

Received: September 30, 1983; accepted: March 24, 1984

SUBSTITUTIVE AROMATIC FLUORINATION WITH CHLORINE PENTAFLUORIDE*

MAX M. BOUDAKIAN** AND GENE A. HYDE

Olin Chemicals, New Haven, Connecticut 06511 (U.S.A.)

SUMMARY

In contrast to limited substitutive fluorination of aromatics with halogen fluorides such as ClF, ClF₃, BrF₃ and IF₅, fluorination is the predominant reaction path with ClF₅. Under non-catalytic liquid phase conditions, benzene was converted to fluorobenzene (54% yield) and chlorobenzene (37% yield), respectively. For a heterocyclic substrate, i.e. 2,4,6-trifluoropyrimidine, substitutive fluorination predominated over chlorination. Three possible fluorination mechanisms are discussed. A transition complex of ClF₅ with benzene is favored. Enhanced exchange fluorination of CCl₄ was effected with ClF₅ (CF₂Cl₂>>CFC1₃>CF₃Cl) as compared with ClF₃ (CFC1₃>>CF₂Cl₂).

INTRODUCTION

Growing applications for ring fluorinated aromatics [1] have created much interest in the development of new synthesis techniques. While early direct aromatic substitution with fluorine (F₂) gave violent reactions involving ring scission, addition, coupling and polymerization, new fluorination techniques have been developed in recent years: molecular fluorine [2-5]; xenon fluorides [6]; high valency metal fluorides such as silver difluoride [7,8] or cobaltic trifluoride [8]; organic hypofluorites

* Based on an earlier presentation: 'Liquid Phase Aromatic Fluorination With Chlorine Pentafluoride,' 162nd American Chemical Society Meeting, Washington, D.C. September 1971. Paper No. 6 (Division of Fluorine Chemistry)

** Rochester, New York 14611 (U.S.A.)

such as CF_3OF [9,10] or $\text{CH}_3\text{CO}_2\text{F}$ [11]; ionic hypofluorites such as CsSO_4F or RbSO_4F [12,13]; NF_4BF_4 [14]; and, anodic fluorination by controlled potential electrolysis [15].

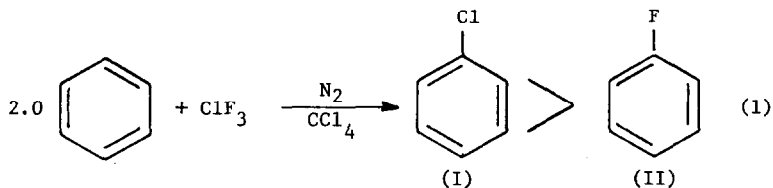
With halogen fluorides such as ClF , ClF_3 , BrF_3 and IF_5 , and aromatics, substitutive fluorination has been a minor reaction path (Table 1).

TABLE 1

Substitutive Aromatic Halogenation With Halogen Fluorides

Interhalogen	Substrate	Solvent	Substitution Product	Ref.
ClF	C_6H_6	CCl_4	$\text{C}_6\text{H}_5\text{Cl}$	16
ClF_3	C_6H_6	CCl_4	$\text{C}_6\text{H}_5\text{Cl} > \text{C}_6\text{H}_5\text{F}$	17
	C_6HF_5	HF	C_6ClF_5	18
BrF_3	C_6H_6	CH_3CN	$\text{C}_6\text{H}_5\text{BrF}_2$	19
	C_6HF_5	$\text{CFCl}_2\text{CF}_2\text{Cl}$; $\text{HF}/\text{SO}_2\text{ClF}$	C_6BrF_5	20
IF_5	C_6H_6		$\text{C}_6\text{H}_5\text{I} >> \text{C}_6\text{H}_5\text{F}$; $\text{C}_6\text{H}_4\text{FI}$	21
	$1,3,5\text{-C}_3\text{H}_3\text{F}_3$		Inert	22
	C_6HF_5		Inert	22

Of the above halogen fluorides, ClF_3 (or modifications) has been the most intensively studied reagent with aromatics. Ellis and Musgrave [17 a-c] established that substitutive chlorination predominated over fluorination when benzene was reacted with ClF_3 (CCl_4 solvent) under catalytic (e.g. CoF_2) or non-catalytic conditions in a steel reactor. (Side reactions such as ring addition, coupling and tar formation contributed to low yields).



