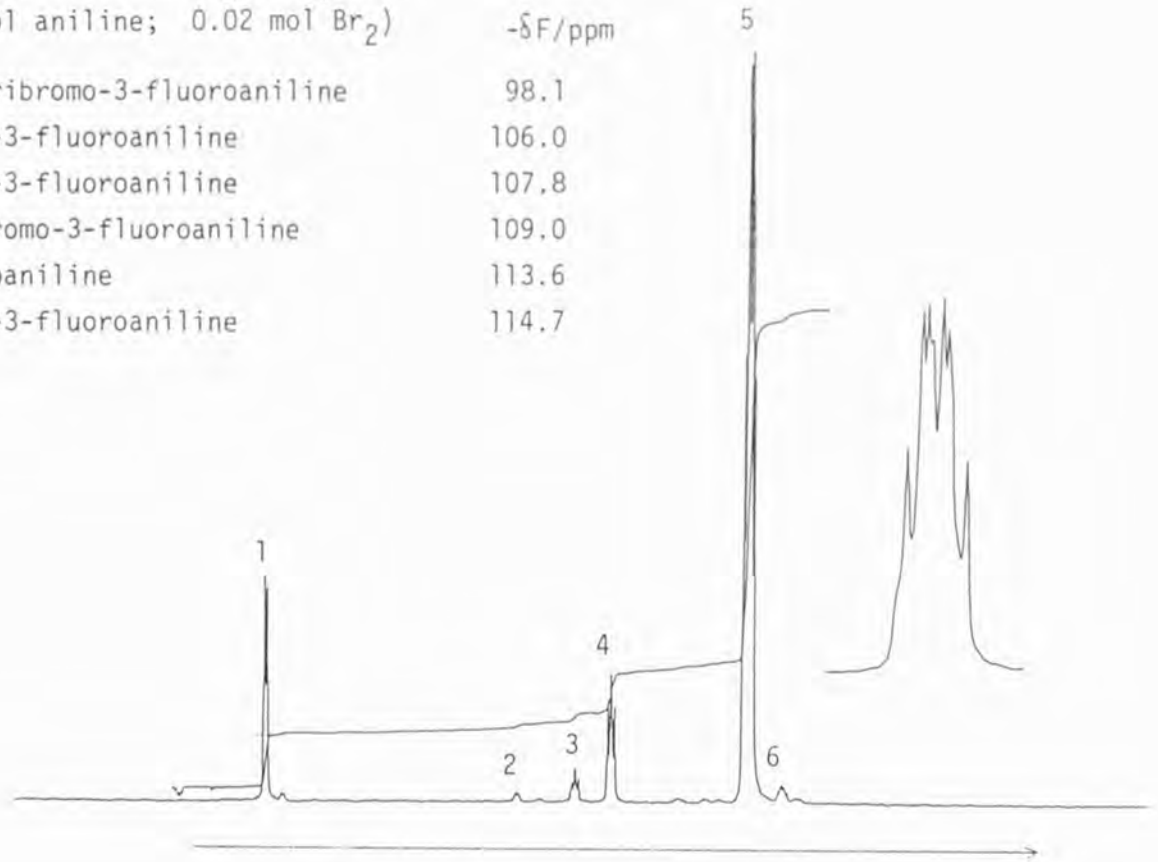


Fig III-8 GLC Chromatogram

3-Fluoroaniline and Br_2 (BrO_3^- / Br^-)
(0.01mol aniline; 0.02mol Br_2)

	%
1) 3-Fluoroaniline	75
2) 6-Bromo-3-fluoroaniline	1
3) 2-Bromo-3-fluoroaniline	1
4) 4-Bromo-3-fluoroaniline	2
5) 4,6-Dibromo-3-fluoroaniline	8
6) 2,4,6-Tribromo-3-fluoroaniline	13

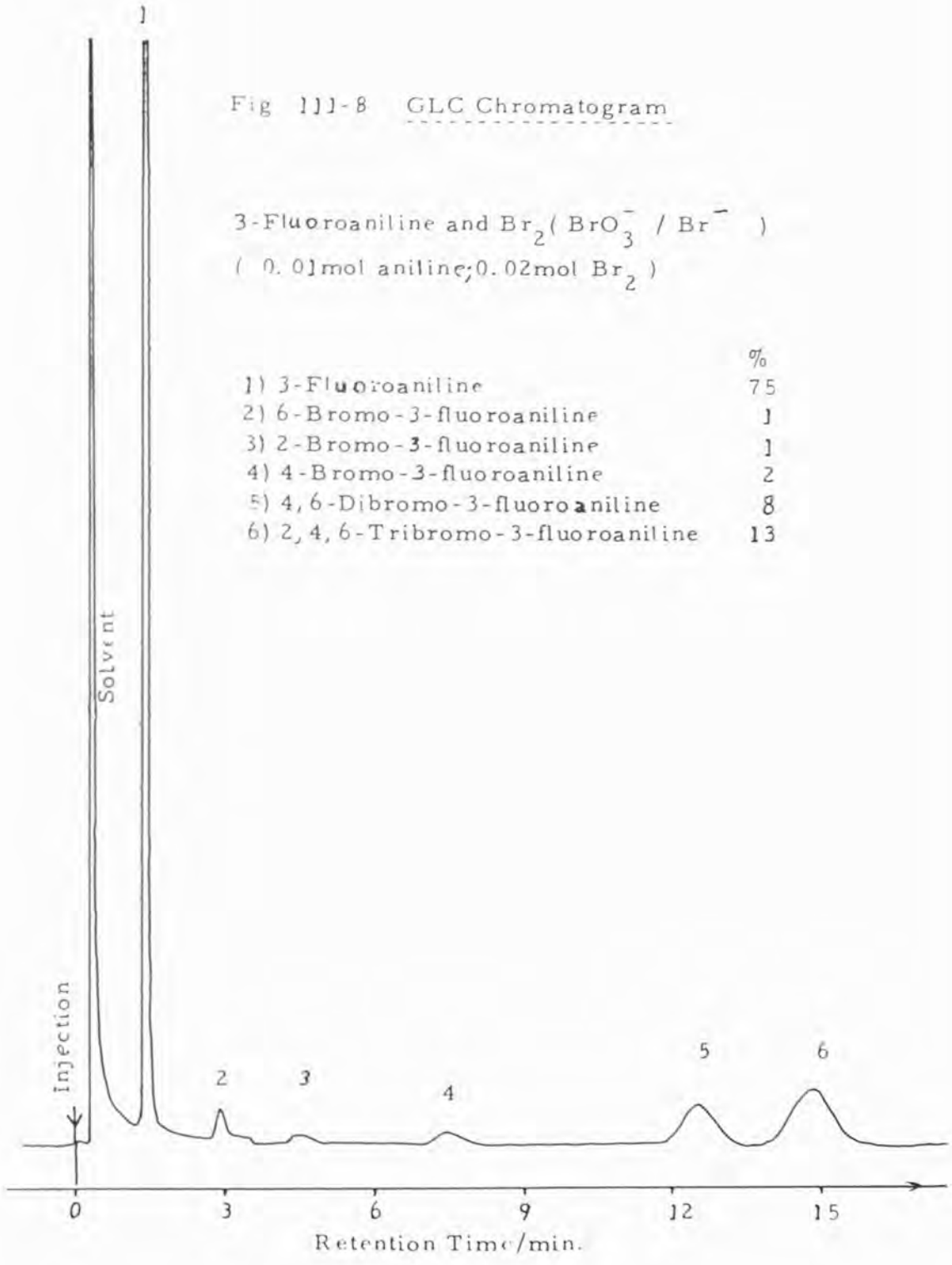
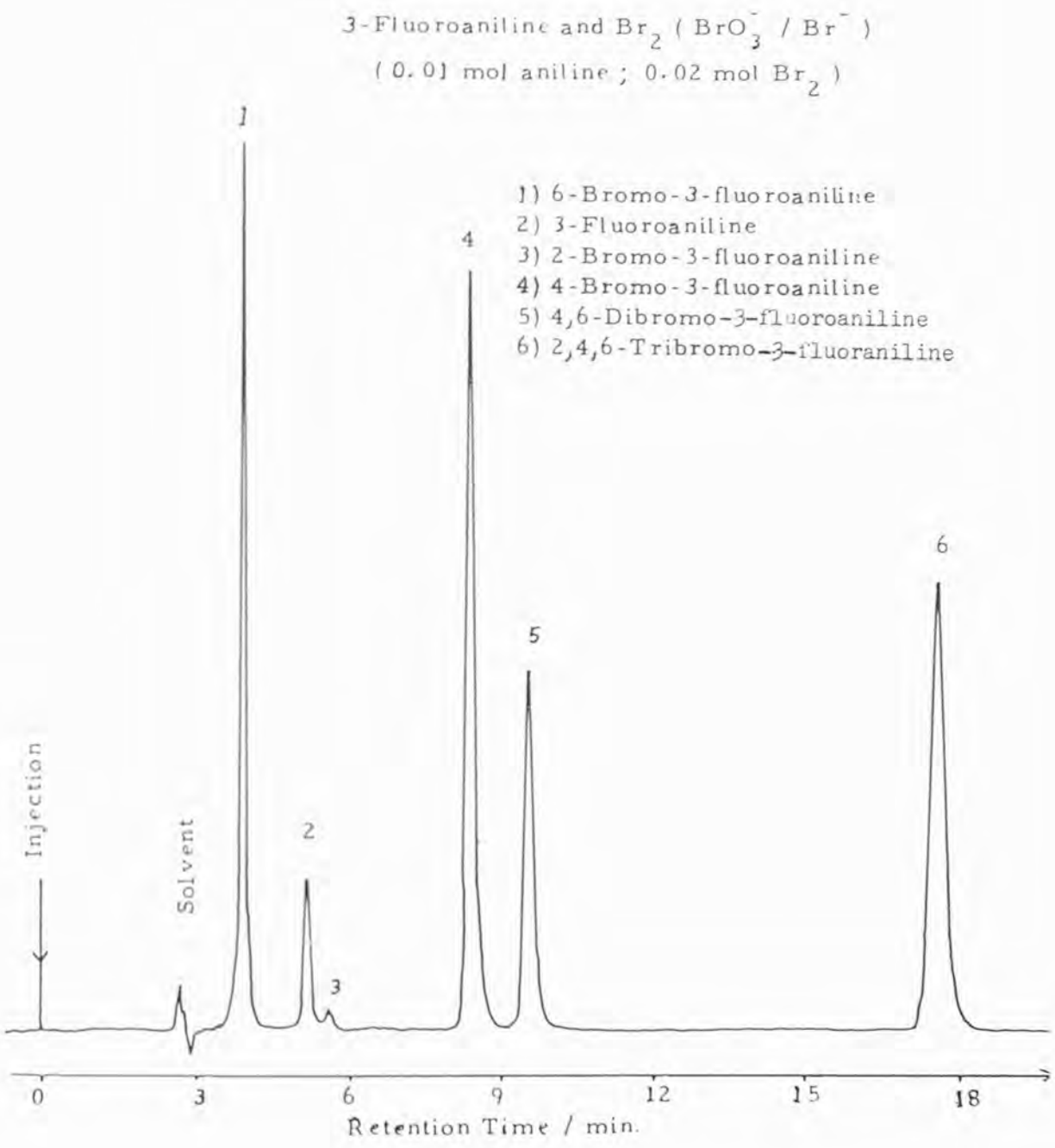


Fig. III-9 HPLC Chromatogram



(δF = -117.5 ppm) which did agree more or less with the compositions obtained from GLC 40% (I), 27% (II), 22% (III) and 11% (IV). HPLC showed the separate retention times as 5.1 min (I), 6.9 min (II), 14.1 min (III) and 9.9 min (IV).

When two molecular proportions of SO_2Cl_2 were used the compositions according to ^{19}F n.m.r. spectroscopy were 44% (I), 2% (II), 37% (III) and 17% (IV). GLC showed 47% (I), 8% (II), 26% (III) and 19% (IV). The retention times appeared in HPLC separation as 5.2 min (I), 6.9 min (II), 14.4 min (III) and 10 min (IV).

In comparison of bromination and chlorination of 3-fluoroaniline the poly-brominated amine was the major product among the brominated products with any ratio of bromine to amine. When chlorination took place in equimolecular ratio the 6-chloro and 4-chloro-3-fluoroaniline were formed. When the ratio of chlorinating agent was increased the 6-chloro- took part in forming the dichloro-3-fluoroaniline which showed the relative instability of 6-chloro-3-fluoroaniline to further substitution.

III.B.3 4-Fluoroaniline

III.B.3a Bromination of 4-fluoroaniline

The products obtained from the bromination of 4-fluoroaniline with aqueous bromine (BrO_3^-/Br^-) were analysed qualitatively and quantitatively by ^{19}F n.m.r. spectroscopy, GLC and HPLC.

^{19}F N.m.r. spectroscopy for equimolecular reactions showed 78% unreacted 4-fluoroaniline (I) (septet; δF = -127.1 ppm), 5% 2-bromo-4-fluoroaniline (II) (quartet; δF = -125.6 ppm) and 17% 2,6-dibromo-4-

fluoroaniline (III) (triplet; δF = -124.9 ppm). GLC showed 77% (I), 5% (II) and 18% (III). In HPLC measurements a calibration curve for each authentic compound was made using 2,6-dibromoaniline as internal standard for all measurements (Fig. III.10 a,b). In the reaction mixture HPLC showed 76% (I), 7% (II) and 18% (III). Generally there is agreement between the analysis which obtained from the three techniques. The same components were obtained when two molecular proportions of bromine were used. The product composition found by ^{19}F n.m.r. spectroscopy was 72% (I), 7% (II), and 21% (III), whereas GLC gave 72% (I), 7% (II) and 21% (III) and HPLC gave 71% (I), 8% (II) and 21% (III).

III.B.3b Chlorination of 4-fluoroaniline

The analysis of products from 4-fluoroaniline with equimolecular amounts with SO_2Cl_2 showed by ^{19}F n.m.r. spectroscopy 63% unreacted 4-fluoroaniline (I) (δF = -127.1 ppm), 28% 2-chloro-4-fluoroaniline (II) (quartet; δF -125.7 ppm) and 9% 2,6-dichloro-4-fluoroaniline (III) (triplet; δF = -124.3 ppm). GLC suggested the composition 63% (I), 29% (II) and 8% (III). HPLC retention times appeared as 4.0 min (I), 5.2 min (II) and 7.7 min (III). The same components were obtained when two molecular proportions of SO_2Cl_2 were used. According to the three techniques analysed the compositions were suggested to be (^{19}F n.m.r. spectroscopy) 63% (I), 28% (II) and 9% (III); by GLC, 63% (I), 31% (II) and 6% (III); whereas HPLC gave the retention times 4.0 min (I), 5.2 min (II) and 7.7 min (III).

