

Effect of the experimental conditions in the transformation of the bis-1,3-trichloromethylbenzene in the presence of HF and a Lewis acid

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Abstract

The transformation of the bis-1,3-trichloromethylbenzene depends on the experimental conditions (temperature, amount of HF and the presence of a Lewis acid). The formation of the 1-trichloromethyl-3-trifluoromethylbenzene is favored in the presence of HF in default. After the consumption of HF, the various fluorinated intermediates compounds were observed to lead to the more thermodynamically stable compounds, i.e., mainly the bis-1,3-trichloromethylbenzene and 1-trichloromethyl-3-trifluoromethylbenzene. These results were explained by theoretical calculations. The presence of a Lewis acid increases the formation of the more stable products at lower temperature. SbCl₅ is the most efficient catalyst corresponding to a decrease of 150 °C to obtain similar results compared with HF alone.

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1. Introduction

Catalytic system HF/Lewis acid or HF alone was commonly used for the fluorination of chlorinated molecules by Cl/F exchanges in order to obtain the corresponding fluorinated compounds [1–7]. The applications are the fluorination of chlorinated hydrocarbons to produce HFCs and also fluorinated aromatics. Indeed these processes which are known since a long time, are more developed since 1990.

The selective fluorination of organic molecules has attracted much interest because a number of partially fluorinated organic molecules are reported to show interesting chemical and physical properties and in some cases biological activities [8–10]. It is really admitted now that the presence of fluorine atom or –CF₃ groups increased strongly the biological activity of molecules used in pharmacochemical and agrochemical applications.

The incorporation of fluorine or fluorinated groups (such as –CF₃) into organic molecules significantly increases both the

pharmacokinetic and pharmacodynamic properties of a drug [11–15]. Many efforts have been made to increase the potency of biological active compounds by replacing hydrogen or other halogen atoms by a fluorine atom. Fluorination of aliphatic or aromatic halides can mainly be carried out by using alkali metal fluoride (i.e., potassium fluoride), hydrofluoric acid (HF) or elemental fluorine (F₂). Because of the fact that it is safe to handle and cheap, KF is very practical in the preparation of fluoroorganic compounds [16]. However, some halide compounds need vigorous conditions to be fluorinated and most of the time, HF is required. Typically, such processes include either vapor phase fluorination reactions or liquid phase fluorination reactions. The reaction of an organic halide with hydrofluoric acid can be carried out in the presence of a Lewis acid as a catalyst. The most widely used catalyst for liquid phase fluorinations is antimony pentachloride or antimony mixed halides [17,18].

Moreover, new routes were developed by using a catalyst and HF by Cl/F exchanges from the chlorinated starting material in order to obtain selectively the desired fluorinated products without by product. An example is the preparation of substituted trichloromethyltrifluoromethylbenzenes from

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the corresponding chlorinated products. The transformation of the bis-1,3-trichloromethylbenzene was studied in order to obtain selectively the formation of 1-trichloromethyl-3-trifluoromethylbenzene used as intermediate for the synthesis of fungicide [19]. As reported by Baasner and colleagues [2–6], this reaction can be carried out without or with a catalyst, with or without HF. In the presence of HF alone, the uncatalyzed fluorination proceeds in several stages corresponding to the fluorination in the two trichloromethyl groups. Consequently, there is no possibility to fluorinate selectively a trichloromethyl group whatever the experimental conditions (temperature, pressure and time). The authors described that the presence of a catalyst such as antimony pentachloride introduced a high degree of selectivity into this fluorination reaction. The amount of HF was stoichiometric and in these conditions the formation of the 1-trichloromethyl-3-trifluoromethylbenzene was observed corresponding to one of the most thermodynamically stable product. The authors also reported in another work the use of catalysts such as iron trichloride, aluminium trichloride, or antimony halides. With these systems the fluorination was not selective. They also described the formation of the 1-trichloromethyl-3-trifluoromethylbenzene by halogen transfers between the bis-1,3-trichloromethylbenzene and the bis-1,3-trifluoromethylbenzene.

The purpose of the present paper is to determine the effect of the experimental conditions to obtain selectively the 1-trichloromethyl-3-trifluoromethylbenzene. Various parameters were studied such as the temperature, the amount of HF with various catalysts. In order to establish the reaction scheme, the transformation of intermediates was also studied in the presence of the catalyst or in the presence of HCl (the by product of the Cl/F exchanges) in order to show the reversibility of the reaction.

To clarify some aspects of the proposed reaction scheme, theoretical calculations restricted to the reactions without catalyst were carried out and are reported here.

2. Experimental part

2.1. Chemical products

All commercially available reagents were used without further purification. Hydrogen fluoride was purchased from Air

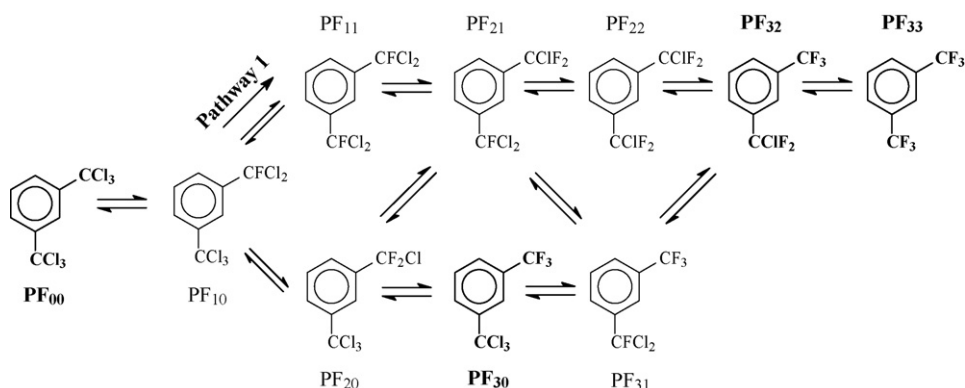
Liquid; SbCl₅ from VWR, MoCl₅ and TiCl₄ from Aldrich and the bis 1,-trichloromethylbenzene from TCI.