A later modification of the ClF_3 -benzene system was Pavlath's discovery [23 a-c] that difluorochloronium ion, ClF_2^+ (generated by addition of Lewis acids, e.g. BF_3 , to give $\text{ClF}_2^+\text{BF}_4^-$), enhanced substitutive fluorination. In contrast, Yakobson *et al.* [18,22] recently found that fluorinated aromatics, e.g. 1,3,5-trifluorobenzene, pentafluorobenzene and 4-H-heptafluorotoluene, do not undergo substitutive aromatic fluorination with ClF_2^+ , BrF_2^+ , BrF_4^+ and IF_4^+ salts.

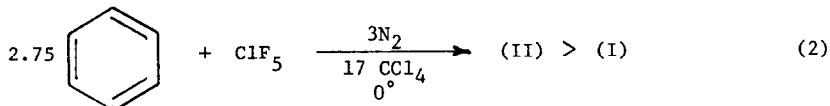
A major advance in recent halogen fluoride chemistry was the discovery of the new interhalogen, chlorine pentafluoride, and the rapid development of alternate synthesis routes [24-28]. A study was undertaken to assess substitutive halogenation patterns of ClF_5 with benzene under 'liquid-phase' conditions [29].

RESULTS AND DISCUSSION

Substitutive Fluorination of Benzene With Chlorine Pentafluoride

Substitutive halogenation studies with benzene were conducted under non-catalytic conditions in CCl_4 solvent at low and high ClF_5 concentrations.

At low ClF_5 concentrations (1.0 ClF_5 :2.75 C_6H_6 :3.0 N_2 :16.8 CCl_4), nearly all (97%) of the consumed benzene was accounted for as products arising from aromatic substitution (Table III). Fluorination predominated over chlorination as evidenced by 53.8% and 36.5% corrected yields of fluorobenzene (II) and chlorobenzene (I), respectively.



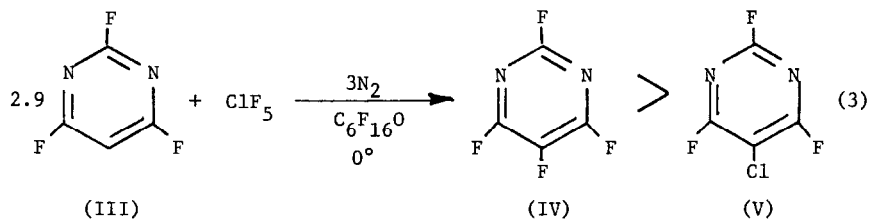
In contrast to the corresponding ClF_3 -benzene system [17], there was negligible evidence for side reactions arising from addition, coupling or polymerization. Infrared examination of the cold traps (-15° , -78° and -134°) showed no evidence of chlorofluoromethanes. (The latter observations are reminiscent of Ellis and Musgrave's findings [17 a,b] that halogen exchange between CCl_4 and ClF_3 did not occur if a more easily halogenated substrate such as benzene was present).

Attempts failed to enhance substitutive fluorination at high ClF_5 concentrations (1.0 ClF_5 :1.3 C_6H_6 :2.0 N_2 :8.4 CCl_4). While all of the benzene was consumed, only 32.4% could be accounted for as substitution products (Table IV). o- and/or p-Difluorobenzene (5.2% yield) represented the maximum degree of fluorination. The absence of (II) suggests that in-situ generation of the latter was followed by conversion to non-volatile products. (In contrast to the absence of chlorofluoromethanes at low ClF_5 concentrations, higher ClF_5 levels effected competitive CCl_4 exchange fluorination to give CCl_3F and CCl_2F_2).

