Interactions between amines and aromatic fluoro derivatives. ^{19}F NMR investigation in [$^2H_8$]toluene

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^{19}F NMR chemical shifts of some nitro-fluorobenzenes and of 2-fluoropyridine are recorded in [$^2H_8$]toluene in the presence of variable amounts of amines (butylamine, piperidine and aniline). The fluorine resonances are shifted upfield by addition of the amine, except for addition of aniline to the solution of 2,4-dinitrofluorobenzene. The shift differences in ^{19}F spectra are related to an association between the amine and fluoroderivative, mainly involving hydrogen bonding interactions. The data on the apparent stability of the observed complexes are related to the catalytic behaviour of amines in some aromatic nucleophilic substitutions.

Non-covalent interactions between neutral molecules are of interest not only from a general point of view to investigate solute–solute or solute–solvent interactions, but also to learn more on the particular aggregations of neutral nucleophiles (*e.g.* amines) and aromatic derivatives containing electron withdrawing groups such as halogeno nitro derivatives, which react in S_NAr reactions.

In previous papers[1,2,3] we emphasized the importance of the interactions between a nucleophile and an electrophile to give molecular complexes which may be responsible for particular kinetic features in some aromatic nucleophilic substitution reactions.

In apolar solvents, the kinetic rate constant value (s^{-1} mol^{-1} dm^3) of the reactions between nitro-activated halogenobenzenes and aliphatic or aromatic amines, obtained under pseudo first order conditions, increases proportionally to the initial amount of the nucleophile. The experimental reaction order related to the amine may raise the overall order of reaction to a value of 3. This behaviour was related to the departure of the proton and of the leaving group from zwitterionic intermediate in a rate determining step.[4,5]

A different explanation of the observed kinetic behaviour was suggested by us,[3] on the basis of a spectrophotometric investigation that showed the presence (immediately after mixing) of a new species involving the substrate and the nucleophile (or a catalyst if present in the reaction mixtures) in a quickly established equilibrium preceding the substitution process.

Previous investigations[3,6] examining the reaction mixtures of nitro-halogenobenzenes and amines, indicate the possible presence of some specific interactions leading to different molecular complexes, such as charge-transfer or hydrogen bonding complexes. Different kinds of associations, depending on the nature of the amine (or of the catalyst), of the substrate and of the solvent were observed.

To learn more of the nature of the molecular complexes, we report several results for the addition of a variable amount of amine (both aromatic and aliphatic) to some fluoro derivatives (with particular attention to nitro-fluorobenzenes) on the ^{19}F chemical shifts in a poorly polar solvent ([$^2H_8$]toluene).

Results and discussion

Table 1 reports selected ^{19}F, ^{13}C and ^1H NMR spectral data of the fluoro derivatives (Fig. 1) in [$^2H_8$]toluene and some instances of the effect of the addition of amines.

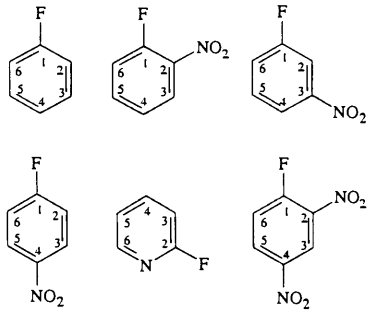


Fig. 1

The first observation concerns the qualitative effect of the amine addition on the ^{19}F signals. In all cases the fluorine signal was shifted upfield by addition of the amine except for 2,4-dinitro-fluorobenzene whose ^{19}F signal was shifted downfield. This fact indicated that the association between the amines and the fluoro derivatives concerned, involved several kinds of interactions. The behaviour of the aromatic amines differed from that of aliphatic ones, probably because several prevalent attractive forces were operating. Except in the case of 4-NO_2-fluorobenzene, whose protons undergo a significant ^1H NMR shift on addition of butylamine, the ^1H and ^{13}C NMR chemical shift changes were too small and consequently not useful to evaluate quantitatively the complexation.