2.2. Transformation of the bis-1,3-trichloromethylbenzene

The transformation of the bis-1,3-trichloromethylbenzene was performed in a 100 mL stainless steel autoclave under an initial pressure of 10 bar. The temperature was regulated and controlled by means of a thermocouple placed in a thermometric well in the furnace wall. At the early stage of the experiment, the bis-1,3-trichloromethylbenzene (from 0.04 to 0.25 mol) and the catalyst (0 to 2.5 mmol) were introduced in the autoclave. The difference in temperature between an HF cylinder warmed by means of a heating cord and the autoclave cooled in liquid nitrogen enabled the required amount of HF (from 0.25 to 1 mol) to be transferred to the reaction medium. The reaction then took place with continuous stirring, at the desired temperature (from 50 to 200 °C) and under autogene pressure. At the end of the reaction, the autoclave was cooled down and vented with dry dinitrogen in order to eliminate the HCl and the unreacted HF. The contents were quenched with 30 mL of water/decane mixture (50/50), using a 316 L stainless steel tank. After extraction with decane, the organic phase was dried with MgSO₄ and analyzed by GC. The fluorinated products and the chlorinated reactant were quantified by gas chromatography using an internal standard quantification method with decane as the internal standard. The yield corresponds to the mol.% of the bis-1,3-trichloromethylbenzene transformed into various products (by-products included). Yields of 100% were not attained, because of the uncertainty of the experiment. The conversion of the bis-1,3-trichloromethylbenzene represented the amount transformed into fluorinated products. The chromatograph was a Varian 3800 equipped with 30 m VF-5 ms capillary column (Varian) with a temperature program from 50 to 300 °C. The various products were identified by coupling GC–MS and by ¹⁹F NMR and by comparison with commercial products.

2.3. Transformation of the fluorinated intermediates





















The various fluorinated intermediates of the transformation of the bis-1,3-trichloromethylbenzene were named PF_{ij} where *i* and *j* were the number of fluorine atoms present in each halogenated



Scheme 1. Transformation of the bis-1,3-trichloromethylbenzene.

Table 1

Name of the various fluorinated intermediates (PF_{ij}) of the transformation of the bis-1,3-trichloromethylbenzene (*i* and *j* corresponding to the number of fluorine atom in each halogenated methyl groups)

PF _{ij}	PF ₀₀	PF ₁₀	PF ₁₁	PF ₂₀	PF ₂₁	PF ₃₀	PF ₃₁	PF ₂₂	PF ₃₂	PF ₃₃
										
Products										

methyl group (Table 1). For example, the fluorinated product named PF₁₁ indicated that the two fluorine atoms are not present in the same halogenated methyl group but one in each group unlike PF₂₀.

These various products were not commercial except PF₀₀, PF₃₃ and PF₃₀. The others intermediates were obtained (with a purity superior to 95%) by distillation of the organic phases of the various experiments of the transformation of the PF₀₀. These compounds were characterized by proton and fluor NMR.

The transformation of these various fluorinated intermediates (PF_{ij} = 0.0323 mol) was performed in the same apparatus than the transformation of the PF₀₀ at 50 °C in the presence of SbCl₅ alone (0.323 mmol) or in the presence of HCl (5 bar) alone at 140 °C.

3. Computational details

All structures involved in the proposed reaction scheme were fully optimized using the B3LYP density functional method [20]. A split valence basis set was used for all atoms, increased with polarization and diffuse functions (C, H: 6-311G(d,p); F: 6-311+G(d); Cl: 6-311G(2d)). Small effects like thermal and zero point energy corrections were neglected. As a consequence of the CX₃ nearly free rotations, several rotamers were obtained for most of these structures. However, the separation between the lowest and the highest energy rotamers never exceeded 0.5 kcal/mol. Therefore, the results for the lowest energy rotamers, only, are considered in the present study. The calculations were carried out with the *Gaussian* 03 package [21].

4. Results and discussion

4.1. Effect of the experimental conditions and the Lewis acid used

The transformation of the bis-1,3-trichloromethylbenzene was studied at 50 °C in experimental conditions established for the transformation of the trichloromethoxybenzene [7] with various amount of HF alone or in the presence of SbCl₅ as the reference catalyst (Table 2), the amount of HF varying from 2 equivalents to 8 equivalents from PF₀₀. The conversion of PF₀₀ depends on the amount of HF used, and on the amount of SbCl₅. In the presence of HF alone, an increase of the conversion from 65 to 98% was noticed with the amount of HF from 2 equivalents to 8 equivalents. In fact, in the presence of HF alone, the degree of fluorination of the intermediates increased from PF₁₀ (main product with 2 equivalents of HF) to PF₂₂ (main product with HF in excess: 8 equivalents). In all cases, the fluorination of the two –CCl₃ groups was noticed, no accumulation of fluorine atoms in the same halogenated methyl group was observed. The presence of SbCl₅ (whatever the amount), the reference of catalyst for this kind of Cl/F exchanges, modified the selectivity of the fluorinated products. Indeed, with HF in low concentration (2 equivalents), PF₃₀ became the main product corresponding to the total fluorination of one of the –CCl₃ group without fluorination of the other. Then, when the amount of HF increased (4 and 8 equivalents), PF₃₃ (the hexafluorinated product) was the main product.