The inability to further fluorinate fluorobenzene to give polyfluorobenzenes is not surprising. Ellis and Musgrave [17 b] found that, while fluorobenzene was completely consumed upon reaction with ClF_3 (CoF_2 catalyst/ CCl_4 solvent), only p-chlorofluorobenzene and addition products were formed. Likewise, the reaction of p-difluorobenzene and ClF_3 resulted in complete conversion of the substrate; no substitution products were found. (Similar inability to effect poly-substitutive fluorination under liquid phase conditions with molecular fluorine (F_2) were noted by Grakauskas: at low F_2 /benzene stoichiometry, appreciable substitution and minor polymer formation was noted; at higher molar ratios, this product distribution was reversed [2]).

Substitutive Fluorination of 2,4,6-Trifluoropyrimidine With Chlorine Pentafluoride

In contrast to fluorinated benzenes, fluorinated heterocyclics exhibit slightly different behavior toward halogen fluorides. For example, sluggish fluorination (33.9% conversion) was noted when 2,4,6-trifluoropyrimidine was reacted with ClF_5 in FLUORINERT® Liquid FC-75. Substitutive halogenation (fluorination again predominating) represented a minor reaction path: 2,4,5,6-tetrafluoropyrimidine (IV), 14.8% yield (corrected); 5-chloro-2,4,6-trifluoropyrimidine (V), 8.7% yield (corrected). (Ring cleavage of the perfluorocyclic ether solvent by ClF_5 is not possible as evidenced by quantitative recovery of FC-75 and ClF_5 after 120 hours at 25°).

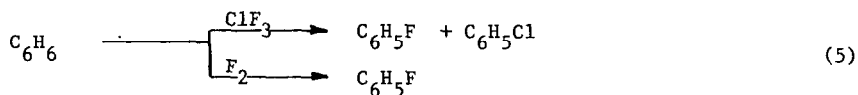


Mechanism

At least three potential fluorination paths could be considered.

(a) Fluorination via ClF₅ Dissociation

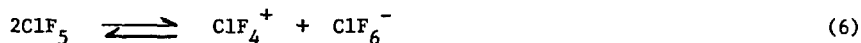
Fluorination could arise from ClF₅ dissociation products at 0°:



However, the negligible rate of ClF₅ dissociation up to 200° (16 hours) reported by Bauer and Sheehan [30] does not support this mechanism.

(b) Self-Ionization of ClF₅

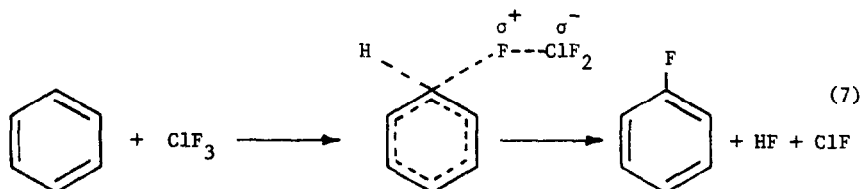
Self-ionization of ClF₅ to generate ClF₄⁺ as the active fluorinating species represents another reaction path:



This sequence does not appear likely. Meinert and Gross established the following order of decreasing self-ionization within the halogen fluorides: BrF₃ > IF₅ > BrF₅ > ClF₃ > ClF₅ [31]. Moreover, the use of CCl₄ solvent, a medium of low dielectric constant employed in the substitutive fluorination of benzene, would not favor self-ionization of ClF₅.

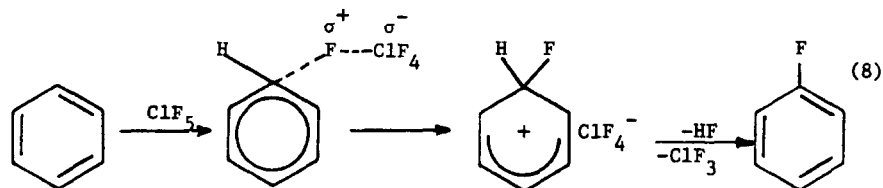
(c) Transition Complex

A transition complex with the aromatic ring was proposed by Musgrave for the non-catalyzed reaction of ClF₃ and benzene [17 c].



