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The role of geometry on regioselectivity and rate of fluorination of fluorene and diphenylmethane with Selectfluor™ F-TEDA-BF_4

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Diphenylmethane and fluorene were used as target molecules in an investigation of the effect of the geometry of aromatic molecules on the regioselectivity and rate of fluorination with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4). In acetonitrile at 80 °C ring fluorination of diphenylmethane was accompanied by oxidation of the saturated carbon atom, while in trifluoroacetic acid only ring fluorination with an *ortho–para* regioselectivity of 1.8 : 1 was observed. Fluorene was converted in acetonitrile as well as in trifluoroacetic acid into 2- and 4-fluoro substituted products in the relative ratio of 2 : 1 and 1.2 : 1, respectively. The reactions in acetonitrile obey a simple rate equation:

$$v = \mathrm{d[F\text{-}TEDA]}/\mathrm{d}t = k_2 \times \mathrm{[F\text{-}TEDA]} \times \mathrm{[Substrate]}$$

and the second order rate constants for the reactions in acetonitrile at 65 °C were determined; values of 0.6×10^{-4} M^{-1} s^{-1} for diphenylmethane and 35.5×10^{-4} M^{-1} s^{-1} for fluorene were obtained. The reaction rates for the various functionalisations of fluorene relative to those for diphenylmethane were found to be considerably influenced by the type of functionalisation. Relative rate factors ($k_{rel} = k_{2(fluorene)}/k_{2(diphenylmethane)}$) with values between 59 for fluorination and 712 for chlorination were determined, while the corresponding data for the biphenyl/diphenylmethane pair were only slightly dependent on the type of functionalisation. A reaction pathway involving electron transfer, thus forming cation radical intermediates, was proposed as the main process in the case of fluorination of fluorene with F-TEDA-BF_4.

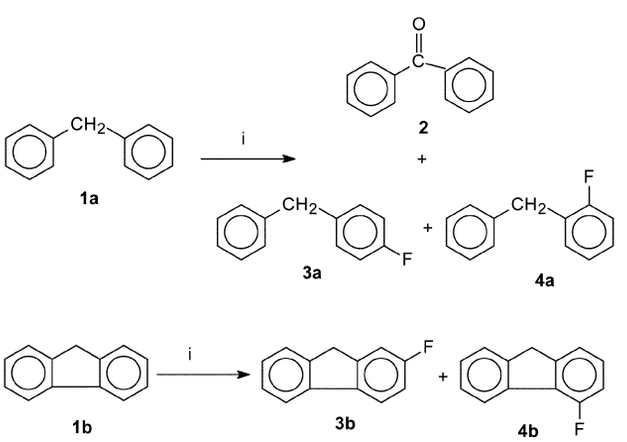
Introduction

Direct introduction of fluorine into aromatic molecules under mild reaction conditions is still only a partly solved problem, particularly if the aromatic ring is not activated.[1] Valuable information about the role of the structure of the fluorinating reagent (F-L) in the fluorination of organic molecules could be obtained if reactions are studied on several target molecules under comparable reaction conditions. Diphenylmethane (DPM, **1a**) and fluorene (**1b**) have been used several times as tools for investigation of the effect of geometry, strain and conjugation in the target molecules on the type and regiochemistry of their transformations.[2–4] On the other hand, kinetic evaluations of the mild introduction of an fluorine atom into organic molecules with electrophilic F-L reagents are rather scarce,[5] mainly due to the high reactivity of these reagents (elemental fluorine, fluoroxy reagents) or the high sensitivity of their reactions to reaction conditions (XeF_2). The introduction and broad synthetic application of organic molecules incorporating a reactive N–F bond as mild easy handling fluorinating reagents with good stability/reactivity characteristics[1d,6] opened new possibilities for more extensive studies on the mild introduction of fluorine into organic molecules also from a kinetic point of view. It seems that from three types of N–F reagents, namely neutral N-fluoro amines (R_1R_2NF type), *N*-fluoropyridinium and related salts, and *N*-fluoro quaternary amine salts ($F–N^+R_1R_2R_3$ Y^- type), the latter, are the most convenient tools for kinetic measurements since their reactivity could be easily followed by iodometric titration.[7] We have already demonstrated that by following a kinetic evaluation of the reactions of the two main representatives of this class of N–F reagents, *i.e.* 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4) and its analogue 1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Accufluor™ NFTh), with various aromatic molecules[8] or alkenes[9] many mechanistic benefits could be obtained.