Fig. III.10a HPLC Chromatogram

4-Fluoroaniline and Br_2 (BrO_3^-/Br^-) (1:1; 0.01 mol)

a) Calibration

1) 2-Bromo-4-fluoroaniline
2) 2,6-Dibromo-4-fluoroaniline
3) 4-Fluoroaniline

(I.S.: 2,6-Dibromoaniline)

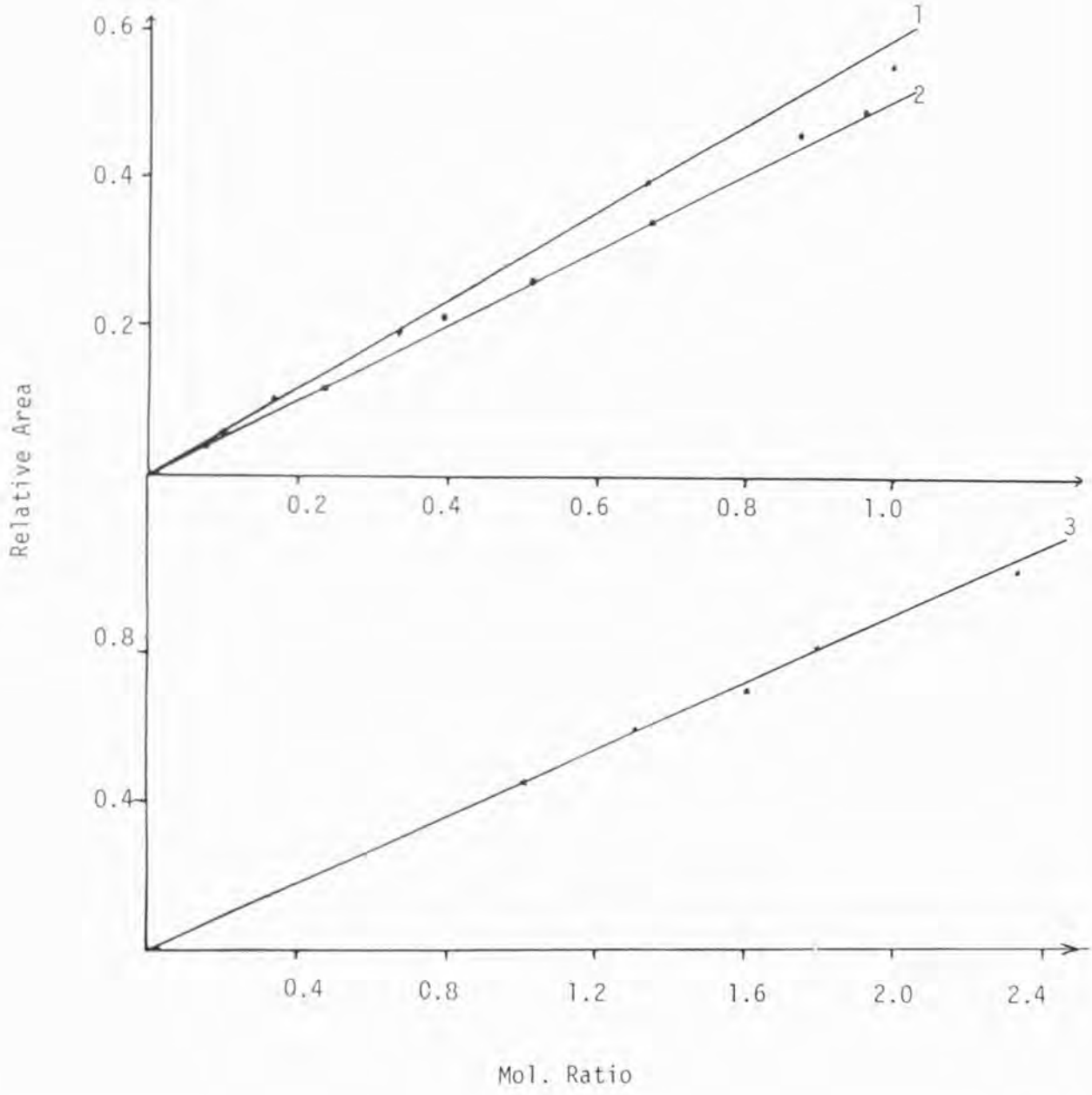
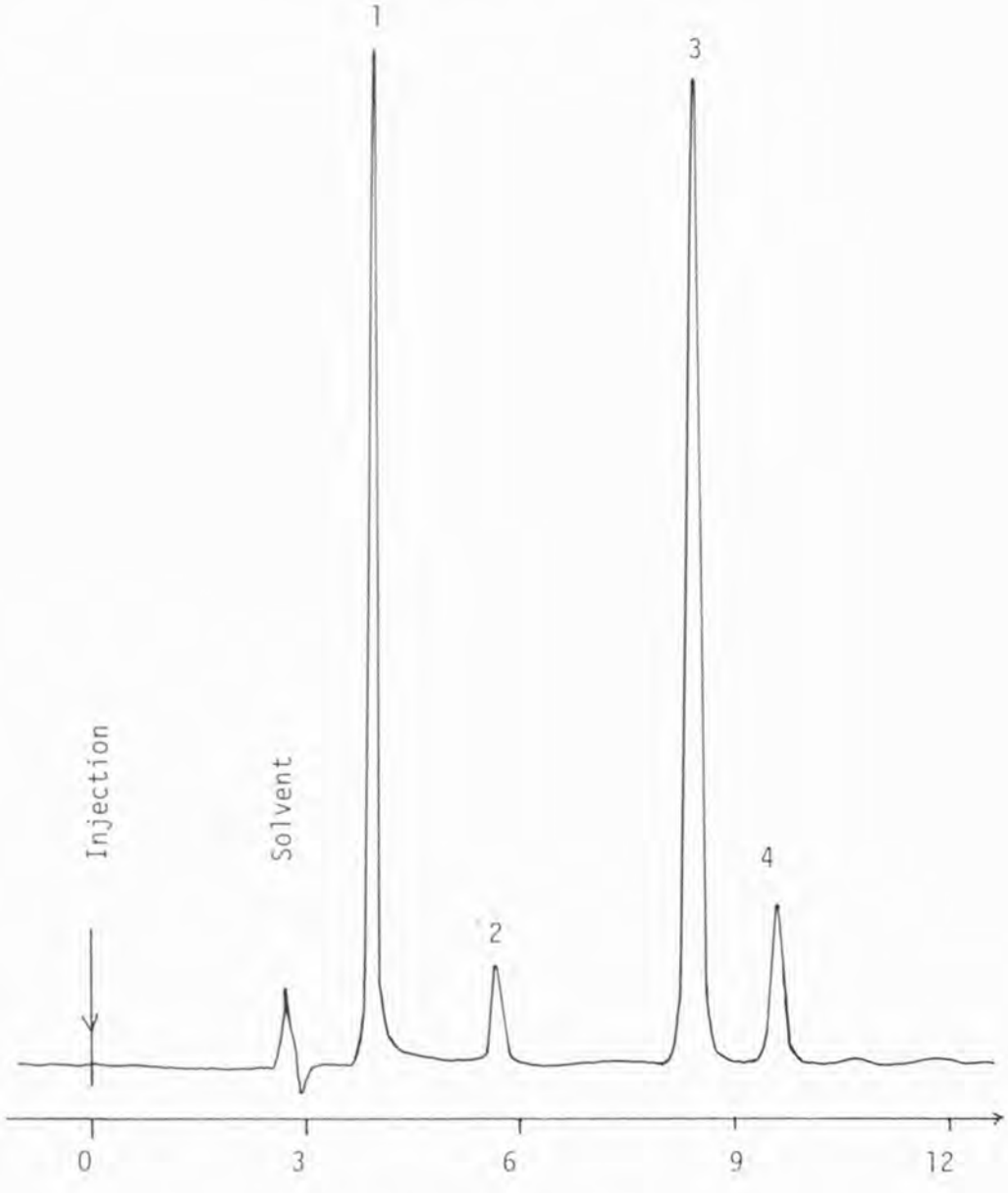


Fig. III.10b HPLC Chromatogram

4-Fluoroaniline and Br_2 (BrO_3^-/Br^-) (1:1; 0.01 mol)
b) Reaction

1) 4-Fluoroaniline
2) 2-Bromo-4-fluoroaniline
3) 2,6-Dibromoaniline (Internal standard)
4) 2,6-Dibromo-4-fluoroaniline



In the bromination of 4-fluoroaniline the ring was activated by mono-bromination which caused poly-bromination while in the chlorination the mono- chloro- is more stable to the reaction conditions.

APPENDIX I

The expected fluorine-19 chemical shifts for the halogenated fluorophenols and fluoroanilines were calculated from previous work on substituted fluorobenzenes.

^{19}F N.m.r. spectra of o-substituted fluorobenzenes have been reported,[74] in which bromine and chlorine atoms in o-position relative to fluorine showed chemical shifts of -7.07 and +1.18 ppm. 1,1,2,2-Tetrachloro-3,3,4,4-tetrafluorocyclobutane was used as internal standard and the solvent was cyclohexane. These values were used to estimate changes in the chemical shift of fluorine in m-fluorophenols and m-fluoroanilines. Examples are given below.

Table AI-1

Compound	δF/ppm
3-Fluorophenol	-112.1
4-Bromo-3-fluorophenol	-112.1 + 7.07 = -105.03
4-Chloro-3-fluorophenol	-112.1 - 1.18 = -113.28
3-Fluoroaniline	-113.6
4-Bromo-3-fluoroaniline	-113.6 + 7.07 = -106.53
4-Chloro-3-fluoroaniline	-113.6 - 1.18 = -114.78

The ^{19}F n.m.r. shifts of m-substituted fluorobenzenes relative to fluorobenzene, in acetone, are given below,[21]

Table AI-2

Compound	δF/ppm
3-Bromofluorobenzene	-2.62
3,5-Dibromofluorobenzene	-4.36
3-Chlorofluorobenzene	-2.34

and these have been used to estimate the effects of substituents upon the chemical shift shown by o-fluorophenols and o-fluoroanilines.

Table AI-3

Compound	δF/ppm
2-Fluorophenol	-141.4
4-Bromo-2-fluorophenol	-141.4 + 2.62 = -138.78
4,6-Dibromo-2-fluorophenol	-141.4 + 4.36 = -137.04
4-Chloro-2-fluorophenol	-141.4 + 2.34 = -139.06
2-Fluoroaniline	-135.7
4-Bromo-2-fluoroaniline	-135.7 + 2.62 = -133.08
4,6-Dibromo-2-fluoroaniline	-135.7 + 4.36 = -131.34
4-Chloro-2-fluoroaniline	-135.7 + 2.34 = -133.36

The chemical shifts for p-substituted fluorobenzenes in n-hexane have been reported[23] with fluorobenzene as reference. The chemical shifts of bromine and chlorine p-position to fluorine were +2.73 and +3.30 ppm respectively.

Examples of values which have been calculated are given below.

Table AI-4

Compound	δF/ppm
3-Fluorophenol	-112.1
6-Bromo-3-fluorophenol	-112.1 - 2.73 = -114.83
6-Chloro-3-fluorophenol	-112.1 - 3.30 = -115.40
3-Fluoroaniline	-113.6
6-Bromo-3-fluoroaniline	-113.6 - 2.73 = -116.33
6-Chloro-3-fluoroaniline	-113.6 - 3.30 = -116.90

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PART II: THERMODYNAMICS

CHAPTER I

I: INTRODUCTION

I. INTRODUCTION

I.A Literature Review

I.A.1 General Methods of Preparation of Bromo-aniline Derivatives

The bromination of aromatic amines is usually achieved by using bromine[1] in acidic medium, bromide/bromate[2] in acidic medium, hydrolysis of the corresponding acetanilides[3] and brominating agents such as a) N-bromosuccinimide[4] b) hydrobromic acid in aqua regia.[5]

Many brominated aniline derivatives are known. Such preparations include mono- and dibromoaniline derivatives which are listed in the following table.

Table I.1 Bromoaniline Derivatives

2,6-Dibromo-4-chloroaniline[6,7]	2-Bromo-4-chloroaniline[3,9]
4,6-Dibromo-2-chloroaniline[6,8]	4-Bromo-2-chloroaniline[3]
2,6-Dibromo-4-nitroaniline[8,13-16]	2-Bromo-4-nitroaniline[12]
4,6-Dibromo-2-nitroaniline[11]	4-Bromo-2-nitroaniline[10]

The partial bromination of aniline derivatives was studied and reported by Francis .[17]

I.A.2 Previous Studies on Aniline Derivatives

I.A.2a Spectrophotometric Studies

Infrared absorption was applied to examine band intensities and band shapes associated with the stretching vibrations of the amino group in a series of m- and p- substituted anilines.[18,19] The relationship between the antisymmetric and symmetric stretching frequencies of these substituted anilines was found by Bellamy and Williams.[19] In the light of this relationship the infrared spectra of some o-substituted anilines[20] showed a different behaviour, which confirmed the presence of hydrogen bonding between the amino group and o-substituted anilines. 2,4,6-Tribromoaniline showed slightly greater deviations than compounds in which there is only one hydrogen in the o-position relative to the amino group. 2,6-Dibromo-4-nitroaniline behaved differently from 2,4,6-tribromoaniline due to the amino group rotation so that conjugation with the benzene ring and with the 4-nitro group was changed because the repulsive terms and the conjugation energy between the amino group and the rest of the molecule are comparable.[20]

Infrared spectra[8,21] and Raman spectra[22-24] were applied to examine 4,6-dibromo-2-chloroaniline, while electronic spectra[25] and Raman spectra[26,27] were applied to examine 2,6-dibromo-4-chloroaniline. Also spectrophotometric measurements were used to determine the basicity constant of 4,6-dibromo-2-nitroaniline at 20, 40 and 60°C.[28]

I.A.2b Thermodynamic Studies

The enthalpies of solution of aniline[29,30] and substituted anilines e.g. 2-chloroaniline[30] in water at infinite

dilution are known. The solubility of anilines in water depends on the nature and position of the substituent. The solubility of 4-nitroaniline, which is slightly soluble in water, was determined by Gross and Saylor.[31] The enthalpies of transfer of some substituted anilines from water to cyclohexane were deduced from the extrapolated distribution coefficients measurements at infinite dilution.[32] The enthalpies of transfer of phenol[33] aniline,[33] 4-chlorophenol and 4-chloroaniline[34] between organic solvents and water were also determined. Complete thermodynamic profiles were obtained[33] for transfer of phenol from octane, toluene, and octanol to water, also for transfer of aniline from toluene to water. 4-Chloroaniline and 4-chlorophenol were among 29 neutral aliphatic and aromatic solutes, for which enthalpies of transfer between alkanes and water were determined by direct calorimetric measurements.[34,35] Both compounds showed exothermic enthalpies of transfer from 2,2,4-trimethylpentane to aqueous buffer (pH 7).

