

## Gas-Phase Alkylation of Fluorobenzene and Substituted Fluorobenzenes by $(\text{CH}_3)_2\text{F}^+$ Ions

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**Abstract:** The gas-phase methylation of selected fluorobenzenes by  $(\text{CH}_3)_2\text{F}^+$  ions has been investigated by a combination of mass spectrometric and radiolytic techniques. The results are compared with those of related alkylation reactions, both in the gas phase and in solution.

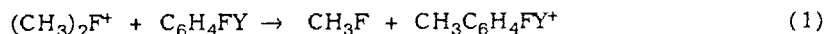
Alkylation of substrates carrying substituents with unshared electron pairs by gaseous carbenium ions, notably  $i\text{-C}_3\text{H}_7^+$ , leads to predominant ortho orientation, first noted in halobenzenes<sup>1</sup>, and subsequently in phenol, anisole and aniline.<sup>2-3</sup>

Such departure from the orientation observed in solution has been traced to the demand for charge delocalization typical of gaseous cations, leading to electrostatic interactions of their positively polarized H atoms with the n electrons of the substituent, and hence to a high local concentration of the electrophile at the ortho positions.<sup>1</sup>

However,  $i\text{-C}_3\text{H}_7^+$  can promote, in addition to alkylation, exothermic protonation of the substrate,<sup>4</sup> and the competition between the two processes can affect the observed positional selectivity.

In the present study the alkylation of selected fluorobenzenes has been carried out with a purely alkylating agent, the  $(\text{CH}_3)_2\text{F}^+$  ion, obtained from the ionization of gaseous  $\text{CH}_3\text{F}$  according to a well-established reaction sequence,<sup>5</sup> using a combination of Chemical Ionization (CI) mass spectrometry and an atmospheric-pressure radiolytic technique.<sup>6</sup>

The CI spectra of  $\text{CH}_3\text{F}$ , recorded at 50°C, 0.5 torr, display  $(\text{CH}_3)_2\text{F}^+$  at  $m/z = 49$  as the predominant ion, together with minor  $\text{CH}_2\text{F}^+$  and  $\text{CH}_3\text{F}(\text{CH}_3)_2\text{F}^+$  peaks (Figure 1a). On addition of fluorobenzene, p-fluorotoluene and p-fluoroanisole the spectra display the corresponding methylated adducts from the exothermic<sup>7</sup> process



where Y = H,  $\text{CH}_3$  and  $\text{OCH}_3$ , as shown in Figures 1b-d.

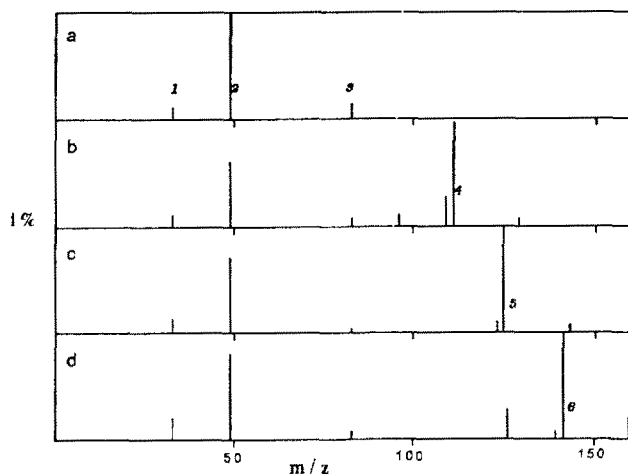


Fig.1. CI mass spectra of neat  $\text{CH}_3\text{F}$ (a), and of  $\text{C}_6\text{H}_5\text{F}$ (b),  $p\text{-CH}_3\text{C}_6\text{H}_4\text{F}$ (c),  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{F}$ (d) in excess  $\text{CH}_3\text{F}$ :

- (1) =  $\text{CH}_2\text{F}^+$
- (2) =  $(\text{CH}_3)_2\text{F}^+$
- (3) =  $(\text{CH}_3)_2\text{F}^+\text{CH}_3\text{F}$
- (4) =  $\text{C}_6\text{H}_5\text{FCH}_3^+$
- (5) =  $p\text{-CH}_3\text{C}_6\text{H}_4\text{FCH}_3^+$
- (6) =  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{FCH}_3^+$

The CI results provide direct evidence for the charged intermediates of the methylation, whose selectivity and orientation have been measured in radiolytic experiments, involving  $\gamma$  irradiation ( $37.5^\circ\text{C}$ ,  $3 \cdot 10^4$  Gy at  $10^4$  Gy  $\text{h}^{-1}$ ) of the gaseous mixtures reported in Table 1. Analysis of the neutral end products, performed by GC and GC/MS,<sup>8</sup> shows that the difluorobenzenes and o-fluoroanisole give no detectable methylated products, whereas fluorobenzene, p-fluorotoluene and p-fluoroanisole undergo efficient alkylation, their products accounting for 20 to 60% of the  $(\text{CH}_3)_2\text{F}^+$  ions formed, depending on the composition of the gaseous system, where the aromatics compete for the charged reactant with other nucleophiles present as impurities (traces of  $(\text{CH}_3)_2\text{O}$  in the  $\text{CH}_3\text{F}$  gas), formed in the radiolysis ( $\text{CH}_3\text{OH}$ ,  $\text{H}_2\text{O}$ , etc.), or deliberately added to the system ( $\text{NH}_3$ ).