The reaction was very fast with SbCl₅, after only 30 min the PF₂₀ and PF₁₀ intermediates disappeared to form PF₃₀ which selectivity increased from 25 to 44% (Fig. 1). After 1 h, the

Table 2

Transformation of the bis-1,3-trichloromethylbenzene

SbCl ₅ (mmol)	HF (eqs)	Yield (mol.%)	Conv. (mol.%)	PF ₃₃ (mol.%)	PF ₃₂ (mol.%)	PF ₂₂ (mol.%)	PF ₃₁ (mol.%)	PF ₂₁ (mol.%)	PF ₃₀ (mol.%)	PF ₁₁ (mol.%)	PF ₂₀ (mol.%)	PF ₁₀ (mol.%)
0	2	95	65	0	0	5	0	10	0	25	3	57
0.625	2	92	71	7	6	2	3	0	70	0	6	6
1.25	2	88	67	9	4	0	4	2	73	0	5	3
2.5	2	82	65	12	5	0	5	3	65	0	6	4
0	4	96	89	1	1	17	0	21	0	25	7	28
1.25	4	78	100	92	5	0	0	0	3	0	0	0
0	8	90	98	1	6	47	0	22	0	12	5	7
1.25	8	86	100	99	1	0	0	0	0	0	0	0
2.5	8	80	100	99	1	0	0	0	0	0	0	0

Effect of the amount of HF and SbCl₅ on the conversion (conv. molar %) and the selectivity (molar %) towards fluorinated products (*T* = 50 °C, *t* = 1 h, PF₀₀ = 0.0625 mol).

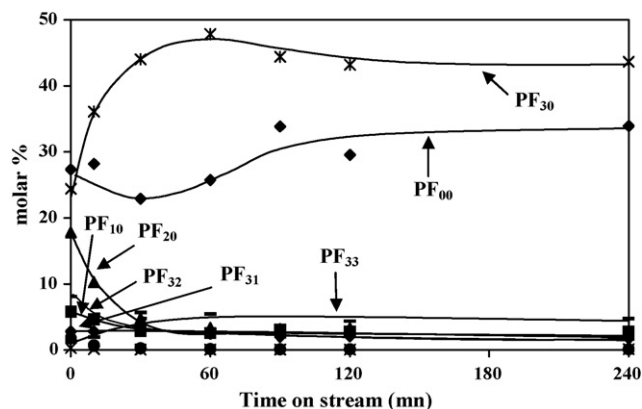


Fig. 1. Transformation of the bis-1,3-trichloromethylbenzene. Effect of the time on stream on the formation of the various fluorinated intermediates PF_{ij} ($T = 50\text{ }^{\circ}\text{C}$, $PF_{00} = 0.125\text{ mol}$, $SbCl_5 = 1.25\text{ mmol}$, $HF/SbCl_5/PF_{00} = 2/0.01/1$).

reaction was stabilized with selectivity towards PF_{30} of 48%, towards PF_{00} of around 33% and towards PF_{33} of 6%. The other products were formed in few amounts. In the presence of $SbCl_5$ and at $50\text{ }^{\circ}\text{C}$, the formation of the PF_{20} , PF_{30} and PF_{31} isomers were observed rather than their PF_{11} , PF_{21} , PF_{22} isomers.

Performances of various Lewis acids ($TiCl_4$, $MoCl_5$, WCl_6 , $TaCl_5$, $SbCl_5$, SbF_3Cl_2 , SbF_5 and $NbCl_5$) with different metals and degree of oxidation were compared in the same conditions ($T = 50\text{ }^{\circ}\text{C}$ and 2 equivalents of HF) Table 3. The various Lewis acids were selected depending on their chemical properties with various scale of Lewis acid and also their capacity for the Cl/F exchanges. In all cases, yields are good and similar for the whole of the catalysts. These results are compared to those obtained without catalyst. The conversion of PF_{00} was around the same whatever the catalyst except $TiCl_4$, $MoCl_5$ and WCl_6 . The selectivity towards fluorinated intermediates was different according to catalysts. With $TiCl_4$, PF_{10} (28%), PF_{11} (34%) and PF_{21} (20%) were the main intermediates corresponding to a fluorination on the two $-CCl_3$ groups. With $MoCl_5$ or WCl_6 as catalyst, the conversion was slightly lower (85%) and PF_{20} (around 40%), PF_{21} (around 20%) and PF_{22} (around 14%) were the main products. In these experimental conditions, these two Lewis acids supported the formation of other isomers, i.e., PF_{20} rather than PF_{11} from PF_{10} but not that of PF_{30} from PF_{20} . PF_{20} and PF_{30} were the main products with equivalent selectivity with

Table 3
Transformation of the bis-1,3-trichloromethylbenzene

Lewis acid	Yield (%)	Conv. (%)	PF_{33} (%)	PF_{32} (%)	PF_{22} (%)	PF_{31} (%)	PF_{21} (%)	PF_{30} (%)	PF_{11} (%)	PF_{20} (%)	PF_{10} (%)
–	95	65	0	0	5	0	11	0	25	4	55
$TiCl_4$	96	95	1	1	6	0	20	1	34	9	28
$MoCl_5$	94	85	0	2	12	1	20	3	4	43	15
WCl_6	93	85	0	2	15	0	19	1	3	46	14
$TaCl_5$	92	72	0	8	7	6	6	30	1	33	9
$SbCl_5$	88	72	10	4	0	5	3	70	0	5	3
SbF_3Cl_2	85	64	10	5	2	3	2	68	2	7	1
SbF_5	90	66	8	5	2	3	2	68	2	6	4
$NbCl_5$	88	66	18	4	0	3	2	66	0	4	3

Effect of the amount of HF and the Lewis acid ($TiCl_4$, $MoCl_5$, WCl_6 , $TaCl_5$, $SbCl_5$, SbF_3Cl_2 , SbF_5 , $NbCl_5$) on the conversion (conv.) and the selectivity towards fluorinated products ($T = 50\text{ }^{\circ}\text{C}$, $t = 1\text{ h}$, $PF_{00} = 0.125\text{ mol}$, $HF = 0.25\text{ mol}$, $HF/PF_{00} = 2/1$, catalyst = 1, 25 mmol).