ClF would then serve as a chlorinating agent, in agreement with the likely polarization, $\overset{\sigma^+}{\text{Cl}}-\overset{\sigma^-}{\text{F}}$, to give chlorobenzene, as previously demonstrated by Gambaretto, *et al.* [16]. (A potential intermediate in Musgrave's transition complex mechanism could be $\text{C}_6\text{H}_5\text{ClF}_2$. Nesmeyanov, *et al.* [19] formed phenylbromosodifluoride, $\text{C}_6\text{H}_5\text{BrF}_2$, from benzene and BrF_3 /acetonitrile).

A modified transition complex mechanism proceeding via an arenium cation could be envisaged for the corresponding non-catalyzed ClF_5 -benzene system:



ClF_3 generated from the above sequence would then participate by the Musgrave transition complex path with benzene depicted in equation (7) [17 c] [32].

Reaction of Chlorine Fluorides With Carbon Tetrachloride

ClF_5 effected exchange fluorination of CCl_4 (absence of aromatic substrate) to give a mixture of chlorofluoromethanes: $\text{CF}_2\text{Cl}_2 \gg \text{CFCl}_3 > \text{CF}_3\text{Cl}$ (Table 2). The corresponding study by Ellis and Musgrave for ClF_3 and CCl_4 gave chlorofluoromethanes of a lesser degree of fluorination: $\text{CFCl}_3 \gg \text{CF}_2\text{Cl}_2$ [17 b].

TABLE 2

Reaction of Chlorine Fluorides With CCl_4

Chlorine Fluoride	Ref.	Molar Ratio			Temp.	Time (hr)	Molar Ratio		
		ClF_x	CCl_4	N_2			CF_3Cl	CF_2Cl_2	CFCl_3
ClF_5	This Study	1.0	13.2	3.0	0°	1.5	1.0	7.5	1.3
ClF_3	[17 b]	1.0	11.0	3.4	0°	6.8	(--)	(--)	1.0
		1.0	10.7	4.1	25°	8.4	(--)	1.0	7.0

EXPERIMENTAL

Reagents

ClF_5 (IR assay, > 99%) was prepared from KCl and F_2 [28 a,b]. Benzene, Baker & Adamson (Reagent ACS Grade). Carbon tetrachloride, Mallinckrodt (A.R. Grade). 2,4,6-Trifluoropyrimidine (gc, 99.9%) was prepared from 2,4,6-trichloropyrimidine and KF in sulfolane [34]. FLUORINERT® Liquid FC-75, mainly perfluoro-(2-n-butyltetrahydrofuran) and perfluoro-(2-n-propyltetrahydropyran), was obtained from 3M Co.

Gas Liquid Chromatography

ClF_5 with benzene: 15% Igepal C0880-Chromosorb W (80/100 mesh); column, 2 m., 1/4 in. i.d.; column temp., 75-250° at 10°/min.; injection port temp., 210°; detector temp., 210°; flow rate, 7 sec./10 cc.

ClF_5 with 2,4,6-trifluoropyrimidine: 15% SE30-Chromosorb W (80/100 mesh); column, 3 m., 1/4 in.; column temp., 60°; injection port temp., 150°; detector temp., 160°; flow rate, 6.3 sec./10 cc.

Apparatus

The reactor was an adaptation of a type described by Miller, et al [35] for gas-liquid reactions featuring a high speed (3500 rpm) wire gauze 'micro-bubble' stirrer. The design features of this apparatus avoids high spots and permits rapid mixing of the gaseous and liquid phases.

General Fluorination Procedure

The substrate was mixed with the solvent (0°) and the stirrer brought up to speed (3500 rpm). The system was flushed with nitrogen (15 min.) and ClF_5 flow started (after nitrogen flow had stabilized). Cold traps (-15°, -78° and -134°, respectively) were attached to the reactor. At the end of the fluorination, the system was again flushed with nitrogen (15 min.), the ice-bath removed and the reactor contents allowed to warm to 25°. The reaction mixture was processed as described in the individual experiments.