The ionic nature of the methylated products is ensured by the presence of a radical scavenger ( $\text{O}_2$ ) and is confirmed by the depression of the absolute yields upon addition of gaseous bases, which intercept the charged reactants.

The selectivity of the alkylation increases at the higher  $\text{CH}_3\text{F}$  pressures and in the presence of bases, *i.e.* under conditions favouring kinetic control. Under such conditions,  $(\text{CH}_3)_2\text{F}^+$  is a well-behaved, if rather indiscriminant electrophile, *e.g.* its  $k_{\text{C}_6\text{H}_5\text{F}}/k_{\text{C}_6\text{F}_6}$  ratio is  $0.34 \pm 0.05$ , in contrast with the anomalous 1.4 ratio typical of  $i\text{-C}_3\text{H}_7^+$ .<sup>9</sup>

Furthermore,  $(\text{CH}_3)_2\text{F}^+$  does not alkylate appreciably the strongly deactivated isomeric fluorobenzenes, which instead react with  $i\text{-C}_3\text{H}_7^+$  nearly at the same rate as  $\text{C}_6\text{H}_6$ . The o/2p ratio is also considerably different in the isopropylation and in the methylation of  $\text{C}_6\text{H}_5\text{F}$ , being respectively 4.6 and 0.8. Such a striking difference can be traced to the following factors, or to their combination: *i*-incursion of proton transfer from  $i\text{-C}_3\text{H}_7^+$  to  $\text{C}_6\text{H}_5\text{F}$ , occurring at different rates at the various positions, and hence

affecting the orientation of isopropylation, ii-an inherently lower ability of  $(\text{CH}_3)_2\text{F}^+$  to interact with the F atom of  $\text{C}_6\text{H}_5\text{F}$ ,<sup>10</sup> and/or to promote ortho alkylation once the interaction has occurred and, iii-association of  $(\text{CH}_3)_2\text{F}^+$  with  $\text{CH}_3\text{F}$ , noticeable even under CI conditions (Fig. 1a) and certainly extensive at 720 torr. The interaction with the F atom of  $\text{CH}_3\text{F}$  would reduce the tendency of  $(\text{CH}_3)_2\text{F}^+$  to electrostatically bind to the F atom of the substrate.

Table 1. Selectivity and Orientation of the Gas Phase Methylation of Fluorobenzenes by  $(\text{CH}_3)_2\text{F}^+$  Ions.

SYSTEM COMPOSITION <sup>a</sup> (torr)				$k_S/k_B$	ISOMERIC COMPOSITION OF PRODUCTS (%)		
Substrate	$\text{C}_6\text{H}_6$	$\text{CH}_3\text{F}$	$\text{NH}_3$				
Fluorobenzene:	1.09	750			56	13	31
	0.98	750	3		57	15	28
	0.62	100			64	13	23
	2.00	0.38	750	0.35	57	16	27
	1.20	1.26	750	0.29	56	14	30
	1.01	1.20	750	0.39	51	16	33
	0.54	0.62	100	0.57	62	17	21
	0.82	0.72	20	0.78	61	17	23
p-F-Toluene:	1.20	750				66	34
	1.25	750	3			62	38
	0.81	100				65	35
	1.06	0.94	750	0.66		66	34
	1.12	0.89	750	0.68		66	34
	0.68	0.59	100	0.83		65	35
p-F-Anisole:	1.48	750					
	1.26	1.30	750	0.36	76	24	
	1.09	0.89	750	0.47	75	25	
	1.09	0.89	750	0.47	71	29	
	1.21	0.95	100	0.57	69	31	

<sup>a</sup>) All systems contained  $\text{O}_2$  at pressures from 5 to 10 torr, depending on the total pressure.

As a matter of fact, the selectivity of  $(\text{CH}_3)_2\text{F}^+$  in  $\text{CH}_3\text{F}$  differs considerably from that of  $\text{i-C}_3\text{H}_7^+$  in  $\text{C}_3\text{H}_8$ , approaching instead that of Friedel-Crafts alkylations under non-isomerizing conditions,<sup>11</sup> although the somewhat higher ortho orientation suggests operation of a limited coordination effect on the reactivity of

gaseous  $(\text{CH}_3)_2\text{F}^+$ , in the case of  $\text{C}_6\text{H}_5\text{F}$

			$f_o$	$f_m$	$f_p$
$i\text{-C}_3\text{H}_7^+$	gas, $\text{C}_3\text{H}_8$		3.7	0.19	0.79
$(\text{CH}_3)_2\text{F}^+$	gas, $\text{CH}_3\text{F}$		0.52	0.16	0.67
$\text{C}_2\text{H}_5\text{Br}/\text{GaBr}_3$	liquid, $\text{C}_2\text{H}_4\text{Cl}_2$		0.36	0.12	0
$i\text{-C}_3\text{H}_7\text{Br}/\text{AlCl}_3$	liquid, $\text{CH}_3\text{NO}_2$		0.34	0.03	0.95

As a final remark, the relatively low reactivity of fluoroanisoles, and the low extent of substitution ortho to the  $\text{OCH}_3$  group confirm analogous results on the methylation of anisole, traced to predominant O-alkylation by  $(\text{CH}_3)_2\text{F}^+$ .<sup>10a</sup>

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#### References and Notes

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