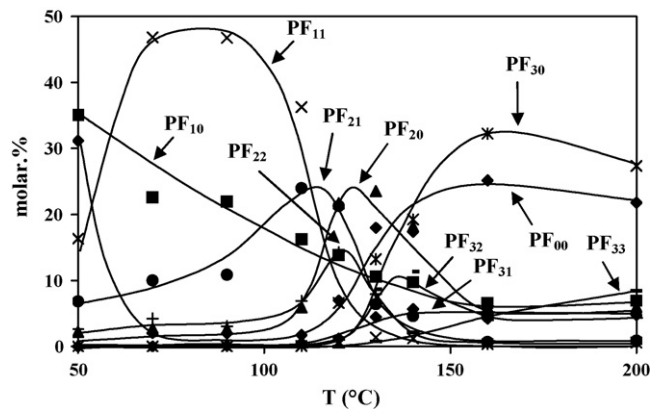


Fig. 2. Transformation of the bis-1,3-trichloromethylbenzene. Effect of the temperature on the formation of the various fluorinated intermediates PF_{ij} in the presence of HF alone ($T = 50\text{--}200\text{ }^{\circ}\text{C}$, $PF_{00} = 0.125\text{ mol}$, $HF = 0.25\text{ mol}$, $HF/PF_{00} = 2/1$).

$TaCl_5$ whereas in the presence of the other Lewis acids ($SbCl_5$, SbF_3Cl_2 , SbF_5 and $NbCl_5$), PF_{30} was the main product (selectivity of 70%). These Lewis acids favored the formation of PF_{30} rather than PF_{21} from PF_{20} and the conversion (around 70%) with these systems was lower than with $TiCl_4$, $MoCl_5$ and WCl_6 highlighting the reformation of PF_{00} after the HF consumption in default and thus a redistribution of the atoms of halogens.

4.2. Effect of the temperature of the reaction

The effect of the temperature was also studied under favorable conditions to the formation of PF_{30} , i.e., in the presence of HF in default (Fig. 2). The results can be divided in three parts:

- (1) Between 50 and $90\text{ }^{\circ}\text{C}$ corresponding to the total disappearance of PF_{00} and the formation of PF_{10} , PF_{11} and PF_{21} which in this case, corresponding to the fluorination of the two $-CCl_3$ groups.
- (2) Between 110 and $120\text{ }^{\circ}\text{C}$ corresponding to the intermediate conditions and the decrease of the amount of PF_{11} to produce PF_{21} (22% at $120\text{ }^{\circ}\text{C}$), PF_{22} (14%) and its isomer PF_{20} (22%). In this range of temperature, the fluorination of PF_{10} into PF_{20} was possible.

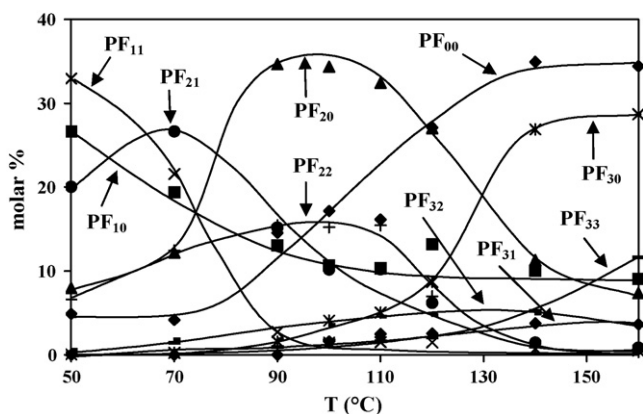


Fig. 3. Transformation of the bis-1,3-trichloromethylbenzene. Effect of the temperature on the formation of the various fluorinated intermediates PF_{ij} in the presence of $TiCl_4$ ($T=50\text{--}200^\circ\text{C}$, $PF_{00}=0.125$ mol, $HF=0.25$ mol, $TiCl_4=1.25$ mmol, $HF/TiCl_4/PF_{00}=2/0.01/1$).

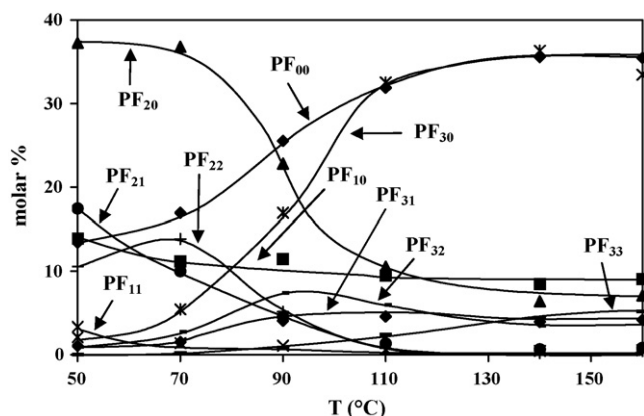


Fig. 4. Transformation of the bis-1,3-trichloromethylbenzene. Effect of the temperature on the formation of the various fluorinated intermediates PF_{ij} in the presence of $MoCl_5$ ($T=50\text{--}200^\circ\text{C}$, $PF_{00}=0.125$ mol, $HF=0.25$ mol, $MoCl_5=1.25$ mmol, $HF/MoCl_5/PF_{00}=2/0.01/1$).