Solubility is an indirect measurement to obtain thermodynamic properties. Standard free energies and enthalpies of transfer of 4-nitroaniline from water to aqueous mixtures of some ionic and non-ionic media like potassium bromide, urea, propylene glycol, glycerol, dioxane and 1,2-dimethoxyethane were determined from solubility measurements at different temperatures.[36] By the same technique free energies and entropies of transfer at 25°C of 4-nitroaniline from water to various aqueous alcohols were determined.[37]

Some other thermodynamic parameters were reported, such as: a) The standard enthalpy of combusion of 4-nitroaniline[38-40] and enthalpy of formation of 4-nitroaniline.[41] b) The latent heats of fusion of 2-chloroaniline and 4-chloroaniline were determined at melting-point temperatures.[42] c) The heats of neutralisation and the basic strengths of 2-chloroaniline, 4-chloroaniline and 4-nitroaniline in acetonitrile were measured by automatic thermometric titrations using hydrobromic acid in acetonitrile as a titrant.[43]

Generally, from the thermodynamic point of view there are no thermodynamic data on the bromination of aniline derivatives in the previous work. Some preliminary work on the thermochemistry of bromination of phenols and anilines is available.[44] Isoperibol solution calorimetry was used to measure the enthalpy of bromination of phenol to 2,4,6-tribromophenol, aniline to 2-bromoaniline, aniline to 4-bromoaniline and 2,4-dibromoaniline to 2,4,6-tribromoaniline. From these measurements the standard enthalpies of formation of 2,4,6-tribromophenol and 2,4,6-tribromoaniline were calculated. Also the enthalpies of formation of these compounds were obtained from measuring the enthalpies of combustion using a rotating-bomb calorimeter.

The object of the present work is to establish thermochemical data on the bromination of aniline derivatives such as 2-chloroaniline, 4-bromo-2-chloroaniline, 4-chloroaniline, 2-nitroaniline and 4-nitroaniline using solution calorimetric measurements, in addition to solubility measurements on 4-bromoaniline, 2,6-dibromoaniline and 2,4,6-tribromoaniline. Static-bomb calorimetry is suitable for burning organic compounds containing C, H, O and N. However, organic iodides are the only halides which can be determined by this method. Rotating-bombs are very rare, but may be

used for burning organic compounds containing chlorine or bromine and incorporating a suitable reducing agent can be used to react with the products. A solution of halogen hydracid will then be the only compound containing halogen in the final state. In this case isoperibol solution calorimetry was found more convenient to derive the enthalpy of formation of bromoaniline derivatives. Isoperibol solution calorimetry can be used successfully with reactions of short duration (less than 15 min). The development of solution calorimetry is fully described elsewhere.[44]

Applying the thermometric titration technique on the bromination of aniline derivatives is useful for qualitative and quantitative analysis. By adding the bromine stepwise to the solution of aniline derivatives, the thermometric titration curves revealed the breakpoints when equimolecular amounts of bromine were added. From these breakpoints the number of bromination steps may be informed. Also the concentration of the titrant can be calculated at each step of the reaction. The enthalpy of the bromination reaction can be measured. In this work we measured the enthalpy of the bromination of aniline derivatives using isoperibol solution calorimetry and thermometric titrations.

I.B Aim of Work

Halogenated phenols and anilines are introduced to the environment in several ways e.g. directly as industrial effluents and indirectly as transformation products in the manufacture of herbicides.[45,46] The toxic effect[47] on living organisms is extended through the pollution of surface water[48,49] and soil.[6] Nitroanilines have a potential hazard[50] associated with their thermal behaviour, which need thermal stability-hazard analysis to assure their safe processing, handling and storage. For these reasons the work on these compounds is important. There are few thermochemical data for such compounds.

The enthalpy of solution of 2,4,6-tribromophenol, 4-bromoaniline, 2,6-dibromoaniline and 2,4,6-tribromoaniline was determined from solubility measurements in toluene and n-propanol. This was achieved by applying the dynamic precipitation method.

The enthalpy of bromination of 2-chloroaniline, 4-bromo-2-chloroaniline, 4-chloroaniline, 2-nitroaniline and 4-nitroaniline was determined using the solution calorimetry technique.

CHAPTER II

II: SOLUBILITY

II SOLUBILITY

II Dynamic precipitation method for solubility determination[51]

When a chemical system is in equilibrium, no apparent change takes place, but a dynamic equilibrium is assumed with two opposing reactions proceeding at the same rate. A saturated solution is a simple case of equilibrium. Solubility is defined as the weight of solute that will dissolve in a given weight or volume of solvent to give a saturated solution at a specified temperature. The solubility data can be used for calculating the differential heats of solutions at saturation.

In this work, a dynamic precipitation method was used to determine solubility curves for 2,4,6-tribromophenol, 4-bromoaniline, 2,6-dibromoaniline and 2,4,6-tribromoaniline in toluene and n-propanol.

II.A. Experimental

II.A.1 Materials and Methods

2,4,6-Tribromophenol (Aldrich) was recrystallized four times from pet. ether (60 - 80^{o}C), 4-bromoaniline (H & W) was recrystallized four times from dilute alcohol, 2,6-dibromoaniline (Aldrich) was recrystallized four times from dilute alcohol and 2,4,6-tribromoaniline (H & W) was recrystallized three times from ethanol.

All the crystalline solids were ground and kept dry in a desiccator under vacuum over silica gel.

The purity of these compounds were checked by gas liquid chromatography and constant melting point; 2,4,6-tribromophenol m.p. 92°C lit.[52] 92°C and 95°C; 4-bromoaniline m.p. 62 - 64°C, lit. 63 - 66°C[52] and 66°C;[1] 2,6-dibromoaniline m.p. 82°C, lit.[52] 83 - 84°C and 2,4,6-tribromoaniline m.p. 115°C, lit. 118°C, 119 - 120°C[52] and 120°C.[1]

Toluene and n-propanol were used as solvents. Toluene (M & B) was purified by redistillation under atmospheric pressure at 111°C and kept over 4A molecular sieve; n-propanol (M & B) was purified by redistillation under pressure of 760 mm Hg at 94 - 96°C and kept over 4A molecular sieve.

A conical tube was used for the solubility measurements. An exact weight of sample was inserted into the tube. An exact known volume of solvent was added from a burette (graduated up to 0.02 cm^3). The mixture was heated in a water bath with constant stirring until the solid dissolved. The tube was then clamped in a beaker of suitable size to reduce droughts. Then the solution was allowed to cool with constant stirring. The temperature at which the crystal first appeared was measured by a thermometer (graduated to 0.1°C). The heating and cooling were repeated until constant results were obtained ($\pm$ 0.2°C). Another known volume of solvent was added and the procedure repeated to obtain further results. The dilution, heating and cooling were continued as far as was practical.

II.B. Results and Calculations

The solubility data of 2,4,6-tribromophenol, 4-bromoaniline, 2,6-dibromoaniline and 2,4,6-tribromoaniline in toluene and n-propanol are recorded in Tables II.1-8. Fig. II.1 and 2, show the solubility curves of molality (S) vs.temperature (T) and Fig. II.3 and 4, show the graphs of lnS vs. $\frac{1}{T}$.

The differential heats of solutions of these compounds were calculated from the graphs of lnS vs. $\frac{1}{T}$ by applying the following equation:-

$$\ln S = \frac{-\Delta_{sol} H^{\ominus}}{R} \cdot \frac{1}{T} + \frac{\Delta_{sol} S^{\ominus}}{R} \qquad (1)$$

S = solubility in mol/1000g of solvent.

$\Delta_{sol}H^{\ominus}$ = heat of solution / J mol^{-1}.

R = gas constant/JK^{-1} mol^{-1}.

$\Delta_{Sol}S^{\ominus}$ = entropy of solution/JK^{-1} mol^{-1}.

Equation (1) was obtained from the van't Hoff equation[53] relating the equilibrium constant and the absolute temperature.

$$\frac{d\ln S}{dT} = \frac{\Delta_{sol}H^{\ominus}}{RT^2}$$

Integrated form

$$\log S = \frac{-\Delta_{sol}H^{\theta}}{2.303R} \cdot \frac{1}{T} + \text{constant}$$

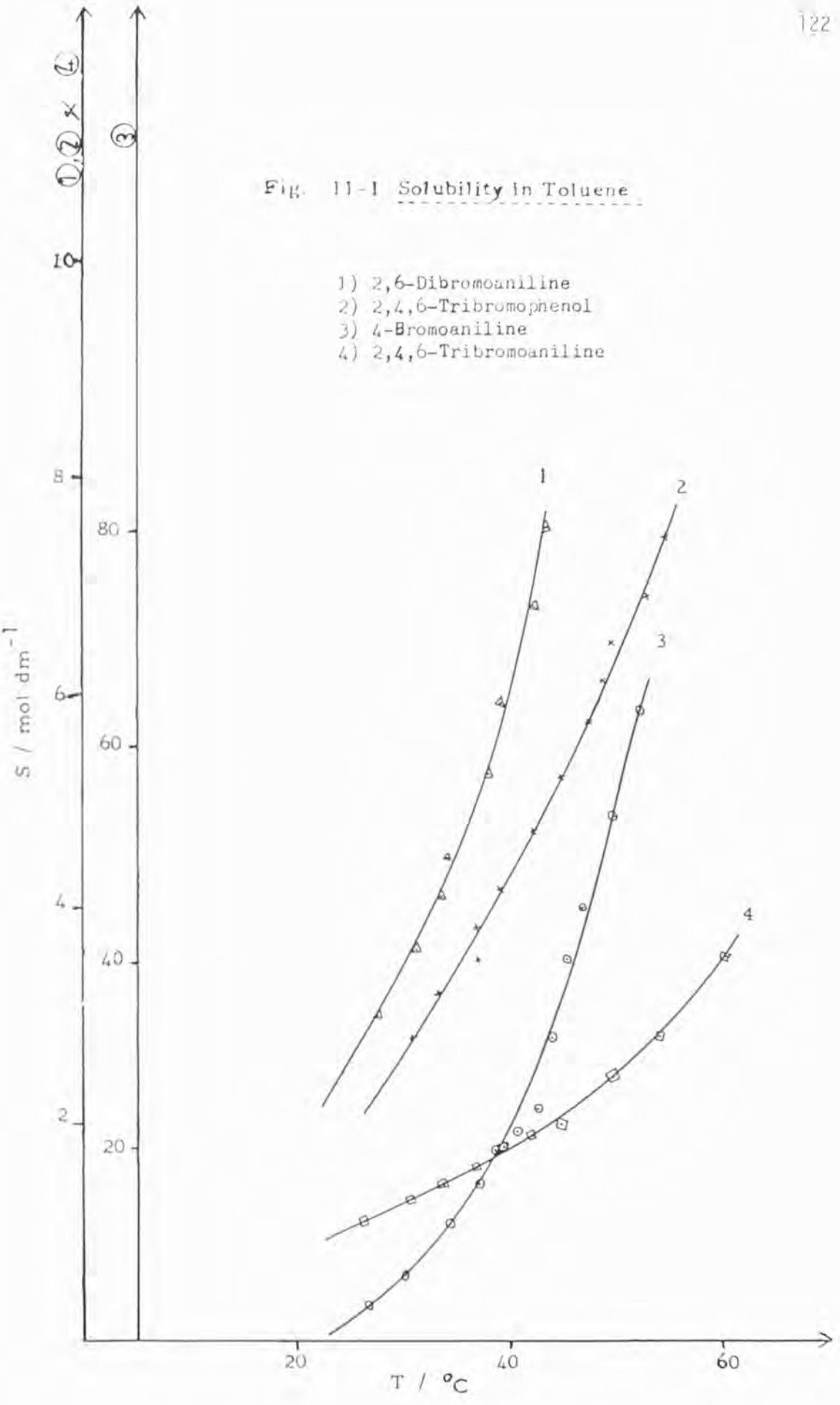
$$\log \frac{S_2}{S_1} = \frac{\Delta_{sol}H^{\theta}}{2.303R} \cdot \frac{(T_2 - T_1)}{(T_2T_1)}$$

S_1, S_2 = solubilities in mol/1000 g of solvent at absolute temperatures T_1 and T_2.

The calculated differential heats of solutions at saturation for these compounds are recorded in Table II.9 and 10, a least squares regression programme was applied.[54]

Fig. 11-1 Solubility in Toluene

1) 2,6-Dibromoaniline
2) 2,4,6-Tribromophenol
3) 4-Bromoaniline
4) 2,4,6-Tribromoaniline