These results were in apparent contradiction with previously reported data in which proton signals of 2,4-dinitro-fluorobenzene (DNFB) in chloroform were shifted upfield by the addition of aniline. The reason for this discrepancy might be due to the different solvation of DNFB in toluene and in chloroform. This assumption agrees with recent reports,[3,7,8] where it is asserted that the electron accepting substrate is solvated by the electron donating solvent (toluene) as depicted in Scheme 1.

$$ArF + ArH \rightleftharpoons ArF{\cdot}ArH$$

Scheme 1

Aniline competes with toluene in complexing with DNFB, whereas in chloroform this competition does not exist.

The shift differences in ^{19}F NMR spectra may be related to

Table 1 ^{19}F, ^{13}C and selected ^{1}H NMR data for fluoro derivatives and some instances of the effect of the addition of amines

Compound	Amine[a]	F	C-1	C-2	C-3	C-4	C-5	C-6	H-6	H-2	H-3
Fluorobenzene		−112.96	163.39	115.53	130.18	124.13	130.18	115.53	6.76		
Fluorobenzene	Butylamine	−114.27[b]	163.39	115.54	130.21	124.16	130.21	115.54	6.79		
2-NO_2-Fluorobenzene		−118.22	155.56	137.56	125.95	124.23	134.93	118.02	6.36		
2-NO_2-Fluorobenzene	Butylamine	−119.26[b]	155.62	137.57	126.11	124.43	135.22	118.19	6.43		
2-NO_2-Fluorobenzene	Piperidine	−118.58[b]	155.59	137.57	125.93	124.32	135.09	118.07	6.38		
2-NO_2-Fluorobenzene	Aniline	−120.19[b]	155.50	137.56	125.94	124.13	134.87	117.94			
3-NO_2-Fluorobenzene		−109.78	162.33	111.18	149.29	119.09	130.25	121.03	6.51	7.39	
3-NO_2-Fluorobenzene	Butylamine	−110.17[b]	162.41	111.24	149.44	119.17	130.39	121.16	6.63	7.46	
4-NO_2-Fluorobenzene		−103.52	165.99	115.91	126.13	144.54	126.13	115.91	6.28		
4-NO_2-Fluorobenzene	Butylamine	−105.04[b]	166.09	116.06	126.24	144.68	126.24	116.06	6.53		
4-NO_2-Fluorobenzene	Piperidine	−103.66[b]	166.10	116.07	126.24	144.62	126.24	116.07	6.42		
2-F-Pyridine		−66.91		164.23	109.41	140.44	120.93	148.00			6.29
2-F-Pyridine	Butylamine	−67.78[b]		164.24	109.47	140.54	120.99	148.05			6.36
2,4-Dinitro-fluorobenzene		−108.12	158.17	137.55	122.02	143.33	129.33	118.68	6.08		
2,4-Dinitro-fluorobenzene	Aniline	−107.66[b]	158.15	137.56	122.00	143.33	129.48	118.75	6.14		

[a] [Amine] ≈ 1 mol dm^{-3}. [b] The ^{19}F data of the complex fluoroaromatic–amine refers to the value extrapolated from eqn. (1).

Table 2 Apparent stability constants (K_c) and analytical data treatment [by eqn. (1)] for the effect of the addition of amines to the chemical shift of some aromatic fluoroderivatives in [$^2H_8$]toluene at 21 °C. Errors are standard deviations

Substrate	Amine	K_c (mol^{-1} dm^3)	A[a]	b[b]	n[c]	R[d]
2-Nitro-fluorobenzene	Butylamine	0.20	(3.40 ± 0.1) × 10^{-3}	(1.73 ± 0.07) × 10^{-2}	15	0.990
2-Nitro-fluorobenzene	Piperidine	4.3	(9.90 ± 0.2) × 10^{-3}	(2.28 ± 0.1) × 10^{-3}	10	0.997
2-Nitro-fluorobenzene	Aniline	0.32	(1.80 ± 2) × 10^{-3}	(3.04 ± 0.1) × 10^{-2}	13	0.995
4-Nitro-fluorobenzene	Butylamine	0.057	(2.33 ± 0.06) × 10^{-3}	(4.09 ± 0.06) × 10^{-2}	11	0.999
4-Nitro-fluorobenzene	Piperidine	0.50	(2.62 ± 0.3) × 10^{-2}	(5.18 ± 0.02) × 10^{-2}	7	0.998
3-Nitro-fluorobenzene	Butylamine	0.41	(8.99 ± 2) × 10^{-3}	(2.21 ± 0.1) × 10^{-2}	10	0.998
Fluorobenzene	Butylamine	0.096	(2.70 ± 1) × 10^{-3}	(2.78 ± 0.6) × 10^{-2}	8	0.999
2-Fluoropyridine	Butylamine	0.18	(4.06 ± 1) × 10^{-3}	(2.28 ± 0.4) × 10^{-2}	9	0.993
2,4-Dinitrofluorobenzene	Aniline	0.32	(7.70 ± 2) ± 10^{-3}	(2.37 ± 0.05) × 10^{-2}	11	0.998
2,4-Dinitrofluorobenzene	Aniline	0.7[e]				
2,4-Dinitrofluorobenzene	Butylamine	27[f]				
2,4-Dinitrofluorobenzene	Piperidine	79[f]				