- (3) Beyond 120°C , PF_{30} and PF_{00} were the main products. The increase of the temperature favored the redistribution of the halogenated atoms (fluorine and chlorine) leading to the main products PF_{30} and PF_{00} .

The change of the transformation of PF_{00} was also reported in similar experimental conditions in the presence of $TiCl_4$ (Fig. 3), $MoCl_5$ (Fig. 4) and $SbCl_5$ (Fig. 5) as Lewis acids. They were chosen according to their results obtained at 50°C . Indeed, with this temperature, in the presence of $TiCl_4$, the main product PF_{11} corresponded to the fluorination of the two $-CCl_3$ groups; with $MoCl_5$ the Cl/F exchanges would take place on the same $-CCl_3$ group and finally $SbCl_5$, the reference catalyst, where the formation of PF_{30} was the main product.

Whatever the Lewis acid used, the same distribution of the products was observed but the temperature was decreased depending on the Lewis acid used. Indeed, the presence of a Lewis acid accelerated the rate of the Cl/F exchanges. The comparison of these various systems showed that the formation of PF_{30} can be obtained at a temperature of 160°C for HF alone, at 140°C with $TiCl_4$, at 110°C with $MoCl_5$ and at 50°C with $SbCl_5$. These results could be explained by the fact that $SbCl_5$ was more acid than the others and was the most efficient catalyst for Cl/F exchanges.

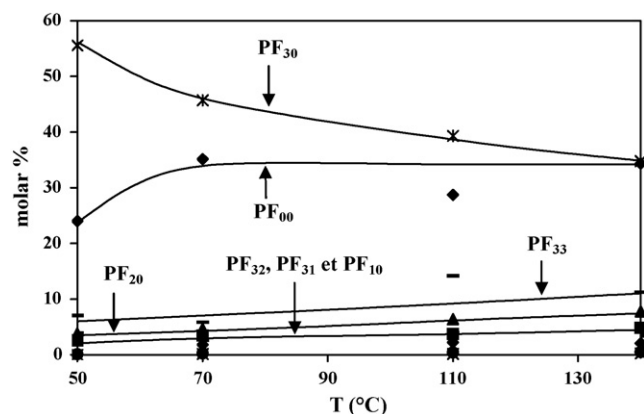


Fig. 5. Transformation of the bis-1,3-trichloromethylbenzene. Effect of the temperature on the formation of the various fluorinated intermediates PF_{ij} in the presence of $SbCl_5$ ($T=50\text{--}200^\circ\text{C}$, $PF_{00}=0.125$ mol, $HF=0.25$ mol, $SbCl_5=1.25$ mmol, $HF/SbCl_5/PF_{00}=2/0.01/1$).

4.3. Transformation of the fluorinated intermediates

The transformation of the various fluorinated intermediates was studied without HF at 50°C with $SbCl_5$ (Table 4) and with HCl (by-product of the Cl/F exchange) (Table 5) at 140°C in order to show the reversibility of the various reactions. In general, the reactivity of the various intermediates depended on their

Table 4

Transformation of the various fluorinated intermediates PF_{ij} (conversion and selectivity) in the presence of $SbCl_5$ ($SbCl_5: 0.323$ mmol, $T=50^\circ\text{C}$, $P_i=10$ bar of nitrogen, $t=1$ h)

PF_{ij}	Yield (%)	Conv. (%)	PF_{33} (%)	PF_{32} (%)	PF_{22} (%)	PF_{31} (%)	PF_{21} (%)	PF_{30} (%)	PF_{11} (%)	PF_{20} (%)	PF_{10} (%)	PF_{00} (%)
PF_{33}	78	0	100	0	0	0	0	0	0	0	0	0
PF_{32}	73	9	7	90	0	3	0	0	0	0	0	0
PF_{22}	81	100	28	10	0	4	1	51	0	1	1	4
PF_{31}	75	92	16	27	0	8	0	49	0	0	0	0
PF_{30}	78	18	0	5	0	4	0	82	0	1	0	8
PF_{21}	81	93	1	15	17	4	8	13	1	25	5	11
PF_{20}	92	75	1	6	6	2	4	16	2	25	10	28
PF_{11}	88	100	2	5	0	2	0	37	0	9	6	39
PF_{10}	90	95	0	0	0	0	0	20	0	4	6	70

Table 5

Transformation of the various fluorinated intermediates in the presence of HCl (HCl: 5 bar, $T = 140\text{ }^{\circ}\text{C}$, $P_i = 10$ bar of nitrogen, $t = 1$ h)