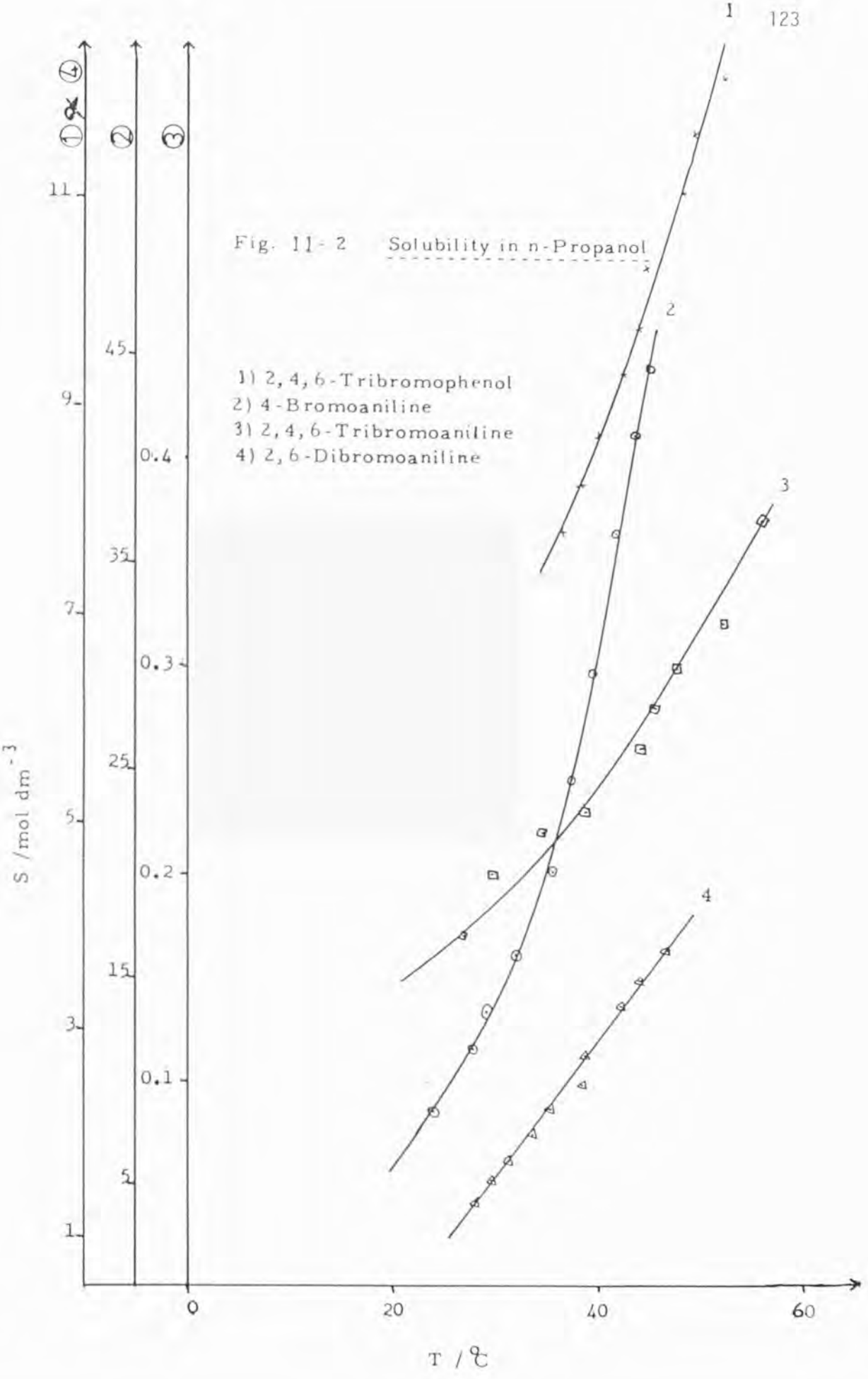


Fig. 11-2 Solubility in n-Propanol

Fig. II - 3 Plot of ln S vs $\frac{1}{T}$ in Toluene

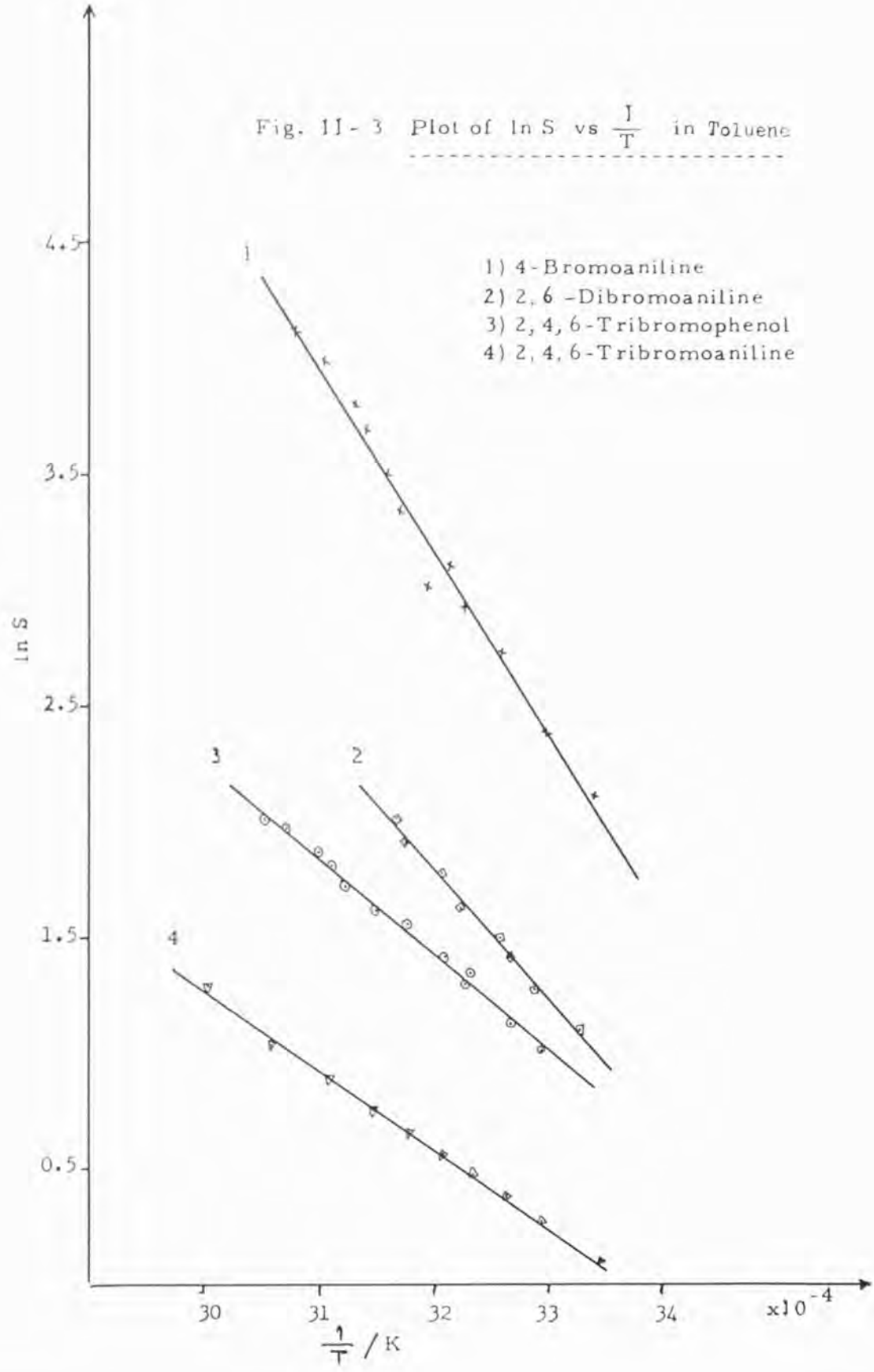


Fig. 11-4 Plot of ln S vs $\frac{1}{T}$ in n-Propanol

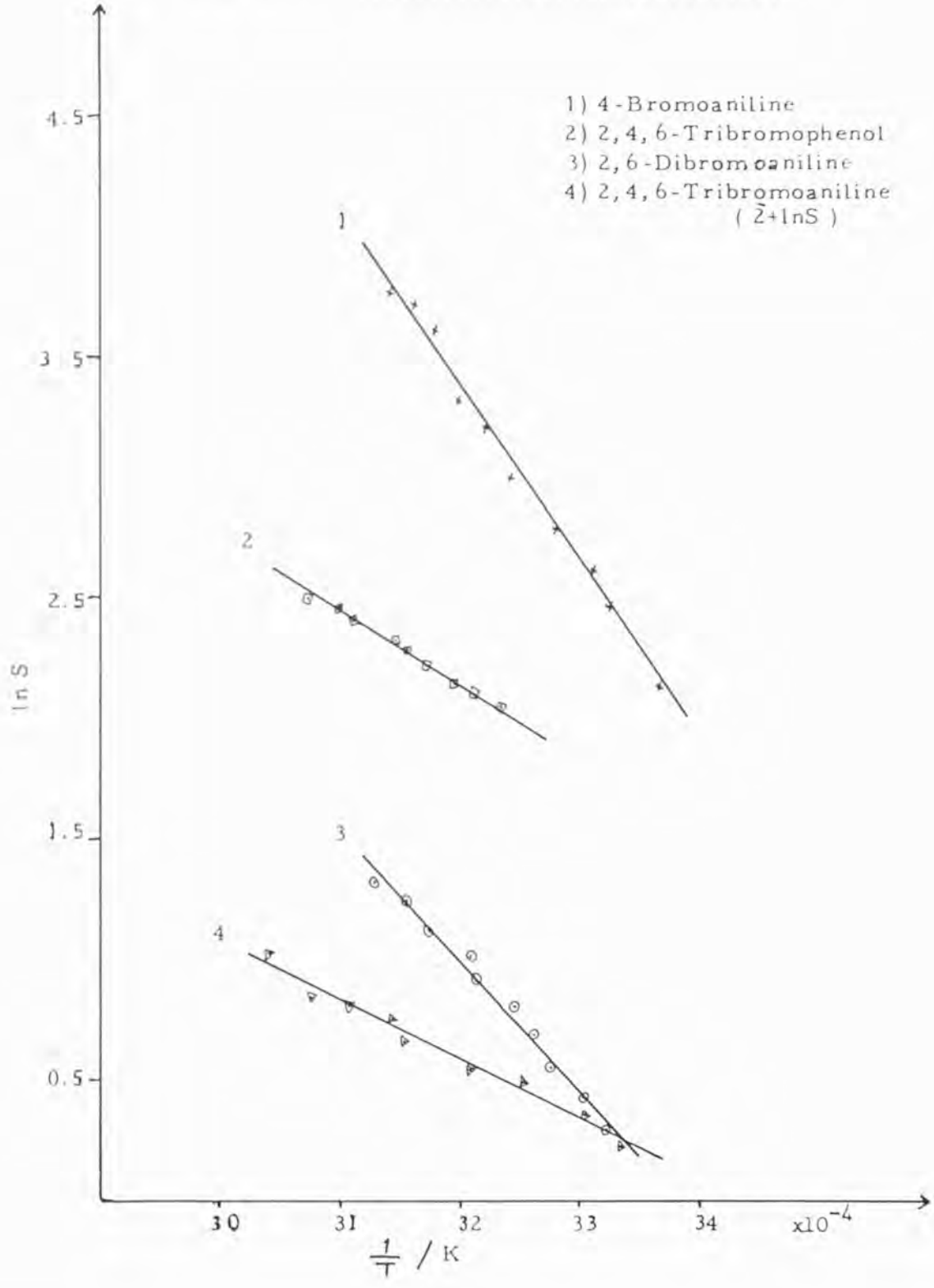


Table II.1

Solubility of 2,4,6-Tribromophenol in Toluene

Mass of 2,4,6-Tribromophenol = 13.5608 g

Density of Toluene = 0.8671 g/cm^3

Volume of toluene/cm^3	S/mol dm^{-3}	lnS	Mean temp/^{o}C	T/K	$\frac{10^4}{T}$/K
6.34	7.49	2.01	54.4	327.55	30.53
6.84	6.94	1.94	52.5	325.65	30.71
7.30	6.51	1.87	49.4	322.55	31.00
7.72	6.15	1.82	48.4	321.55	31.10
8.26	5.75	1.72	47.0	320.15	31.23
9.04	5.25	1.66	44.3	317.45	31.50
10.02	4.74	1.56	41.8	314.95	31.75
11.34	4.19	1.43	38.6	311.75	32.08
12.34	3.85	1.35	36.4	309.55	32.31
13.44	3.53	1.26	36.7	309.85	32.27
14.68	3.23	1.17	32.9	306.05	32.67
16.94	2.80	1.03	30.6	303.75	32.92

Table II.2

Solubility of 4-Bromoaniline in Toluene

Mass of 4-Bromoaniline = 6.2148* g, 9.3315 g

Volume of toluene/cm^3	S/mol dm^{-3}	lnS	Mean temp/^oC	T/K	$\frac{10^4}{T}$/K
1.84	22.65*	3.12	38.1	311.25	32.13
2.16	19.29*	2.96	36.8	309.95	32.26
0.98	63.84	4.16	51.7	324.85	30.78
1.18	53.93	3.99	49.1	322.25	31.03
1.38	45.34	3.81	46.3	319.45	31.30
1.54	40.63	3.70	45.0	318.15	31.43
1.88	33.28	3.50	43.5	316.65	31.58
2.36	26.51	3.28	42.4	315.55	31.69
3.06	20.45	3.02	40.2	313.35	31.91
4.02	15.56	2.74	33.7	306.85	32.59
5.72	10.94	2.39	29.8	302.95	33.00
7.54	8.30	2.12	26.3	299.45	33.39

Table II.3

Solubility of 2,6-Dibromoaniline in Toluene

Mass of 2,6-Dibromoaniline = 4.9701 g

Volume of toluene/cm^3	S/mol dm^{-3}	lnS	Mean temp/^oC	T/K	$\frac{10^4}{T}$/K
3.02	7.56	2.02	42.6	315.75	31.67
3.34	6.84	1.92	41.8	314.95	31.75
3.84	5.95	1.78	38.7	311.85	32.07
4.32	5.29	1.67	37.6	310.75	32.18
5.06	4.51	1.51	33.8	306.95	32.58
5.52	4.14	1.42	33.3	306.45	32.63
6.26	3.65	1.29	31.0	304.15	32.88
7.54	3.03	1.11	27.4	300.55	33.27

Table II.4

Solubility of 2,4,6-Tribromoaniline in Toluene

Mass of 2,4,6-Tribromoaniline = 2.6647 g

Volume of toluene/cm^3	S/mol dm^{-3}	lnS	Mean temp/^oC	T/K	$\frac{10^4}{T}$/K
2.60	3.58	1.28	60.0	333.15	30.02
3.28	2.84	1.04	53.8	326.95	30.59
3.86	2.41	0.88	48.6	321.75	31.08
4.37	2.13	0.76	44.5	317.65	31.48
4.82	1.93	0.66	41.6	314.75	31.77
5.30	1.76	0.56	38.8	311.95	32.06
5.78	1.61	0.48	36.3	309.45	32.32
6.36	1.46	0.38	33.4	306.55	32.62
7.16	1.30	0.26	30.4	303.55	32.94
8.46	1.10	0.10	25.7	298.85	33.46

Table II.5

Solubility of 2,4,6-Tribromophenol in n-Propanol

Mass of 2,4,6-Tribromophenol = 14.7724 g

Density of n-Propanol = 0.8017 g/cm^3

Volume of n-propanol/cm^3	S/mol dm^{-3}	lnS	Mean temp/^{o}C	T/K	$\frac{10^4}{T}$/K
4.58	12.16	2.50	52.4	325.55	30.72
4.78	11.65	2.46	49.4	322.55	31.00
5.02	11.09	2.41	48.3	321.45	31.11
5.38	10.35	2.34	44.7	317.85	31.46
5.70	9.77	2.28	43.7	316.85	31.56
5.98	9.31	2.23	42.2	315.35	31.71
6.38	8.73	2.17	39.7	312.85	31.96
6.76	8.24	2.11	38.1	311.25	32.13
7.16	7.78	2.05	36.1	309.25	32.34