In our continuing interest in transformations of organic molecules with F–L reagents we now report investigations on the reactions of fluorene and diphenylmethane with F-TEDA-BF_4.

Results and discussion

After a 48 hour reaction of diphenylmethane (DPM, **1a**, Scheme 1) with F-TEDA-BF_4 in acetonitrile at 80 °C, beside recovered starting material and some tar, only 13% of fluorinated products were detected in the crude reaction mixture. The main reaction process appeared to be the oxidation of the benzyl position, which after consuming the traces of water



Scheme 1 *Reaction conditions*; i: F-TEDA-BF_4, solvent (MeCN or TFA), T = 50–80 °C, rt 2–48 h.

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Table 1 Effect of reaction conditions on ring fluorination of fluorene and diphenylmethane with F-TEDA-BF_4

Substrate	Solvent	Yield[a] (%)	Regioselectivity 3	4
Ph_2CH_2	MeCN[b]	13[c]	24	76
1a	MeCN[d]	14[e]	28	72
	TFA[f]	66	36	64
Fluorene	MeCN[g]	27	67	33
1b	MeCN[h]	29	62	38
	TFA[i]	24[j]	55	45

[a] Yields of fluorinated products were calculated from ^{19}F NMR of the crude reaction mixture using octafluoronaphthalene as internal reference; product distributions were determined from ^{19}F NMR. [b] 80 °C, 48 h. [c] 32% of benzophenone **2** was also formed. [d] 80 °C, 48 h, $PhNO_2$. [e] 14% of benzophenone **2** was also formed. [f] 60 °C, 4 h. [g] 80 °C, 4.5 h. [h] 80 °C, 4.5 h, $PhNO_2$. [i] 50 °C, 2 h. [j] 20% of unstable trifluoroacetyl product was formed.

Table 2 Role of the type of ring functionalisation on the regioselectivity of substitution of fluorene, diphenylmethane (DPM) and biphenyl (BP)

Reaction	*ortho*–*para*-Substitution (**4**/**3**) Fluorene	DPM	BP
Fluorination:			
F-TEDA-BF_4	0.50	3.2	3.5[8a]
XeF_2[10]	0.50	0.8	1.1
Nitration[11]	0.45	0.8	2.2
Detritiation[11]	0.32	0.8	1.2
Chlorination[11,12]	0.13	1.2	0.6

present in the solvent, resulted in 32% yield of benzophenone **2**. Fluorofunctionalisation at the *ortho* position prevailed over the *para* one (Table 1). Reaction in the presence of nitrobenzene, usually used as a radical scavenger, gave a very similar product distribution of fluorosubstituted products but the oxidation process was inhibited and only 14% of benzophenone was formed. Side chain functionalization was eliminated and the amount of fluorinated products increased when trifluoroacetic acid was used as solvent (Table 1).

Fluorene **1b** was transformed with F-TEDA-BF_4 at 80 °C in acetonitrile to a mixture of two fluorinated products assigned as 2-fluorofluorene **3b** and 4-fluorofluorene **4b** in 2 : 1 relative ratio and 27% overall yield, while besides recovered **1b** and some tar material, no side chain functionalised product was observed in the isolated crude reaction mixture. The presence of nitrobenzene had no significant effect on the course of the reaction, while the use of trifluoroacetic acid diminished the regioselectivity of the fluorination and up to 20% of an unstable trifluoroacetyl substituted derivative was additionally detected in the crude reaction mixture.

Further, we investigated the regioselectivity and kinetics of various types of ring functionalisation of fluorene and compared them with those of diphenylmethane and biphenyl. The results are collected in Tables 2 and 3. Product distribution in the case of fluorination of fluorene with F-TEDA-BF_4 in MeCN as well as with XeF_2[10] is very similar to nitration with fuming HNO_3 in Ac_2O[11] (Table 2). A much higher proportion of 2-substitution was observed in the case of chlorination[11,12] with Cl_2 and detritiation in TFA,[11] while bromination with Br_2 proceeded almost regiospecifically to position 2.[13] On the other hand, quite different regioselectivity was observed in the fluorination of both biphenyl[8a] and diphenylmethane with F-TEDA-BF_4, where a high degree of *ortho* fluorination took place, contrary to the predominant *para* (relative to the biphenyl moiety) functionalisation of fluorene.