PF _{ij}	Yield (%)	Conv. (%)	PF ₃₃ (%)	PF ₃₂ (%)	PF ₂₂ (%)	PF ₃₁ (%)	PF ₂₁ (%)	PF ₃₀ (%)	PF ₁₁ (%)	PF ₂₀ (%)	PF ₁₀ (%)	PF ₀₀ (%)
PF ₃₃	80	0	99	1	0	0	0	0	0	0	0	0
PF ₃₂	78	1	1	97	1	1	0	0	0	0	0	0
PF ₂₂	89	9	0	2	92	0	2	0	0	2	0	2
PF ₃₁	75	88	11	36	0	12	0	37	0	1	2	1
PF ₃₀	80	4	0	0	0	3	0	97	0	0	0	0
PF ₂₁	76	23	0	0	7	0	78	0	1	13	0	<1
PF ₂₀	78	17	0	0	0	0	8	0	1	82	4	5
PF ₁₁	87	66	0	0	2	0	20	0	34	9	27	8
PF ₁₀	83	89	0	0	0	1	1	10	1	12	11	64

degree of fluorination and of the repartition of the fluorine atoms in the $-\text{CCl}_3$ groups. In all cases, the yields were corrects. Whatever the experimental conditions, PF₃₃ and PF₃₂ were unreactive and demonstrated their high stability. However, PF₂₂ reacted very easily with SbCl₅ (Table 4) to form mainly PF₃₀ (51%) and PF₃₃ (28%). The formation of the products corresponds to a redistribution of the halogenated atoms (Cl and F) to form products with $-\text{CF}_3$ groups (PF₃₀ and PF₃₃) corresponding to a lower and a higher degree of fluorination. PF₂₂ remained unreactive with HCl. Its isomer PF₃₁ was very reactive (with SbCl₅ and HCl) and lead to the formation of PF₃₀, PF₃₂ and PF₃₃. PF₃₀ was transformed (around 20%) with SbCl₅ in PF₀₀, PF₃₁ and PF₃₂ which indicates that the formation of the chlorinated product PF₀₀ can be formed after the uptake of HF. Conversely, its isomer PF₂₁ was highly transformed (93%) with SbCl₅ and to a lower extend with HCl (23%). The main product was PF₂₂ (17%) and PF₂₀ (25%) in the presence of SbCl₅ which confirms that the way to produce PF₃₁ from PF₂₁ was unfavorable. In fact all of the PF_{ij} produced PF₀₀, PF₃₀ and PF₃₃ except PF₃₀, PF₃₃ and PF₃₂. PF₁₀ and PF₃₁ in the presence of HCl were the most reactive fluorinated intermediates followed by PF₁₁, PF₂₁, PF₂₀ and PF₂₂. The redistribution of halogen from low fluorinated intermediates with a $-\text{CCl}_2\text{F}$ group was favored.

From these experimental results, a reaction scheme could be proposed whatever the experimental conditions with or without a catalyst (Scheme 1). First HF was fastly consumed by the hexachlorinated reactant to form the fluorinated intermediates PF₁₁, P₂₁ and PF₂₂ which were the most reactive. After, when the conditions were more favorable (i.e., high temperature and or the presence of a Lewis acid), all the intermediates except PF₀₀, PF₃₃ and PF₃₂ reacted with HCl or a Lewis acid to produce PF₀₀, PF₃₀ and PF₃₃. This distribution involves the intermediates PF₂₀,

PF₃₀ and PF₃₁ rather than their isomers PF₁₁, PF₂₁ and PF₂₂. The low reactivity of PF₃₀, PF₃₂ and PF₃₃ indicates that their formation is more favorable than their transformation.

4.4. Theoretical approach

To validate this reaction scheme each step was studied through theoretical calculations (stability of the various intermediates, carbocations involved and the reversibility of the various reactions).

4.4.1. Stability of the carbocations and the various intermediates

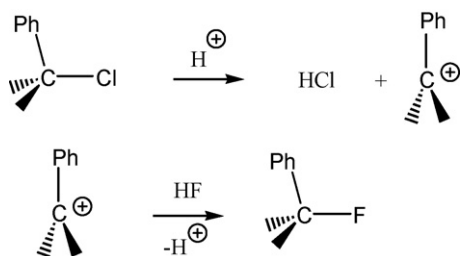
Chlorine/fluorine exchange reactions in the presence of hydrogen fluoride are expected to occur through a SN1 mechanism (Scheme 2).

The first step is an acid catalyzed loss of chloride generating a carbenium ion. This carbenium, stabilized by the phenyl substituent, then reacts with a HF molecule. In such a mechanism, the rate-limiting step is the endothermic formation of the carbenium species. According to the Hammond postulate, the corresponding transition state is close to the carbenium structure. An important consequence is that rates of competing reactions can be compared. For example, in the second fluorination step, PF₁₀ could be transformed into PF₁₁ or PF₂₀ (Scheme 1).

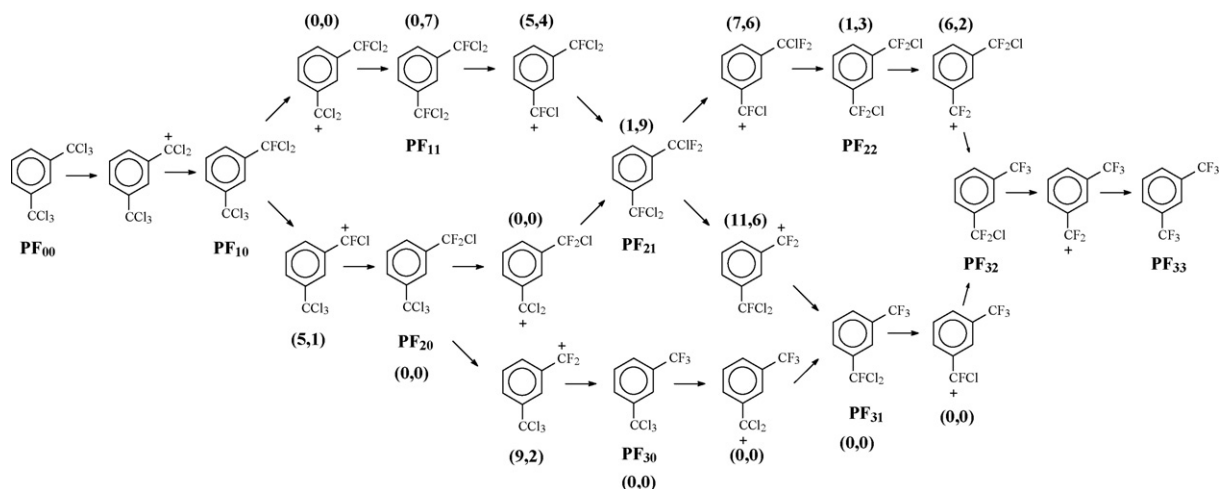
The pathway involving the lower energy carbenium is expected to be more favorable. For this reason, the relative energies of the isomeric PF_{ij} intermediates and carbenium ions have been calculated and are reported on Scheme 3. The carbenium ion leading to PF₁₁ is more stable by 5.1 kcal/mol with respect to the one leading to PF₂₀. The formation of PF₁₁ is thus favored, in agreement with the experimental data (Table 2). As in the second fluorination, there are two competing reactions in the fourth fluorination step where PF₂₁ could be transformed into PF₂₂ and PF₃₁ (Schemes 1 and 3).