Reaction of Benzene with ClF₅(a) Low ClF₅ Concentration

ClF₅ (0.0575 Mol, 7.50 g) was fed at a rate of 7.5 g/hr diluted 1:3 with nitrogen (ClF₅ flow rate: 21.5 standard cc/min; N₂ flow rate: 65 standard cc/min) into a cooled (0°) solution of benzene (0.1580 Mol, 12.34 g) dissolved in CCl₄ (0.964 Mol, 159.5 g) contained in a glass reactor. The reaction mixture (162 g) was successively treated with 100 ml of saturated aqueous sodium bicarbonate (2 x), water (3x) and dried over magnesium sulfate. (The crude and treated reaction products had identical infrared spectra). Product composition was determined by GLC and mass spectroscopy (Table 3).

TABLE 3

Low ClF₅ Concentration: Fluorination of Benzene by ClF₅

Starting Materials

ClF ₅ (moles)	0.0575
Benzene (moles)	0.1580
CCl ₄ (ml)	100
Molar Ratio (Benzene/ClF ₅)	2.75/1
Benzene Consumed (moles)	0.0842

<u>Products</u>	<u>Moles</u>	<u>Corrected Yield</u>
Fluorobenzene	0.0453	53.8%
p-Chlorofluorobenzene	0.0034	4.0%
o-Chlorofluorobenzene	0.0022	2.6%
Chlorobenzene	0.0307	36.5%
C ₆ H ₄ F ₂ , C ₆ H ₃ F ₃ and C ₆ H ₃ ClF ₂	<u>Traces</u>	---
Moles (Out)	0.0816	
% Accountability	96.9%	
(Based on benzene consumed)		

IR spectroscopy of the cold trap contents (combined wt, 6.58 g) showed no evidence of CF_3Cl , CF_2Cl_2 or CFCl_3 ; only CCl_4 , C_6H_6 and SiF_4 were present. Fractionation (-40°) of the trap contents gave 1.23 g (0.0118 Mol) of SiF_4 . The glass reactor showed significant etching.

(b) High ClF_5 Concentration

ClF_5 (0.1795 Mol, 23.41 g) was fed at an average rate of 15.6 g/hr diluted 2:4 with nitrogen (ClF_5 flow rate: 45 standard cc/min; N_2 flow rate: 60 standard cc/min) into a cooled (0°) solution of benzene (0.2338 Mol, 18.26 g) dissolved in CCl_4 (1.50 Mol, 233.0 g) contained in a copper reactor. The reaction mixture (231 g) was treated with potassium fluoride (17 g) to remove HF. A combination of mass spectral and GLC assay identified the components listed in Table 4. At least 17 other compounds were also present in trace quantities; benzene accountability was only 32.4%.

TABLE 4

High ClF_5 Concentration: Fluorination of Benzene by ClF_5

Starting Materials

ClF_5 (moles)	0.1795
Benzene (moles)	0.2338
CCl_4 (ml)	150
Molar Ratio (Benzene/ ClF_5)	1.30/1
Benzene Consumed (moles)	0.2338

<u>Products</u>	<u>Moles</u>	<u>Corrected Yield</u>
Fluorobenzene	---	---
<u>o</u> - and/or <u>p</u> -Difluorobenzene	0.0121	5.2%
<u>p</u> -Chlorofluorobenzene	0.0127	12.7%
<u>o</u> -Chlorofluorobenzene	0.0090	3.9%
Chlorobenzene	0.0298	5.4%
Dichlorobenzene	<u>0.0121</u>	5.2%
Moles (Out)	0.0757	
% Accountability	32.4%	
(Based on benzene consumed)		

IR spectroscopy of the cold trap contents (combined wt, 26.01 g) showed the presence of CCl_4 , CCl_3F and CCl_2F_2 . The trap contents contained HF (5.10 g, 0.2549 Mol) based on treatment with anhydrous KF.