Table II.6

Solubility of 4-Bromoaniline in n-Propanol

Mass of 4-Bromoaniline = 8.4299 g

Volume of n-propanol/cm^3	S/mol dm^{-3}	lnS	Mean temp/^oC	T/K	$\frac{10^4}{T}$ / K
1.38	44.29	3.79	45.1	318.25	31.42
1.48	41.30	3.72	43.1	316.25	31.62
1.66	36.82	3.61	41.5	314.65	31.78
2.06	29.67	3.37	39.4	312.55	31.99
2.50	24.45	3.20	37.2	310.35	32.22
3.04	20.11	3.00	35.3	308.45	32.42
3.80	16.08	2.78	31.7	304.85	32.80
4.42	13.83	2.63	28.9	302.05	33.11
5.28	11.58	2.45	27.5	300.65	33.26
7.16	8.54	2.14	23.9	297.05	33.6

Table II.7

Solubility of 2,6-Dibromoaniline in n-Propanol

Mass of 2,6-Dibromoaniline = 5.4159 g

Volume of n-propanol/cm^3	S/mol dm^{-3}	lnS	Mean temp/^oC	T/K	$\frac{10^4}{T}$ / K
3.98	3.77	1.33	46.5	319.65	31.28
4.32	3.48	1.25	43.9	317.05	31.54
4.82	3.12	1.14	42.0	315.15	31.73
5.40	2.78	1.02	38.5	311.65	32.09
6.02	2.49	0.91	38.0	311.15	32.14
6.78	2.22	0.80	35.0	308.15	32.45
7.60	1.98	0.68	33.5	306.65	32.61
8.68	1.73	0.55	32.1	305.25	32.76
9.68	1.55	0.44	29.4	302.55	33.05
11.18	1.34	0.29	27.9	301.05	33.22

Table II.8

Solubility of 2,4,6-Tribromoaniline in n-Propanol

Mass of 2,4,6-Tribromoaniline = 1.5612 g

Volume of n-propanol/cm^3	S/mol dm^{-3}	$\bar{2}$ + lnS [@]	Mean temp/^oC	T/K	$\frac{10^4}{T}$/K
15.78	0.37	1.02	55.9	329.05	30.39
18.30	0.32	0.87	52.1	325.25	30.75
19.82	0.30	0.80	47.5	320.65	31.19
20.88	0.28	0.74	45.2	318.35	31.42
22.72	0.26	0.65	43.9	317.05	31.54
25.33	0.23	0.54	38.7	311.85	32.07
27.44	0.22	0.49	34.4	307.55	32.52
30.02	0.20	0.39	29.5	302.65	33.04
35.00	0.17	0.23	26.7	299.85	33.35

@ $\bar{2}$ + lnS = − lnS +2 −2

e.g $\bar{2}.8$ = − 1.2 + 2 − 2

Table II.9

Solubility Data in Toluene

Compound	$\Delta_{sol}H^{\ominus}$ (kJ mol^{-1})	Solubility at 25°C (g mol dm^{-3})	$\Delta_{sol}S^{\ominus}$ (JK^{-1} mol^{-1})	-m	c	r
2,4,6-Tribromophenol	33.90	2.24	120.40	407.74	14.482	0.995
4-Bromoaniline	65.94	7.04	237.39	793.14	28.553	0.990
2,6-Dibromoaniline	46.65	2.56	164.26	561.07	19.757	0.996
2,4,6-Tribromoaniline	28.09	1.07	94.74	337.83	11.395	0.999

Table II.10

Solubility Data in n-Propanol

Compound	$\Delta_{sol}H^{\ominus}$ (kJ mol^{-1})	Solubility at 25°C (g mol dm^{-3})	$\Delta_{sol}S^{\ominus}$ (JK^{-1}mol^{-1})	-m	c	r
2,4,6-Tribromophenol	24.01	5.53	94.74	288.77	11.395	0.995
4-Bromoaniline	61.95	9.40	226.42	745.18	27.234	0.997
2,6-Dibromoaniline	44.93	1.18	152.05	540.37	18.288	0.994
2,4,6-Tribromoaniline	20.22	0.17	52.99	243.21	6.373	0.989

m = Slope $(\frac{-\Delta_{sol}H^{\ominus}}{R})$

c = Intercept with lnS axis $(\frac{\Delta_{sol}S^{\ominus}}{R})$

r = Correlation Coefficient.

CHAPTER III

III: SOLUTION CALORIMETRY

III. SOLUTION CALORIMETRY

Isoperibol solution calorimetry is a technique in which the temperature of the contents of a reaction vessel in a constant temperature environment is monitored as a function of time. A homemade calorimeter, operated in a partial differential isoperibol mode, which has been described fully elsewhere,[55,56] was used for measuring the enthalpies of bromination of 2-chloroaniline, 4-bromo-2-chloroaniline and 4-chloroaniline in aqueous sodium bromide and perchloric acid medium.

III.A Brief description of the solution calorimeter

A well-stirred water bath kept at 25.0°C was used. The stirring was achieved by a paddle-wheel driven by a 1400 rpm motor. The bath was thermostatted by a precision temperature controller (Tronac Inc. model PT 1040) and chiller (Grant Ltd. model LC10). The water bath was insulated round the sides and bottom by polystyrene sheets and the surface of the water by polyolefin spheres.

The calorimeter vessels are of a glass Dewar-type. They are thin-walled (1 mm) borosilicate glass. One is used for the reaction, and the other is used as a reference. They are of 200 cm^3 capacity and are provided with aluminium lids. The solution in the vessels was stirred by glass stirring rods, driven by constant speed servo-motors.

Glass ampoules were used to introduce the starting materials to the solution in the reaction vessel. These were blown from B5 sockets with two fragile bulbs which were broken against the stirrer spike and the wall of the calorimeter to start the reaction.

The thermistors (YSI 44011, 100 k Ω at 25°C) were contained in a glass tube fitted in the screw-top aluminium lid. A differential thermistor bridge (Carwyn Instruments Ltd., model 104A) was used to measure the difference in temperature between the reaction and reference vessels. The output from the bridge was displayed on a potentiometric chart recorder.

Electrical calibration of the reaction vessel was achieved by passing a current from a constant-voltage source through a calorimetric heater which is a 100 ohm resistor (Tronac Inc., type R24). The voltage across this resistor was measured by using a digital voltmeter. The current through the circuit was measured by the same voltmeter as the voltage across a 10 ohm resistor in series with the calorimetric heater. The time was measured by a timer connected to the calibration circuit. From the voltage, current and the time, the energy of calibration was measured.

III.B Experimental

III.B.1 Materials and Methods

2-Chloroaniline (BDH) was redistilled under reduced pressure b.p. 92°C/18.5 mm Hg, lit.[1] b.p. 113 - 117°/20 mm Hg; 4-bromo-2-chloroaniline was recrystallized three times from dilute ethanol, m.p. 70 - 72°C, lit.[3] 70.5 - 72°C and 4-chloroaniline was recrystallized four times from pet. ether (b.p. 30 - 40°C), m.p. 70 - 71°C lit. 71°C[1] and 69°C.[52]

The purity of each of these halogenated anilines was checked by a) Gas liquid chromatography using a carbowax 1500 (20%), gas chrom P column at 190°C; b) Sharp melting point c) Differential scanning calorimetry which showed 99.99% purity (Appendix II).

Two grades of sodium bromide were used (Koch-Light Ltd, Puriss A.R. grade & Fluka AG, Puriss A.R.). Puriss A.R. grade of sodium bromate was used (Koch-Light Ltd.) and perchloric acid as supplied (BDH).

III.B.1a Synthesis of bromoderivatives

The brominated product of 2-chloroaniline and 4-chloroaniline was prepared by bromination of chloroaniline with bromine (Br^-/BrO_3^-).

1.3 g of aromatic amine in 50 cm^3 deionised water was treated dropwise with bromine solution (2.0 g of sodium bromide and 1.006 g of sodium bromate were dissolved in 25 cm^3 deionised water, then 2.0 cm^3 perchloric acid was added to liberate bromine). The bromoderivatives were purified by recrystallization from pet. ether (40 - 60°C) for 2-chloroaniline and ethanol for 4-chloroaniline. The purity and the structure of 4,6-dibromo-2-chloroaniline were confirmed by a) m.p. 96°C, lit[52] 95°C; b) gas liquid chromotography; c) micro-analysis: C, 25.46; H, 1.48; N, 4.92; $C_6H_4Br_2NCl$ requires C, 25.25; H, 1.41; N, 4.91%. The purity and the structure of 2,6-dibromo-4-chloroaniline were confirmed by a) m.p. 98 - 100°C; b) gas liquid chromatography; c) micro-analysis: C, 25.55; H, 1.03; N, 4.88; $C_6H_4Br_2NCl$ requires C, 25.25; H, 1.41; N, 4.91%.

III.B.1b Calorimetric Method

III.B.1b1 Test Reaction

The measurement of the enthalpy of neutralization of tris (hydroxymethyl) aminomethane [THAM] [$(HOCH_2)_3CNH_2$] (BDH, Aristar grade) in 0.1M hydrochloric acid (BDH, AVS) was used as a test reaction for the operation of the calorimeter. The THAM was ground to a fine powder and heated for 4 h in an oven at 80°C. The THAM was cooled and stored in a vacuum desiccator over silica gel. The mechanical crushing and grinding of the THAM can leave an amount of energy (40 to 90 J mol^{-1}) stored in the solid.[57] For that reason the annealing became necessary to return the solid to its original energy state. By knowing the exact masses of THAM which were corrected to vacuo (Appendix I), the value of the enthalpy of neutralization was obtained. The results are recorded in Table III.1. The mean value of $\Delta_N H^{\ominus}$ is -29.70 $\pm$ 0.05 kJ mol^{-1}; lit.[57]: $\Delta_N H^{\ominus}$ = -29.767 $\pm$ 0.009 kJ mol^{-1} at 25°C.

The neutralization reaction of the THAM in 0.1M HCl is an exothermic reaction. THAM has been used before as a test substance for solution calorimetry.[58]

III.B.1b2 Enthalpy of Reaction of Halogenated Anilines

The measurement of the enthalpy of reaction of bromination of 2-chloroaniline, 4-bromo-2-chloroaniline and 4-chloroaniline was carried out using the same calorimeter. 200.00 cm^3 of deionised water was transferred to the reference vessel. Another 200.00 cm^3 of a mixture of sodium bromide (0.5 M) and perchloric acid (0.5 M) saturated with the end product was transferred to the reaction vessel. The solution was prepared by dissolving dried sodium bromide

(51.49 g) in dilute perchloric acid (500 cm^3, 1M) and deionised water was added to make the total volume 1.000 dm^3. The molarity of perchloric acid was checked by titration against a standard solution of sodium hydroxide using phenolphthalein as indicator. The solution then saturated with the dibromo-chloroaniline by adding an excess of this compound and heating to ~60°C. The solution was cooled and stored at 25°C in the thermostated bath. The solution was filtered immediately before transferring to the reaction vessel.

An empty stoppered ampoule was weighed (to $\pm$ 0.00001 g), loaded with chloroaniline, and reweighed. The ampoule was then fixed to the ampoule holder on the aluminium lid. The two vessels were clamped in the thermostated bath and left overnight to equilibrate. A known weight of sodium bromate was added to the reaction vessel solution through a funnel placed in the vessel lid. The bromine was then liberated. The solution was cooled down nearly to equilibrium by adding a small amount of liquid nitrogen to the cooling tube in the reaction vessel which was fixed to the vessel lid. The system was allowed to come back to thermal equilibrium by leaving it for ~1.5 h. The chart paper was checked by using the millivolt source to correspond to 80 mV. Then the chart recorder pen was positioned to ~1/3 of the chart recorder paper. A 20 min period was recorded before starting the reaction. The ampoule holder was unclamped with care and the ampoule bulbs turned towards the stirrer spike which helped to break the top bulb, and the other bulb was then broken against the vessel wall. The reaction product was formed and the mother liquor assumed a faint yellow colour. Another 30 min

period was recorded. Then the reaction vessel was cooled to nearly equilibrium using liquid nitrogen through the cooling tube in the vessel. The system was left for another 1.5 h to come back to thermal equilibrium.

Electrical calibration was then performed. An approximately 30 min period was recorded to get a sufficient base line. The heating circuit was then switched on simultaneously with the timer, and the recorder pen recorded the same displacement as the reaction period. The voltage across the heater and the standard resistor were recorded. The heating circuit was switched off and the elapsed time recorded. The recorder pen was left to record a period of ~25 min.

At the end of the experiment the reaction vessel was taken out of the thermostated bath and allowed to stand. The precipitated product was then settled, and the mother liquor was decanted to leave the precipitate in ~50 cm^3 of the reaction medium. The brominated product was extracted by diethyl ether, dried over magnesium sulphate, filtered and the solvent was removed by rotary evaporator. The dry product was compared with the authentic compound. The micro-analysis for the product of bromination of 2-chloroaniline showed C, 25.30; H, 1.44; N, 4.82%. The product of the bromination of 4-bromo-2-chloroaniline showed C, 24.71; H, 1.48; N, 4.48%. The product of the bromination of 4-chloroaniline showed C, 25.47; H, 1.50; N, 4.48%. $C_6H_4Br_2NCl$ requires C, 25.25; H, 1.41; N, 4.91%.

III.C Results and Calculations

The results obtained from the calorimetric measurements for the bromination of 2-chloroaniline and 4-bromo-2-chloroaniline in sodium bromide (0.5M) and perchloric acid (0.5 M) are recorded in Table III.2 and Table III.3.

The results obtained from the calorimetric measurements for the bromination of 4-chloroaniline in sodium bromide (0.75 M) and perchloric acid (0.75 M) are recorded in Table III.4.

The heat due to the ampoule breaking was negligible[55]. The enthalpy of bromination of chloroanilines was calculated from the following equation:-

$$\Delta_r H^{\ominus} = \frac{-P.(V/10)t.\ \Delta_r T.M}{1000\ .\ \Delta_c T.W} \qquad KJ\ mol^{-1}$$

where:

P = voltage across heater resistor/volts

V = voltage across 10 ohm resistor/volts

t = time of heating/sec.

$\Delta_r T$ = corrected output voltage change of the reaction period/volts

$\Delta_c T$ = corrected output voltage change of the calibration period/volts

M = molecular weight of the compound/g

W = weight of the compound/g.

In this type of calorimeter there is some heat exchange between the calorimeter and its surroundings for which a correction must be made.

For that purpose the Graphical Extrapolation based on Dickinson's method[59] was applied, which is conveniently applied to a fast reaction and calibration. Dickinson found that the mean temperature of a reaction period (T_m) would occur at 63% of the total heat evolution, Fig. III.1. In practice the extrapolation is usually carried out at 0.6 ΔT. When the tangents to the calorimetric curve are extrapolated to T_m, the corrected temperature will be obtained as the difference between the corrected temperature before the reaction $T_{i(corr)}$ and the corrected temperature after the reaction $T_{f(corr)}$.