The carbenium ion leading to PF₂₂ is more stable by 4.0 kcal/mol than the one leading to PF₃₁. This result is consistent with the formation of a significant amount of PF₂₂ whereas PF₃₁ was not observed (Table 2).

At this stage, the most theoretically reactions correspond to the pathway 1 in Scheme 1. This result is consistent with the data reported in Table 2. It is noticeable that these fluorination steps at 50 °C are under kinetic control since PF₁₁ is the main product in the second fluorination though PF₂₀ is slightly



Scheme 2. SN1 mechanism for the fluorination of chloromethylbenzene derivatives in liquid HF.



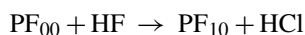
Scheme 3. Relative energies (kcal/mol) of the PF_{ij} and of the corresponding carbocations (values in brackets).

more stable (0.7 kcal/mol) and PF₂₂ is the main product in the fourth fluorination though PF₃₁ is more stable by 1.3 kcal/mol (Scheme 3).

However, an observation seems to contradict this theoretical analysis. From our hypotheses, the formation of PF₂₀ should be negligible because at 50 °C, a 5.1 kcal/mol difference in barrier heights corresponds to a rate constants ratio of roughly 10⁻⁴. Surprisingly, for HF/PF₀₀ = 2/1, the amount of PF₂₀ is 3% and cannot be considered so negligible when compared to 25% for PF₁₁ (Table 2). Looking at the reaction scheme, we note that PF₂₀ could be obtained through a reverse reaction (i.e., a chlorine atom replaces a fluorine atom) from PF₂₁.

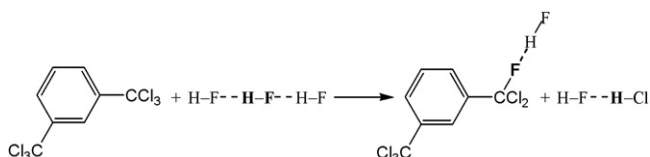
4.4.2. Reverse reactions and PF_{ij} reactivities

To check if such reverse reactions can take place in our reactive medium, we have estimated the energies of reactions for each step of the proposed reaction scheme. For the first fluorination step, for example, we considered the reaction:



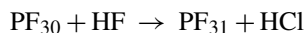
The calculations show that all these reactions are exothermic in the gas phase. The energies of reaction lie between -6.9 and -7.8 kcal/mol. However, given the strongly H-bonding character of HF, it seems necessary to account for the environment of all species involved in these reactions. We chose to include explicitly two additive HF molecules in the calculations. For example, the reaction considered above was modeled as described in Scheme 4.

In these model reactions, each atom of the HF reactant is solvated with an additive HF molecule. The modelling of the products is justified by the fact that the H and F atoms of the



Scheme 4. Model reaction for the first fluorination of PF₀₀.

reactant HF molecule are still solvated in the products. The F atom is in the -CCl₂F moiety of PF₁₀ while the H atom is in the HCl molecule. The number of additive HF molecules may be questionable for reactions involving compounds with more than one F atom, as in the reaction:



In this case we assume that the solvation of the -CF₃ moiety is approximately the same for PF₃₀ and PF₃₁. Consequently, this effect cancels out when calculating the energy of reaction. The calculations show that these model reactions are indeed predicted to be significantly less exothermic than the corresponding gas phase reactions. The energies of reaction, thus, calculated range between -2.0 and -3.3 kcal/mol, and therefore, the reverse reactions considered above are likely to occur in our reactive medium. The experimental results concerning the reactivities of the PF_{ij} intermediates under 5 atm HCl pressure confirm this trend (Table 5). All PF_{ij} except PF₃₀, PF₂₂, PF₃₂ and PF₃₃ undergo such reverse reactions in these conditions.

Moreover, according to the proposed reaction scheme, two reverse reactions can take place for some PF_{ij}. For example, PF₂₁ gave a significant amount of PF₂₀ (13%) compared to PF₁₁ (1%) and one can remark that the carbenium ion leading to PF₁₁ in this reverse reaction is indeed destabilized by 5.4 kcal/mol with respect to the one leading to PF₂₀. Similar remarks can be made for PF₃₁ which gave PF₃₀ (37%) whereas PF₂₁ was not detected. The carbenium ion corresponding to PF₂₁ is destabilized by 11.6 kcal/mol.

The agreement between the experimental PF_{ij} reactivities and the relative stabilities of the carbenium ions permit to conclude that most steps of the proposed reaction scheme can be considered as equilibria according to the literature [2].