The regioselectivity of nitration of fluorene was rationalised by the fact that MNDO calculations[14] showed that fluorene

Table 3 Effect of structure variation on the relative rates of ring functionalization

Reaction	$k_{fluorene}/k_{diphenylmethane}$	$k_{biphenyl}/k_{diphenylmethane}$
Fluorination	59	1.7
Nitration[11]	52	2.1
Detritiation[11]	103	1.7
Chlorination[11,12]	712	2.7

bears a larger coefficient of electron density at C-2 (0.39) than at C-4 (0.278) in its HOMO.[15] The similar product distribution in fluorination and nitration suggests that similar reaction pathways should be involved in both processes, and that they should be quite different from those concerning chlorination and bromination where substitution at C-2 was exclusive or at least predominant. A similar dichotomy in product distribution in bromination on the one hand, and nitration and fluorination on the other was already observed in the reactions of dibenzofuran,[8a,10] where the latter ones also resemble the distribution of HOMO electron density. This difference in regioselectivity was explained by the different stability of the σ-complex (late transition state) and π-complex (early transition state).

The rate of reactions of fluorene and diphenylmethane with F-TEDA-BF_4 was measured by following the progress of consumption of the reagent by iodometric titration. The rate of the reactions in MeCN at 65 °C obeyed a simple second order rate equation:

$$v = d[\text{F-TEDA}]/dt = k_2 \times [\text{F-TEDA}] \times [\text{substrate}]$$

and the functionalisation of fluorene (Fig. 1) was found to be much faster ($k_2 = 35.5 \times 10^{-4}$ M^{-1} s^{-1}) than diphenylmethane ($k_2 = 0.6 \times 10^{-4}$ M^{-1} s^{-1}) or biphenyl[8a] ($k_2 = 1.0 \times 10^{-4}$ M^{-1} s^{-1}).

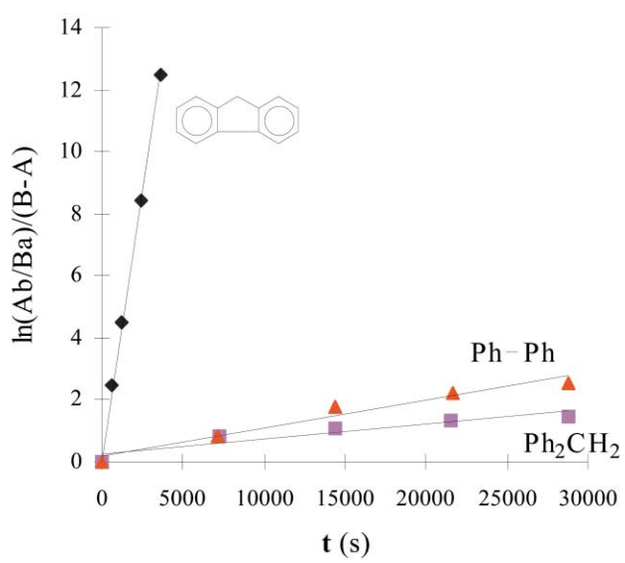
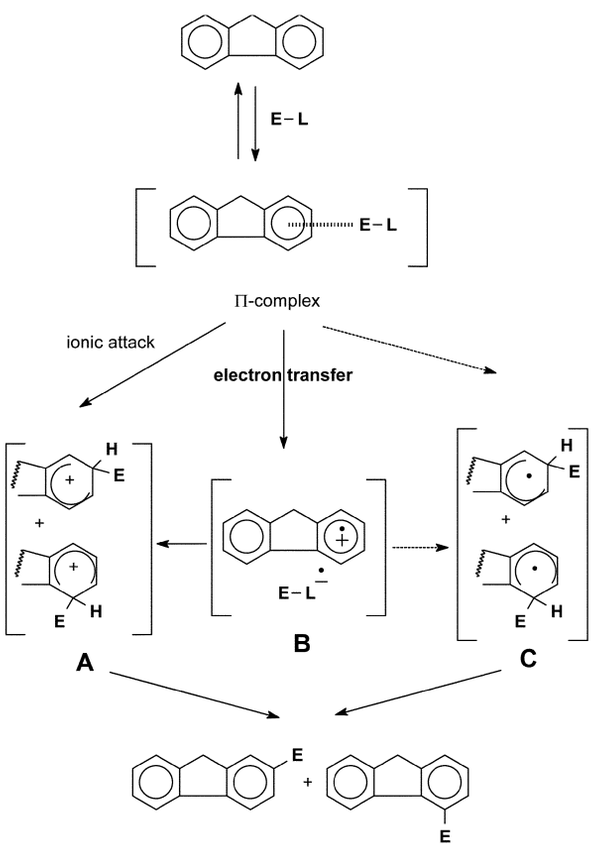


Fig. 1 Effect of substrate structure on the rate of fluorination with F-TEDA-BF_4 in acetonitrile at 65 °C.