For the electrical calibration the heat evolution is usually linear with time and the extrapolation is carried out at 0.5 ΔT.

The confidence limits for the experimental measurements given in this section were calculated using Program LIM 95. This Program was written in Fortran 77 and run on the Royal Holloway and Bedford New College, DEC VAX 11/780 computer.[54]

Fig. III.1 Diagram Showing the Graphical Extrapolation Method of DICKINSON

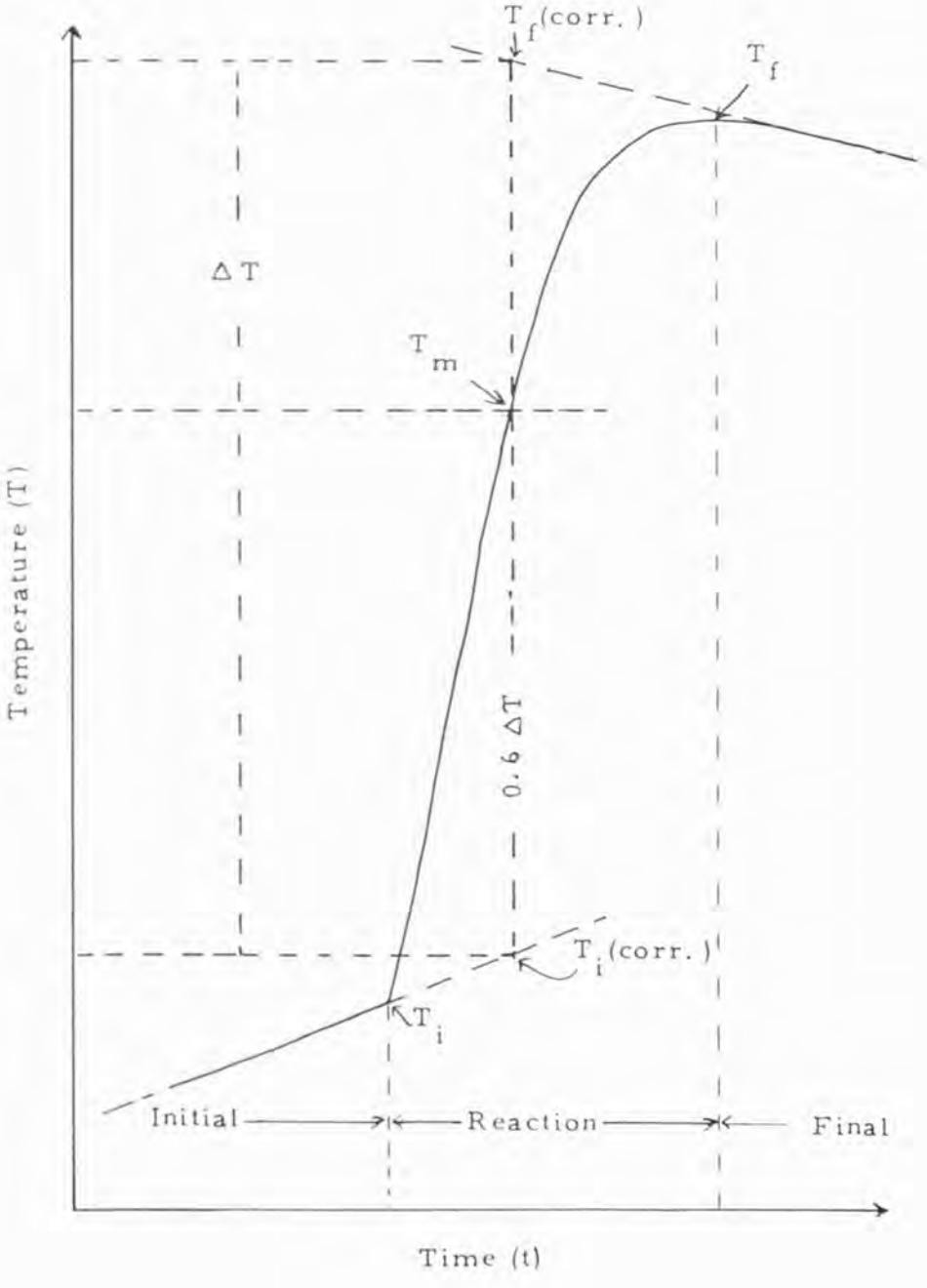


Table III.1

Enthalpy of Neutralization of THAM in excess 0.1M HCl

w/g	dilution, n^*	$-\Delta_N H^\ominus$ KJ mol^{-1}
0.14915	2256	29.66
0.15410	2184	29.67
0.12948	2599	29.74
0.17238	1952	29.74
0.33899	993	29.75
0.42770	787	29.64

$\Delta_N H^\ominus_{(mean)}$ = -29.70 ± 0.05 KJ mol^{-1}

lit.[57] $\Delta_N H^\ominus$ = -29.767 ± 0.009 kJ mol^{-1}

n^* = mole ratio of water to THAM.

Table III.2

Enthalpy of Bromination of 2-Chloroaniline in Aqueous Sodium Bromide and Perchloric Acid (0.5 M)

o-Chloroaniline (w/g)	Sodium bromate (w/g)	$-\Delta_r H^{\ominus}$ (kJ mol^{-1})
0.01936	0.040	207.60
0.03230	0.060	207.60
0.01974	0.040	207.64
0.02359	0.050	207.61
0.07186	0.120	208.75

$\Delta_r H^{\ominus}_{(mean)} = -207.84 \pm 0.63$ kJ mol^{-1}

Table III.3

Enthalpy of Bromination of 4-Bromo-2-Chloroaniline in Aqueous Sodium Bromide and Perchloric Acid (0.5 M)

4-Bromo-2-Chloroaniline (w/g)	Sodium bromate (w/g)	$-\Delta_r H^{\ominus}$ (kJ mol^{-1})
0.02817	0.040	88.40*
0.03242	0.045	91.34
0.04176	0.055	91.44
0.03705	0.055	91.24
0.04909	0.065	92.30
0.03964	0.055	90.14

$\Delta_r H^{\ominus}_{(mean)} = -91.29 \pm 0.96$ kJ mol^{-1}

* Rejected at $3\hat{S}$ level.

Table III.4

Enthalpy of Bromination of 4-Chloroaniline in Aqueous Sodium Bromide and Perchloric Acid (0.75 M)

4-Chloroaniline (w/g)	Sodium bromate (w/g)	$-\Delta_r H^\ominus$ (kJ mol^{-1})
0.07919	0.12	190.36
0.07612	0.12	190.32
0.06985	0.12	190.40
0.06833	0.10	190.35
0.07468	0.12	188.20
0.08518	0.12	189.10
0.03525	0.07	188.52

$\Delta_r H^\ominus_{(mean)} = -189.61 \pm 0.90$ kJ mol^{-1}

CHAPTER IV

IV: TITRATION CALORIMETRY

IV. TITRATION CALORIMETRY

When two components A and B react to form a product D, they also

$$aA,aq + bB,aq \longrightarrow dD,c$$

produce a molar heat of reaction, $\Delta_r H^{\ominus}$, which can be calculated from the temperature change, ΔT, in the system. If B is added continuously to A, there will be a continuous change of the temperature of the system. This addition is called a thermometric titration, by which the absolute amount of A is measured. The plot of the temperature, or some function of temperature, of the system against the time in which the volume of the titrant is added is called the titration curve.

IV.A Brief Description of the Titration Calorimeter

The titration calorimetry of 2-nitroaniline and 4-nitroaniline with bromine was carried out using the same calorimeter, which was described earlier in Chapter III, with slight modifications. The reaction vessel was adapted to match the technique. The vessel had the same design as in the ampoule-breaking reaction vessel but was provided with a side-neck used for delivering the titrant (Fig. IV.1.a and b). The titrant was delivered from a 10 cm^3 syringe which had a glass barrel and PTFE plunger. The syringe was actuated by an electric syringe drive (Harvard Apparatus, pump). A 10 cm^3 length of 3 mm in diameter PTFE tubing ran from the syringe to a glass

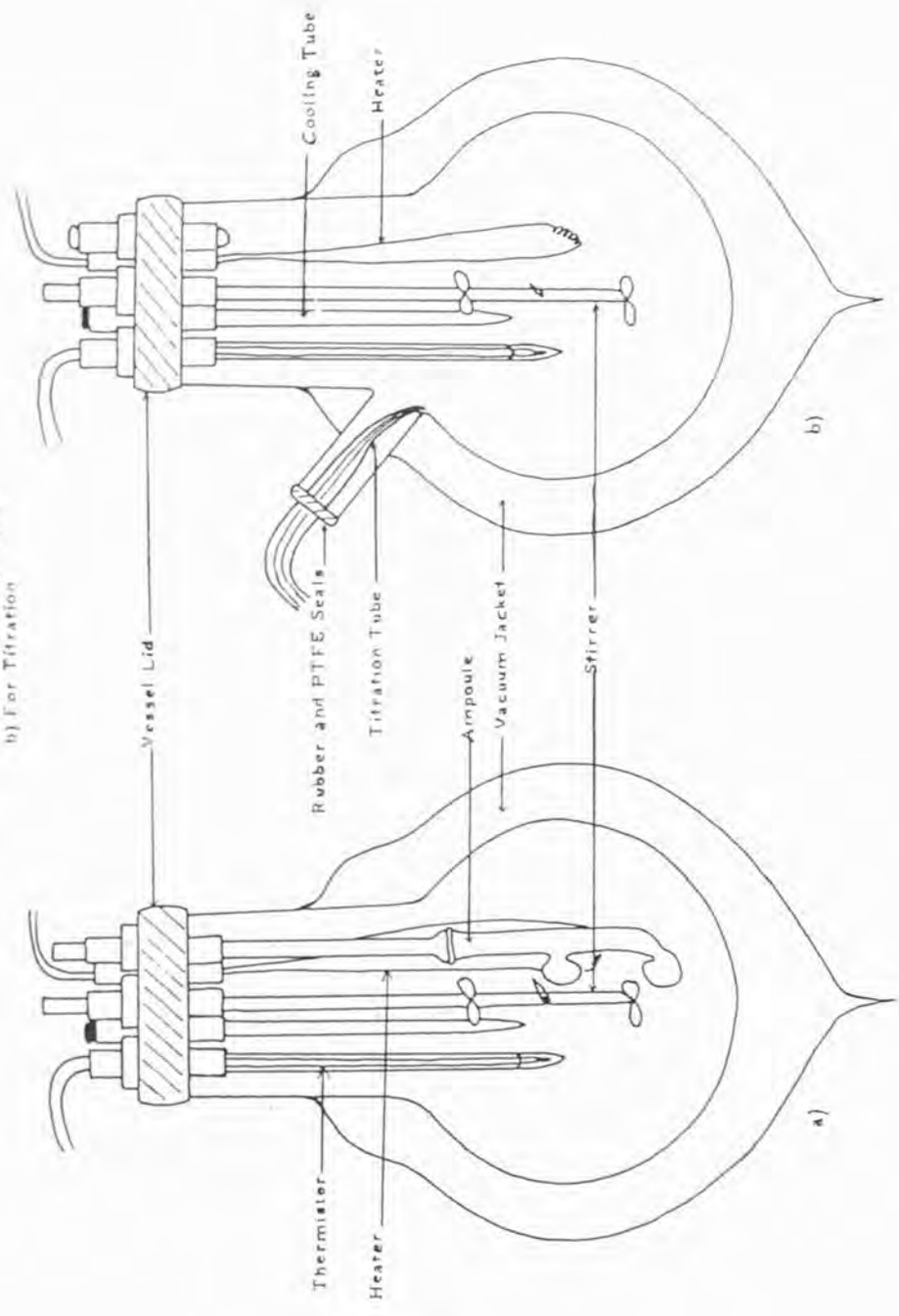


FIG. IV-1 CALORIMETER VESSEL
a) For Breaking Ampoule
b) For Titration

three-way tap connected to PTFE tubing (5 metre length, 2 mm diameter) connected to the reaction vessel. The tubing was coiled around a piece of brass tube (5 cm in diameter), which was immersed in the thermostated bath. The volume of the tubing was about 16 cm^3 and it acted as titrant reservoir. The PTFE tubing was connected to a glass tube which ran from the outside of the reaction vessel through the side-neck. The titrant tube was held into the side-neck by a rubber screw seal at its top end; the seal prevented the reaction vessel from flooding from the bath. The end of the titrant tube was drawn to a capillary of 0.5 mm in diameter, which touched the inside wall of the vessel.

IV.B Experimental

IV.B.1 Materials and Methods

2-Nitroaniline (BDH) was recrystallized three times from dilute ethanol, m.p. 72 - 73°C, lit.[60] 69.5 - 70.5°C. Also 4-nitroaniline was recrystallized three times from dilute ethanol, m.p. 148 - 149°C, lit.[1] 148°C.

The purity of both compounds was further checked by differential scanning calorimetry, which showed 99.99% purity.

Sodium bromate (Puriss A.R. grade-Koch-Light Ltd.), sodium bromide (Fluka, AG puriss A.R.), perchloric acid (GPR; 60% (BDH)) and hydrobromic acid (GPR; 60% (BDH)), were used.

IV.B.1a Synthesis of the Bromoderivatives

The 4,6-dibromo-2-nitroaniline and the 2,6-dibromo-4-nitroaniline were prepared beforehand and used as check materials to compare with the brominated product of 2-nitroaniline and 4-nitroaniline from the calorimetric reaction.

The bromination was carried out as follows: 1.4 g of aromatic amine suspended in 50 cm^3 de-ionised water was treated dropwise with bromine solution (1.1 g of sodium bromate and 2 g of sodium bromide were dissolved in 25 cm^3 de-ionised water, then 2 cm^3 of perchloric acid was added to liberate bromine). The reaction was stirred well for 30 min. The precipitate was filtered off and washed with a little distilled water, left to dry overnight, and finally recrystallized from ethanol/heptane.

The purity and the structure of 4,6-dibromo-2-nitroaniline were checked by a) gas liquid chromatography, b) microanalysis, which showed C, 24.62; H, 1.28; N, 9.43. $C_6H_4Br_2N_2O_2$ requires C, 24.35; H, 1.36; N, 9.46%.

The purity and the structure of the isomeric 2,6-dibromo-4-nitroaniline were checked by a) m.p. 202 - 203°C, lit.[16] 202 - 204°C. b) microanalysis which showed C, 25.01; H, 1.46; N, 9.57%.

IV.B.1b Calorimetric Titration Method

IV.B.1.b.1. Test Reaction

A performance test of the syringe was made by delivering distilled water (0.32 cm^3/min). A known volume of the water was collected from the titrant delivery tube at

a measured time (7.1 cm^3 delivered within 22.2 min). This was repeated three times, and the same delivery rate was used for all subsequent titrations.