4.4.3. Effect of the temperature of the reaction

Other experimental results concerning the temperature effect can be clarified. The composition of the reactive medium is indeed strongly temperature dependent (Fig. 2). For example, the main products are PF₀₀ (26%), PF₃₀ (33%) and PF₃₃ (11%) at 200 °C for HF/PF₀₀ = 2/1 and without catalyst. The amounts

of PF_{ij} intermediates clearly tend to the thermodynamic equilibrium at this temperature since PF₃₀ and PF₃₃, stabilized with –CF₃ substituents, are major products. The large amount of PF₀₀ results from the composition in starting reactants in this experiment (2 mol HF per 1 mol PF₀₀, i.e., a default of HF). The accumulation of fluorine atoms in –CF₃ substituents results in significant amount of PF₀₀. We tried to quantify this analysis by using the calculated total energies for the PF_{ij} intermediates. To this end we considered equilibria such as:



etc.

For each of these equilibria, the energy variation, ΔE , can be calculated. For example, for reaction (1):

$$\Delta E(1) = E(\text{PF}_{00}) + E(\text{PF}_{11}) - 2E(\text{PF}_{10})$$

Then, supposing that the free energy variation ΔG is close to ΔE , the equilibrium constant is calculated as:

$$K(1) = \frac{[\text{PF}_{00}][\text{PF}_{11}]}{[\text{PF}_{10}]^2} = \exp\left(-\frac{\Delta E(1)}{RT}\right)$$

Since there are 10 PF_{ij} compounds, we need 10 equations to obtain the composition of the reactive medium. One equation stands for the phenyl conservation and one another for the fluorine atom conservation [22], therefore, we need eight equilibrium constants such as $K(1)$. After numerical resolution of these equations, we obtained the PF_{ij} percentages. These values are reported in Table 6 together with the experimental percentages. The qualitative agreement between the predicted composition and the experimental observations is satisfactory since in each case, PF₀₀, PF₃₀ and PF₃₃ are the main products. Then, the reactive medium composition is likely to be close to the thermodynamic equilibrium at this temperature.

4.4.4. Interpretation of the relative stabilities of isomeric PF_{ij} and carbeniums

Some remarks can be made about the relative stabilities of isomeric species involved in the proposed mechanism. The carbenium ion leading to PF₁₁ bears a –CCl₂⁺ substituent whereas

Table 6
Observed and predicted values of the various products (Molar %) without catalyst (T = 200 °C, HF/PF₀₀ = 2/1)

	% Observed	% Predicted ^a
PF ₀₀	26	38
PF ₁₀	8	9
PF ₁₁	0	4
PF ₂₀	6	8
PF ₂₁	2	2
PF ₃₀	33	19
PF ₂₂	1	1
PF ₃₁	7	6
PF ₃₂	6	4
PF ₃₃	11	10

^a Thermodynamic equilibrium based on the relative stabilities of PF_{ij} compounds.

the one leading to PF₂₀ bears a –CFCI⁺ substituent. The greater stability of the former carbenium ion results from the better π -donor character of chlorine with respect to fluorine atom. Such trends on the π -donor ability of halogens in cationic species were previously studied and clarified [23]. This observation can be extended to the other carbenium species. In each case, a carbenium ion with a –CCl₂⁺ is more stable by 6.0 kcal/mol on average (5.1; 5.4 and 7.6, Scheme 3) than the isomeric carbenium ion with a –CFCI⁺ substituent. Similarly, a carbenium ion bearing a –CFCI⁺ is always more stable, by 4.7 kcal/mol on average (3.8; 4.0 and 6.2, Scheme 3) than the isomeric carbenium ion with a –CF₂⁺. All these observations are consistent with the better π -donor ability of chlorine with respect to fluorine. Turning now to the relative energies of isomeric PF_{ij} compounds, we remark that in each case, the most stable PF_{ij} is the one with the most fluorine substitutions on one carbon atom. Thus, PF₂₀, PF₃₀ and PF₃₁ are most stable than PF₁₁ (0.7 kcal/mol), PF₂₁ (1.9 kcal/mol) and PF₂₂ (1.3 kcal/mol), respectively. Such trends for fluorine substitutions are usually observed for fluoroalkane compounds and were referred to as “segregation of fluorine rule” [24]. Theoretical studies have shown that the energetic preference for multiple fluorine substitutions on one carbon atom can be attributed to coulombic interactions [25].

5. Conclusion

We can conclude that the transformation of the bis-1,3-trichloromethylbenzene depends on the experimental conditions (temperature, amount of HF and the presence of a Lewis acid). In the presence of HF in excess, the hexafluorinated product was selectively observed whatever the conditions. In order to produce selectively the most important product the 1-trichloromethyl-3-trifluoromethylbenzene, the best conditions were with HF in default. After the consumption of HF, the various fluorinated intermediates compounds were observed to lead to the most thermodynamically stable compounds, i.e., mainly the bis-1,3-trichloromethylbenzene and 1-trichloromethyl-3-trifluoromethylbenzene. Theoretical calculations showed that assuming a SN1 mechanism for the chlorine/fluorine exchange reactions, the system evolves at first that both –CCl₃ groups of PF₀₀ are fluorinated. In addition, the reactions involved have been shown to be reversible. An important consequence is, provided that some conditions are satisfied (presence of catalyst or elevated temperature), that the composition of the reactive medium tends toward the thermodynamic equilibrium. Indeed the presence of a Lewis acid increases the formation of the most stable products depending on their Lewis acidity. SbCl₅ which is the most acid is the most efficient catalyst corresponding to a decrease of 150° to obtain similar results compared with HF alone.

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