By comparing the values for second order rate constants for different types of functionalisation of fluorene, diphenylmethane and biphenyl (Table 3), we can see that the reagent structure plays a very important role in the enhancement of the reactivity of fluorene in comparison to diphenylmethane and biphenyl. Again, the increase in the rate of fluorination with F-TEDA-BF_4 was found to be very similar to nitration, while the relative reactivity of biphenyl compared to diphenylmethane was less affected by the type of reagent.

Organic compounds incorporating a reactive N–F bond are also known as moderate to strong oxidants[16] and F-TEDA-BF_4

is one of the strongest in the group. On the basis of extensive studies, stressing especially nitration reactions, it has already been proved that ion radical intermediates are involved in the reaction of aromatic molecules with reagents of high oxidation ability.[17–21] On the basis of the present results and their comparison with relevant literature studies, the transformation of fluorene could be ascribed as a competitive process between the electron transfer formation of ion radicals **B** and ionic attack leading to a σ-complex **A** (Scheme 2), while radical intermediates **C** are less probable. Since nitration of aromatic molecules has been declared several times to be an electrophilic reaction *via* cation radicals, the similar regiochemistry and kinetics of fluorene transformation suggest that in the case of fluorination with F-TEDA-BF_4 the reaction pathway involving electron transfer could be assumed to be the main process as well.



Scheme 2

Experimental section

Materials

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA, Air Products), fluorene (Janssen Chimica), diphenylmethane (Fluka), nitrobenzene, trifluoroacetic acid (Fluorochem Limited), octafluoronaphthalene (Fluorochem Limited), 2-fluorofluorene (Fluorochem Limited) and methylene chloride (Merck) were obtained from commercial sources and used without further purification, except for kinetic measurements where fluorene and F-TEDA-BF_4 were crystallised and diphenylmethane distilled. Acetonitrile (Merck) was purified by distillation and stored over molecular sieves. ^{1}H and ^{19}F NMR spectra were recorded at 60 or 56.45 MHz with Me_4Si or CCl_3F as internal standards, and gas chromatography was carried out on Varian Models 3700 and 3300.

Fluorination with F-TEDA-BF_4

Substrate (**1a**,**1b**), 1.0 mmol, and 1.0 mmol of F-TEDA were dissolved in 10 mL of solvent (MeCN or TFA) and the solution was heated at 50 to 80 °C for 4.5 to 48 hours (Table 1) until the consumption of reagent, followed by KI starch paper, was complete. The solvent was partially removed under reduced pressure, the residue diluted with 30 mL of CH_2Cl_2, washed with water (10 mL), a saturated solution of $NaHCO_3$ (10 mL) and dried over Na_2SO_4. After evaporating the solvent the crude reaction mixture was analysed by ^{1}H and ^{19}F NMR spectroscopy; yields of fluorinated products were determined with octafluoronaphthalene as internal reference. Results are presented in Table 1.

Pure products were isolated by preparative GLC (FFAP 30% on Chromosorb W A/W 80/100, 180 °C) and the structures determined on the basis of their spectroscopic data compared with known data from the literature or those for independently prepared samples: 4-fluorodiphenylmethane[22] **3a**: $\delta_F = -117.7$ ppm (dd), 2-fluorodiphenylmethane[23] **4a**: $\delta_F = -118.5$ ppm (m); 2-fluorofluorene[24] **3b**: $\delta_F = -116.2$ ppm (ddd), 4-fluorofluorene[24] **4b**: $\delta_F = -120.8$ ppm (m).

In the crude reaction mixture obtained after fluorination of fluorene in trifluoroacetic acid, a signal corresponding to trifluoroacetate ($\delta_F = -76.5$ (s), 20%) was observed in its ^{19}F NMR spectrum, but we were unable to determine the exact structure due to the low stability of the product.

Kinetic measurements of reactions of aromatic molecules with F-TEDA

To 25 mL of a thermostatted solution of 1 mmol of substrate (**1a**,**1b**) in CH_3CN, a thermostatted solution of F-TEDA in CH_3CN (25 mL 0.02 M) was added and stirred at 65 °C. After various times 10 mL aliquots were mixed with 20 mL ice cold 0.02 M KI and the liberated iodine titrated with 0.05 M $Na_2S_2O_3$. The results are presented in the Fig. 1.

Acknowledgements

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