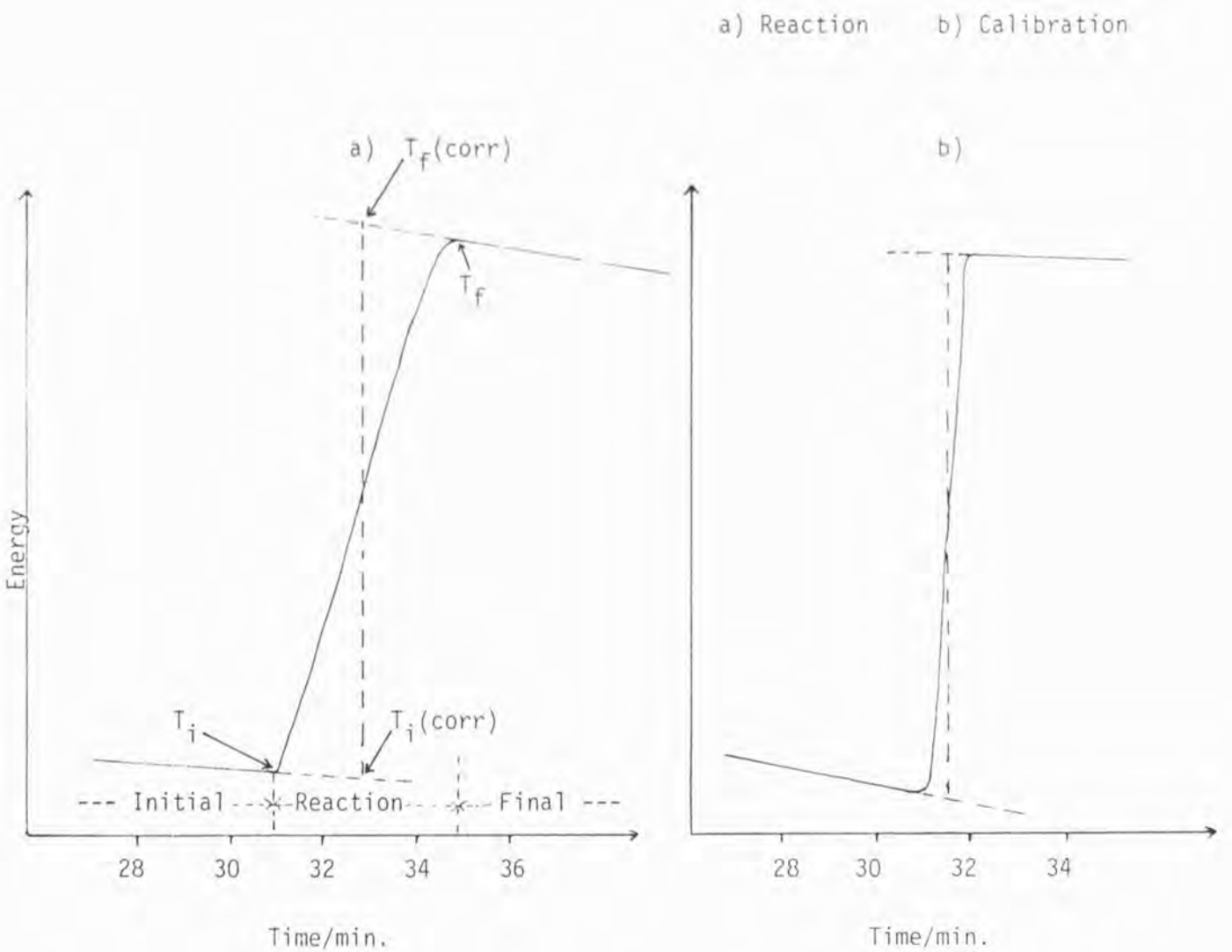
The accuracy of the calorimeter was checked by the measurement of the enthalpy of neutralization of aqueous hydrochloric acid (0.25 M) with aqueous sodium hydroxide (0.0006 M). The results are recorded in Table IV.1. Fig. IV.2, shows the thermometric titration curve for the neutralization reaction and the electrical calibration.

IV.B.2.b.2 Reaction Experiment

The titrant for the bromination was an aqueous solution containing bromine (0.4 M). This solution was prepared by dissolving sodium bromide (51.49 g) in a little de-ionised water and 10.0 cm^3 hydrobromic acid (sg, 1.7; 60%) in a 100 cm^3 volumetric flask. Then sodium bromate (2.0120 g) was added to produce the bromine. De-ionised water was used to complete the solution to the mark. Then the delivery system was filled with this solution, care being taken to exclude air bubbles, and the system then left to equilibrate overnight in the thermostated bath.

The compound for bromination was accurately weighed and transferred quantitatively to the reaction vessel by the aid of 200.00 cm^3 of the aqueous reaction solution. This reaction solution consisted of sodium bromide and perchloric acid (1 M), which was saturated with the final product (dibromonitroaniline). The reaction

Fig. IV.2 Thermometric Titration HCl/NaOH



vessel then was connected to the delivery system through the side-neck, fixed in the bath and left to equilibrate overnight. Pre-reaction was prevented by leaving a small air bubble in the capillary tip.

A period of 30 min was recorded before adding the titrant when the three-way tap was adjusted to the position for connecting the syringe with the tubing. The syringe drive was switched on to deliver the titrant, which was stopped ca. 60 sec after the end point was observed on the chart paper. The reaction vessel was cooled to bring the recorder pen back to the stationary base-line with a little liquid nitrogen through the cooling tube. The system was allowed to equilibrate for ca. 1 h. A period of 20 min was recorded and the calibration heater switched on to give the same chart displacement for the reaction period. The voltage across the heater resistor, the voltage across the 10 ohm resistor, and the elapsed time were recorded.

IV.C Results and Calculations

A blank experiment was performed in order to determine the thermal effect of the addition of the aqueous bromine as a titrant (200.00 cm^3 of the reaction solution was titrated with bromine). The titration period was 5 min, the usual period for a bromination reaction. The cooling effect was found to be 0.03 J/sec.

The results obtained from the thermometric titration of 2-nitroaniline with bromine are recorded in Table IV.2 and Table IV.3 shows the results obtained from the titration of 4-nitroaniline with bromine.

Fig. IV.3 shows the titration curves for the 2-nitroaniline and 4-nitroaniline.

The enthalpy of the reaction of the bromination of the nitroanilines was calculated from the following equation:-

$$\Delta_r H^{\ominus} = \frac{-p.t.(v/10).\ (\Delta_r T/\Delta_c T)-(+a.t')}{1000} .\ \frac{M}{W}\ \text{kJ mol}^{-1}$$

p = voltage across heater resistor/volts.

v = voltage across 10 ohm resistor/volts.

t = time of heating/sec.

$\Delta_r T$ = corrected output voltage change of the reaction period/volts.

$\Delta_c T$ = corrected output voltage change of the calibration period/volts.

M = molecular weight of the compound/g.

W = weight of the compound/g.

a = cooling effect of the titrant/J $sec.^{-1}$.

t' = titration period/sec.

$\Delta_r T$ and $\Delta_c T$ were calculated at 0.5 from applying the extrapolation method in both cases to the reaction and the calibration traces.

The confidence limits for the experimental measurements given in this chapter were calculated using Program LTM 95.[54]

Fig. IV.3 Thermometric Titration

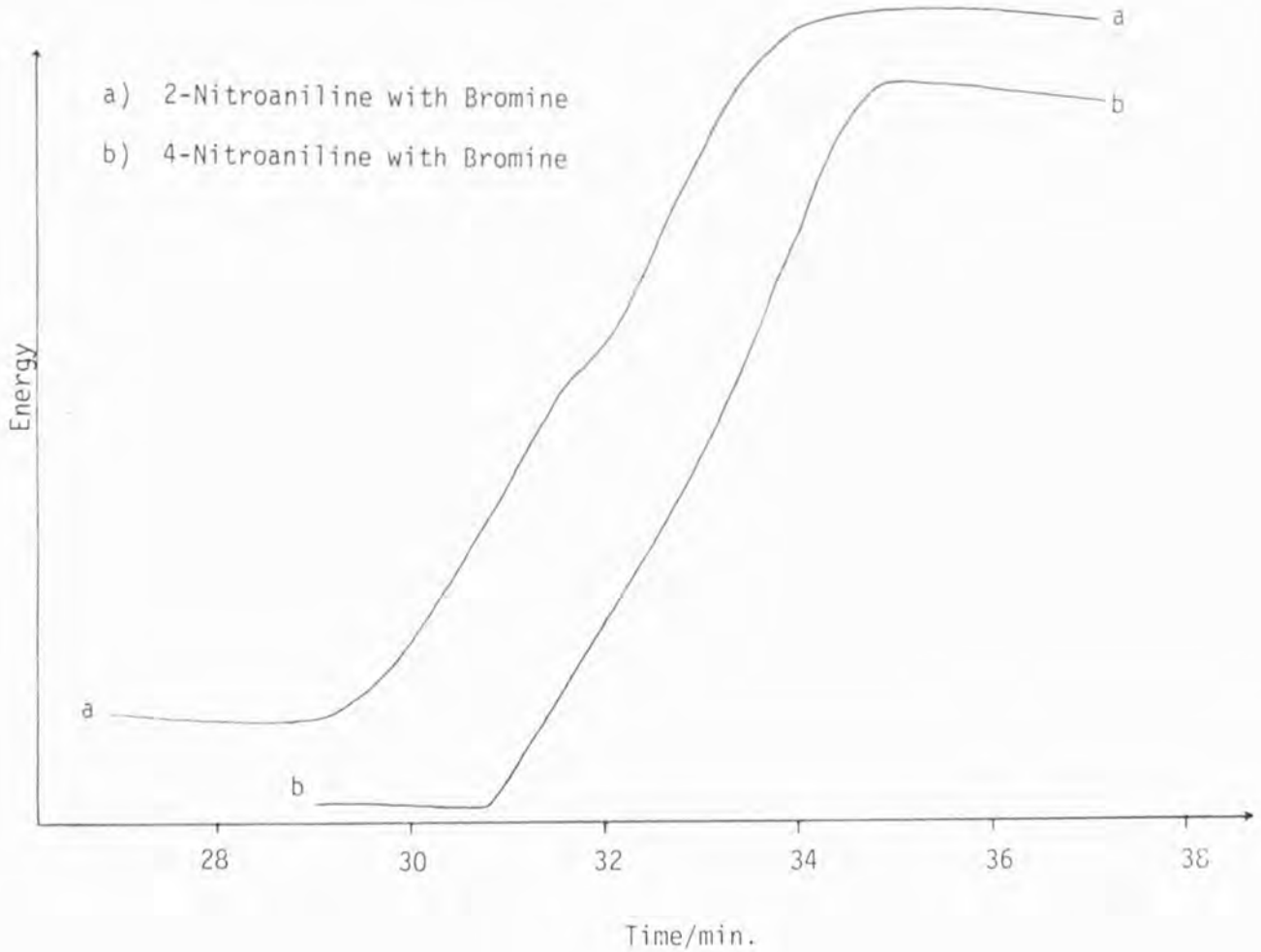


Table IV.1

Enthalpy of Neutralization of Hydrochloric Acid (0.25 M)

with Sodium Hydroxide (0.0006 M)

$-\Delta_r H^{\ominus}$/kJ mol^{-1}
55.26
54.66
56.20
55.63
55.85

$\Delta_r H^{\ominus}_{(mean)} = -55.52 \pm 0.73$ kJ mol^{-1}.

lit.[55] $\Delta_r H^{\ominus}_{(mean)} = -55.74 \pm 0.36$ kJ mol^{-1},

lit.[61] $\Delta_r H^{\ominus}_{(mean)} = -55.73 \pm 0.07$ kJ mol^{-1}.

Table IV.2

Enthalpy of Bromination of 2-Nitroaniline from Thermometric Titrimetry

2-Nitroaniline (w/g)	$-\Delta_r H^{\ominus}$/kJ mol^{-1} 1:1	1:2
0.03308	94.53	197.25
0.03323	94.10	197.13
0.03328	95.62	197.26
0.03324	94.91	197.31
0.03328	94.38	195.56
0.03276	93.47	197.69

Aqueous bromine, 0.4 M, was used throughout.

2-Nitroaniline and Bromine (BrO_3^-/Br^-) (1:1; 0.00024 mol)

$\Delta_r H^{\ominus}_{(mean)} = -94.50 \pm 0.77$ kJ mol^{-1}

2-Nitroaniline and Bromine (BrO_3^-/Br^-) (0.00024 mol aniline 0.00048 mol Br_2)

$\Delta_r H^{\ominus}_{(mean)} = -197.03 \pm 0.78$ kJ mol^{-1}.

Table IV.3

Enthalpy of Bromination of 4-Nitroaniline from Thermometric Titrimetry

4-Nitroaniline (w/g)	$-\Delta_r H^{\ominus}$/kJ mol^{-1}	
	1:1	1:2
0.01105	103.75*	215.55*
0.03314	96.90	195.08
0.03311	95.27	196.10
0.03308	96.95	196.90
0.03314	95.61	197.05
0.03314	95.19	196.96
0.03320	95.44	197.11

* Rejected on statistical grounds

Aqueous Bromine, 0.4 M was used throughout.

4-Nitroaniline and Bromine (BrO_3^-/Br^-) (1:1; 0.00024 mol)

$\Delta_r H^{\ominus}_{(mean)}$ = -95.89 $\pm$ 0.85 kJ mol^{-1}.

4-Nitroaniline and Bromine (BrO_3^-/Br^-) (0.00024 mol aniline 0.00048 mol Br_2)

$\Delta_r H^{\ominus}_{(mean)}$ = -196.53 $\pm$ 0.84 kJ mol^{-1}.

CHAPTER V

V: DISCUSSION OF THE RESULTS

V. DISCUSSION OF THE RESULTS

V.A Solubility

Solubility measurements by dynamic precipitation were found to be useful for indirect measurements of enthalpy of solution. In Chapter II, Tables 9 and 10 show the calculated differential heat of solution at saturation for 2,4,6-tribromophenol, 4-bromoaniline, 2,6-dibromoaniline and 2,4,6-tribromoaniline in n-propanol and toluene.

From the solubility data we can see the enthalpy of solution of these compounds in n-propanol and toluene is endothermic. The higher solubility of 2,4,6-tribromophenol in n-propanol than that in toluene reflects the occurrence of intermolecular hydrogen bonding, as well as intramolecular hydrogen bonding. The slightly higher solubility of 4-bromoaniline in n-propanol than in toluene suggests the occurrence of intermolecular hydrogen bonding. But the lower solubility of 2,4-dibromoaniline and 2,4,6-tribromoaniline in n-propanol than that in toluene reflects that the intramolecular hydrogen bonds are little affected.