Reaction of 2,4,6-Trifluoropyrimidine With ClF_5

ClF_5 (0.0519 Mol, 6.77 g) was fed at a rate of 6.7 g/hr diluted 1:3 with nitrogen (ClF_5 flow rate: 19 standard cc/min; N_2 flow rate: 60 standard cc/min) into a glass reactor containing a solution (0°) of 2,4,6-trifluoropyrimidine (0.150 Mol, 20.16 g) and FLUORINERT® Liquid FC-75 (538 g). The reaction mixture (containing dispersed solids) was treated with anhydrous KF and the solution assayed by GLC: 2,4,6-trifluoropyrimidine conversion, 33.9%; corrected yields: 2,4,5,6-tetrafluoropyrimidine, 14.8%; 5-chloro-2,4,6-trifluoropyrimidine, 8.7%.

Reaction of Carbon Tetrachloride With Chlorine Pentafluoride

Chlorine pentafluoride (0.0772 Mol, 10.07 g) was fed at a rate of 6.7 g/hr diluted 1:3 with nitrogen (ClF_5 flow rate: 19 standard cc/min) into carbon tetrachloride (1.0195 Mol, 157 g) cooled to 0° in a glass reactor. VPC assay of the reaction mixture (147 g) indicated 99.8 Mol % CCl_4 . GLC assay of the -40° , -134° and -196° traps (combined wt, 9.64 g) were qualitatively identical ($\text{CF}_2\text{Cl}_2 > \text{CFCl}_3 > \text{CF}_3\text{Cl}$), along with trace amounts of ClF_5 (characteristic bands at 732 and 786 cm^{-1}). IR and mass spectroscopy gave the following product distribution: CF_2Cl_2 , 0.0587 Mol; CFCl_3 , 0.00995 Mol; and CF_3Cl , 0.00785 Mol.

FLUORINERT® Liquid FC-75 was inert to ClF_5 (3.1/1 molar ratio) after 120 hr/ 25° in a KEL-F® reactor. Vacuum transfer (0°) of the volatiles gave quantitative recovery of ClF_5 . The residual liquid (98% of initial charge) was found by IR spectroscopy to be identical to FC-75.

REFERENCES

- 1 M. M. Boudakian, in M. Grayson and D. Eckroth (Editors), Kirk-Othmer: Encyclopedia of Chemical Technology, Vol. 10, 3rd edn, J. Wiley, New York, 1980, 'Fluorinated Aromatic Compounds,' p. 901.
- 2 V. Grakauskas, J. Org. Chem., 35 (1971) 723 and references cited therein.