The enthalpy of transfer of a solute (i) from one solvent to another can be calculated from the difference between the enthalpy of solution of the solute in two solvents a and b as follows:[34]

$$\Delta_t H^{\ominus}_{i(b \leftarrow a)} = \Delta_{sol} H^{\ominus}_{i,b} - \Delta_{sol} H^{\ominus}_{i,a}$$

In this way the enthalpy of transfer of the previous compounds from toluene to n-propanol was calculated and is tabulated in the following Table.

Table V.1 Derived Thermodynamic Parameters of Transfer from Toluene to n-Propanol

Compound	$\Delta_t G^{\ominus}$ (kJ mol^{-1})	$\Delta_t H^{\ominus}$ (kJ mol^{-1})	$\Delta_t S^{\ominus}$ (JK^{-1}mol^{-1})
2,4,6-Tribromophenol	-2.24	-9.89	-25.66
4-Bromoaniline	-0.72	-3.99	-10.97
2,6-Dibromoaniline	+1.92	-1.72	-12.21
2,4,6-Tribromoaniline	+4.56	-7.87	-41.75

The general feature of these calculations is that the enthalpy of transfer of these compounds from toluene to n-propanol is exothermic. This may reflect the preferential forming of hydrogen bonds between the amino group and n-propanol as well as between the phenolic hydroxyl group and n-propanol. The free energy of transfer ($\Delta_t G^{\ominus}$) was found to be positive or negative depending upon the solute. Also, it was observed that the entropy of transfer ($\Delta_t S^{\ominus}$) is negative, which suggests that the transfer of these compounds from toluene to n-propanol is entropy inhibited.

The general thermodynamic profile of these results is quite predictable after comparison with some results from previous work on the measurements of the enthalpy of transfer by flow microcalorimetry. These are presented in the following Table.

Table V.2 Thermometrics of Solute Transfer Between Two Solvents

Solute	Transfer Process	$\Delta_t G^{\ominus}$(kJ mol^{-1})	$\Delta_t H^{\ominus}$(kJ mol^{-1})	$\Delta_t S^{\ominus}$(Jk^{-1}mol^{-1})
Phenol[33]	Octane → Water	-4.77	-16.32±0.46	-38.49
	Toluene → Water	+1.13	-6.28±0.54	-24.69
Aniline[33]	Toluene → Water	+5.52	-5.02±0.63	-36.40
4-Chloro-phenol[35]	2,2,4-Trimethyl-pentane ⟶ Aqueous buffer (pH 7)	-2.26	-17.20(0.10)*	-48.40
4-Chloro-aniline[35]	2,2,4-Trimethyl-pentane ⟶ Aqueous buffer (pH 7)	+2.74	-10.30 (0.25)*	-43.74

* Standard deviation.

V.B Solution Calorimetry

Bromination using bromine generated from bromide/bromate in acidic medium is well known.[2,17] Such mixtures were used for the bromination of 2-chloroaniline, 4-bromo-2-chloroaniline and 4-chloroaniline in perchloric acid sodium/bromide medium. Bromination of aniline in aqueous solution yields quantitatively, the tribromo compound immediately on addition of bromine.[2] This is consistent with the initial product 4-bromoaniline being less basic than aniline, and consequently there is greater proportion of the former present as free base. However since the NH_2 group is o- and p- directing, then

the expected product from the bromination of 2-chloro- and 4-chloroaniline will be the dibromo analogue with substitution at the available o- and p-positions and in the bromination of 4-bromo-2-chloroaniline the product will be 2-chloro-4,6-dibromoaniline. This agreed with the results obtained by Truedsson[62] for the bromination of 2-chloroaniline and 4-chloroaniline by anodically generated bromine. The bromine entered all the o- and p- positions. He concluded that the substituted aniline containing halogen can be titrated quantitatively with coulometrically generated bromine in water/acetic acid media, with or without added pyridine.

Depending on that fact, the thermodynamic interest for measuring the enthalpy of the reaction of the bromination of the chloroanilines was carried out. The bromine solution was already prepared in the calorimetric cell and the ampoule was loaded with aromatic amine. The thermochemical equation of this reaction at equilibrium can be written as:-

$$\begin{array}{ccccc} C_6H_6NCl,_c + 2Br_{2,aq} & \xrightarrow{\Delta_r H_5^{\ominus}} & C_6H_4NClBr_{2,c} + 2HBr,_{aq} & & (1) \\ \downarrow & & \downarrow & & \\ \Delta_f H_1^{\ominus} & & \Delta_f H_3^{\ominus} & & \\ & \downarrow & & \downarrow & \\ & \Delta_f H_2^{\ominus} & & \Delta_f H_4^{\ominus} & \end{array}$$

$$\Delta_f H_3^{\ominus}\ C_6H_4NClBr_{2,c} = \Delta_f H_1^{\ominus}\ C_6H_6NCl,_c + 2\ \Delta_f H_2^{\ominus}\ Br_{2,aq} + \Delta_r H_5^{\ominus} - 2\Delta_f H_4^{\ominus}\ HBr,_{aq}$$

$$C_6H_5NClBr_{,c} + Br_{2,aq} \xrightarrow{\Delta_r H_5^\ominus} C_6H_4NClBr_{2,c} + HBr_{,aq}$$

$$\downarrow \Delta_f H_1^\ominus \qquad \downarrow \Delta_f H_2^\ominus \qquad \downarrow \Delta_f H_3^\ominus \qquad \downarrow \Delta_f H_4^\ominus$$

$$\Delta_f H_1^\ominus\ C_6H_5NClBr_{,c} = \Delta_f H_3^\ominus\ C_6H_4NClBr_{2,c} + \Delta_f H_4^\ominus\ HBr_{,aq} - \Delta_f H_2^\ominus\ Br_{2,aq} - \Delta_r H_5^\ominus$$

In equation (1) by knowing the enthalpy of formation of the starting material ($\Delta_f H_1^\ominus$), the enthalpy of formation of the aqueous bromine ($\Delta_f H_2^\ominus$), the enthalpy of formation of the aqueous hydrogen bromide ($\Delta_f H_4^\ominus$) and by determining the enthalpy of the reaction ($\Delta_r H_5^\ominus$), then the enthalpy of formation of the brominated product ($\Delta_f H_3^\ominus$) can be obtained. It is a pity in this case that the ancillary data is not all available. The enthalpy of solution of bromine in aqueous sodium bromide/perchloric acid and of sodium bromide in aqueous perchloric acid can be determined by the same isoperibol solution calorimetry[44] and so the enthalpy of formation of aqueous bromine and hydrogen bromide can be obtained. The determination of the enthalpy of formation of the chloroaniline is difficult, and the values available from the literature refer to the temperature at the melting point.[42] Hence the calculations are restricted to the enthalpy of the reaction, which has not been measured before. The results obtained from this work are given in Chapter III. The final products were identified by micor-analysis and by GLC. The mean value for $\Delta_r H^\ominus$ for the bromination of 2-chloroaniline, 4-bromo-2-chloroaniline and 4-chloroaniline was found to be -207.84 $\pm$ 0.63 kJ mol^{-1}, -91.29 $\pm$ 0.96 kJ mol^{-1} and -189.61 $\pm$ 0.90 kJ mol^{-1} respectively.

V.C Titration Calorimetry

2-Nitroaniline and 4-nitroaniline brominated sequentially in acidic medium with bromine,[17] which means that the monobromination is completed first and then the dibromo- product formed. The results obtained are recorded in Chapter IV.

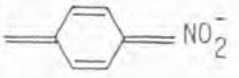
A general view at the thermometric titration curve for the bromination of 2-nitroaniline suggests the following:

$$C_6H_6N_2O_{2,aq} \xrightarrow{Br_{2,aq}} C_6H_5BrN_2O_{2,c} \xrightarrow{Br_{2,aq}} C_6H_4Br_2N_2O_{2,c}$$

We can distinguish two break-points. The first break-point occurred when equimolecular amounts of bromine solution were added. In that stage 4-bromo-2-nitroaniline probably was the main product. The second break-point corresponded to the completion of dibromination. This was confirmed by calculating the volume of bromine solution needed to complete the reaction; 1.6 cm^3 of bromine solution (0.4 M) added within five minutes was enough to complete the dibromination with a slight excess of bromine appearing as a yellow colour. The final product was identified by micro-analysis and GLC. Originally the bromine in the titrant solution occurred as tribromide ion due to the high concentration of the bromide,[63] but the free bromine was released when the titrant was diluted in the reaction vessel and the high bromide ion concentration was reduced.

For the bromination of 4-nitroaniline,

$$C_6H_6N_2O_{2,c} \xrightarrow{Br_{2,aq}} C_6H_5BrN_2O_{2,c} \xrightarrow{Br_{2,aq}} C_6H_4Br_2N_2O_{2,c}$$

the thermometric titration curve showed the most clear break-point at completion. The weakness of the first break-point when one equimolecular amount of bromine reacted may be explained in terms of the low basicity, ascribed to the Zwitter-ionic form which is an important contributor ion to the structure of 4-nitroaniline,[36,37] viz. 

The enthalpy of the bromination of 2-nitroaniline and 4-nitroaniline was calculated at each step of the bromination and the results are tabulated in Tables IV.2 and 3.

The cooling effect due to the addition of the titrant was found to be significant. This was taken into consideration for all calculations of the enthalpy of the reaction.

The same way as in the ampoule breaking mode, the enthalpy of formation of the dibromo compound can be calculated if the enthalpies of formation of bromine (aq) hudrogen bromide (aq) and the starting material (aq) are all known. The difficulties this time are found in determining the enthalpy of formation of the starting material in aqueous solution. The enthalpy of solution determinations for these compounds by solution calorimetry was difficult due to the long time needed to attain solution. In bromination studies the organic substrate was already dissolved and was left overnight to equilibrate.

The general trend of bromination in these two compounds gave results consistent with other results.[62] These other results were reported from the bromination of nitroanilines with anodically generated bromine, which suggested that the nitroanilines are deactivated and were not very prone to react with bromine. Only the mononitroanilines formed the monobromo-nitroaniline.

Comparison between the enthalpies of bromination of the two isomeric nitroanilines shows only slight difference between the two values.

V.D. Further Work

Some other compounds might be brominated, using solution calorimetry to measure the enthalpy of the reaction to help in calculating the enthalpy of formation of the end product or the starting material. Examples of these compounds are: toluidines, fluoroanilines, fluorophenols, chlorophenols, nitrophenols and aminophenols.

APPENDIX I

Correction of Weighings for Buoyancy[64]

When very accurate weighings are necessary, a correction for the buoyancy of the air must be made. It is evident that the weight of an object in vacuo is equal to the weight in the air plus the weight of air displaced by the object minus the weight of air displaced by the balance weights.

$$W_v = W_a + d_a \left(\frac{W_v}{d_b} - \frac{W_a}{d_w} \right) \qquad (1)$$

W_v = weight in vacuo/g

W_a = apparent weight in air/g

d_a = density of the air, 0.0012 g cm^{-3}

d_b = density of the substance/g cm^{-3}

d_w = density of the weights, 8.0 g cm^{-3}.

Since the difference between W_v and W_a does not usually exceed 1 to 2 parts per thousand, equation (1) is written as follows:

$$W_v = W_a + W_a \left[0.0012 \left(\frac{1}{d_b} - \frac{1}{8.0} \right) \right]$$

$$= W_a + kW_a/1000$$

where

$$k = 1.20 \left(\frac{1}{d_b} - \frac{1}{8.0} \right)$$

When a substance of density d_b weighs W_a grams in the air, then $W_a \cdot k$ milligrams must be added to the weight in the air to obtain the weight in the vacuo.

This correction was applied to obtain the accurate weights of THAM.

APPENDIX II

Purity Determination by Differential Scanning Calorimetry

The determination of the purity of organic materials by differential scanning calorimetry (DSC) is well known.[65,66a,66b] This determination based upon the fact that the presence of a minute amount of impurity in the material broadens its melting range and lowers the final melting point of the material from T_o, to a lesser temperature, T_m.

DSC measures directly the thermal energy per unit time, transferred to or from a sample as the temperature of the sample holder is changed at a linear rate, dT/dt,which can be expressed as follows:

$$\frac{dq}{dt} = \frac{dT_s}{dt} \times \frac{dq}{dT_s} \qquad (1)$$

dT_s/dt = scanning rate/K min^{-1}

dq/dT_s = heat capacity of the sample or the energy required to accomplish a transition/Jk^{-1}.

From the van't Hoff equation, the relationship describing the heat flow to or from a sample and the melting point depression of a sample due to the presence of an impurity is obtained:

$$\frac{dq}{dT_s} = \frac{\Delta q\ (T_o - T_m)}{(T_o - T_s)^2} \qquad (2)$$

Δq = total heat of fusion of the sample/J.

T_o = melting point of a 100% pure material/K.

T_m = melting point of sample system/K.

$(T_o - T_m)$ = melting point depression due to impurity/K.

T_s = sample temperature/K

where the melting point depression due to impurity is expressed as:

$$(T_o - T_m) = \frac{RT_o^2 X_2}{\Delta_f H^{\ominus}} \qquad (3)$$

R = molar gas constant, 8.314 J/mol K

X_2 = molar fraction of impurity

$\Delta_f H^{\ominus}$ = molar heat of fusion/J mol^{-1}.

The integration of equation (2) shows that the fraction of the sample, F, which is melted at any particular sample temperature in the melting curve is obtained as:

$$F = \frac{T_o - T_m}{T_o - T_s} \qquad (4)$$

or

$$T_s = T_o - \frac{T_o - T_m}{F} \qquad (5)$$

F = fraction melted.

By substituting equation (3), which defines the melting point depression due to an impurity, into equation (5), the linear equation for the determination of purity by DSC is obtained as below:-

$$T_s = T_o - \frac{RT_o^2 X_2}{\Delta_f H^{\ominus}} \cdot \frac{1}{F}$$

A plot of the sample temperature (T_s) against the reciprocal of the fraction of material melted at that temperature (1/F) should give a straight line with a slope equal to the melting point depression ($R\ T_o^2\ X_2/\Delta_f H^o$) and an intercept equal to T_o.

The fraction of material melted at any sample temperature is determined directly from the DSC scan and is proportional to the peak area under the curve up to that temperature.

Sometimes the van't Hoff plot obtained from the melting curve results is not a straight line; the curve is slightly concave upwards. This concavity is a result of the under-estimation of the amount of melting which has occurred at lower temperatures and not observable in the DSC melting trace. Since the amount of peak area under lower temperature is constant (X), the van't Hoff plot can be linearized by adjusting the value of (X) until a linear plot is obtained.

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