- 3 N. B. Kaz'mina L. S. German, I. D. Rubin and I. L. Knunyants, Dokl. Akad. Nauk SSSR, 194 (1970) 1329.
- 4 S. Misaki, J. Fluorine Chem., 21 (1982) 191 and references cited therein.
- 5 F. Cacace, P. Giacomello and A. P. Wolf, J. Am. Chem. Soc., 101 (1980) 3511.
- 6 R. Filler, Israel J. Chem., 17 (1978) 71.
- 7 H. Schroeder, J. Am. Chem. Soc., 82 (1960) 4115.
- 8 A. Zweig, R. G. Fischer and J. E. Lancaster, J. Org. Chem., 45 (1980) 3597.
- 9 R. Hesse, Israel J. Chem., 17 (1978) 60.
- 10 J. Kollonitsch, L. Barash and G. A. Doldouras, J. Am. Chem. Soc., 92 (1970) 7494.
- 11 O. Lerman, Y. Tor and S. Rozen, J. Org. Chem., 46 (1981) 4629.
- 12 S. Stavber and M. Zupan, J. Chem. Soc. Chem. Commun. (1981) 148.
- 13 D. P. Ip, C. D. Arthur, R. B. Winans and E. H. Appelman, J. Am. Chem. Soc., 103 (1981) 1964.
- 14 C. J. Schack and K. O. Christe, J. Fluorine Chem., 18 (1981) 363.
- 15 A. N. Rozhkov, A. V. Bukhtiarov and I. L. Knunyants, Isv. Akad. Nauk SSSR, Ser. Khim., (1972) 1130.
- 16 G. P. Gambaretto and M. Napoli, J. Fluorine Chem., 7 (1976) 569.
- 17 a. J. F. Ellis and W. K. R. Musgrave, J. Chem. Soc., (1950) 3608.
b. J. F. Ellis and W. K. R. Musgrave, ibid (1953) 1063.
c. W. K. R. Musgrave, Advances in Fluorine Chem., 1 (1960) 21.
- 18 V. V. Bardin, G. G. Furin and G. G. Yakobson, J. Fluorine Chem., 23 (1983) 67.
- 19 A. N. Nesmeyanov, A. N. Vanchikov, I. N. Lisichkina, N. S. Khruscheva and T. P. Tolstaya, Dokl. Akad. Nauk SSSR, 254 (1980) 652.
- 20 T. W. Bastock, M. E. Harley, A. E. Pedler and J. C. Tatlow, J. Fluorine Chem., 6 (1975) 331.
- 21 O. Ruff and R. Heim, Z. anorg. allgem. Chem., 201 (1931) 245.
- 22 V. V. Bardin, G. G. Furin and G. G. Yakobson, Zh. Org. Khim., 16 (1980) 1256.
- 23 a. A. E. Pavlath, U.S. Pat. 2,993,937 (1961).
b. A. E. Pavlath and A. J. Leffler, Aromatic Fluorine Compounds, ACS Monograph No. 155, Reinhold, N.Y., 1962. p. 7.
c. A. E. Pavlath, Abstracts, 133rd ACS Meeting, San Francisco. Division of Organic Chemistry. April 1958, Paper No. 99.
- 24 D. F. Smith, Science, 141 (1963) 1039.

- 25 R. Gatti, R. L. Krieger, J. E. Sicre and H. J. Schumacher, *J. Inorg. Nucl. Chem.*, 28 (1966) 655.
- 26 G. Pilipovich, *et al.*, *Inorg. Chem.*, 6 (1967) 1918.
- 27 W. Maya and H. F. Bauer, U.S. Pat. 3,354,646 (1967).
- 28 G. A. Hyde and M. Boudakian
 a. *Inorg. Chem.*, 7 (1968) 2648.
 b. U.S. Pat. 3,388,970 (1968).
- 29 The term, 'liquid-phase' fluorination, for the ClF₅-benzene system may be a misnomer. (See J. M. Tedder, *Advances in Fluorine Chem.*, 2 (1961) 112 for interpretation of 'liquid-phase' fluorination of F₂ with organic substrates). Likewise for recent studies with aromatics: "...low F₂ solubility makes 'liquid phase' fluorination an essentially 'heterogeneous process' occurring at the gas-liquid interface when the gaseous reagent is bubbled through the substrate solution." [5]
- 30 H. Bauer and D. F. Sheehan, *Inorg. Chem.*, 6 (1967) 1736.
- 31 H. Meinert and U. Gross, *J. Fluorine Chem.*, 2 (1972/73) 381.
- 32 Generation of difluorochloronium ion, ClF₂⁺, an aromatic fluorinating agent [23], from by-products HF and ClF₃, represents another fluorination path. Hyman, *et al.*, [33] have reported the following equilibrium:
- $$\text{ClF}_3 + \text{HF} \rightleftharpoons \text{ClF}_2^+ + \text{HF}_2^-$$
- 33 T. Surles, L. A. Quaterman and H. H. Hyman, *J. Fluorine Chem.*, 3 (1973/74) 293.
- 34 M. M. Boudakian and C. W. Kaufman, U.S. Pat. 3 314 955 (1967).
- 35 W. T. Miller, J. O. Stoffer, G. Fuller and A. G. Currie, *J. Am. Chem. Soc.*, 86 (1964) 51.