[a] $A = 1/\Delta_c$. [b] $B = 1/K_c\Delta_c$. [c] Number of points. [d] Correlation coefficient. [e] In $CDCl_3$, ref. 2. [f] In cyclohexane, ref. 6.

the equilibrium shown in Scheme 2, assuming a stoichiometric ratio ArF : amine = 1 : 1.

$$ArF + HNRR' \underset{}{\overset{K_c}{\rightleftharpoons}} ArF{\cdot}HNRR'$$

Scheme 2

The apparent stability constants of the complexes K_c (mol^{-1} dm^3) may be quantitatively evaluated by eqn. (1):[9]

$$1/[RR'NH] = 1/\Delta_c + 1/K_c\Delta_c\,(1/\Delta\delta) \qquad (1)$$

where $\Delta\delta$ (in Hz), is the chemical shift difference between the substrate and the substrate/nucleophile mixture, Δ_c is the chemical shift of the molecular complex and K_c is the apparent stability constant of the complex.

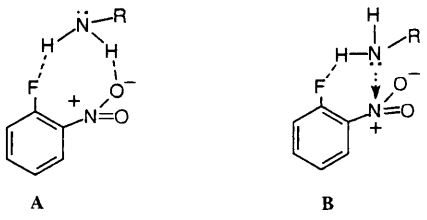
It is very likely that the equilibrium shown in Scheme 2 includes several interactions but, as previously reported[10] for interactions between 2-hydroxypyridine and fluoroaromatics, it is reasonable that the main interaction detected by the present method consists of a hydrogen bonding interaction between fluorine and the N–H group, at least in the case of aliphatic amines. Even if non-specific solvent effects cannot be completely ruled out, the ^{19}F chemical shift difference of 2-nitro-fluorobenzene in [$^2H_8$]toluene (δ_F −118.22 ppm) and in $CDCl_3$ (δ_F −118.03) and the feeble effect recorded in ^{19}F spectra by addition of triethylamine to 2-nitro-fluorobenzene, indicates that the ^{19}F chemical shift changes obtained by the present experiments cannot be attributed to a generic solvent effect.

Table 2 reports the experimentally calculated K_c values. Some analytical data (intercepts and slopes) of eqn. (1) are also reported in Table 2. $1/A$ is the calculated value of the chemical shift of the fluoroaromatic–amine complex. Some observations are worthy of consideration.

Apparently, the effect of increasing the number of the nitro groups did not affect the value of K_c, as tested by the K_c ratio (1 : 1) of 2,4-dinitro-fluorobenzene : 2-nitro-fluorobenzene for the complexes with aniline. A similar behaviour was previously observed[10] in the interactions between 2-hydroxypyridine and nitro-fluorobenzenes: K_c ratio 2,4-dinitro-fluorobenzene : 2-nitro-fluorobenzene was 2.2 : 1.[10]

Alternatively, in the same study[10] the K_c ratio of 4-nitro-fluorobenzene : 2-nitro-fluorobenzene was 2.7 : 1, while in the present investigation, the adduct shown in Scheme 2 is more stable when the nitro group is on the 2 rather than the 4 position for both the primary and secondary amines. A reasonable explanation of the inversion of the trend may be the interaction of the *ortho* nitro group with the amine. Two kinds of association might be invoked: (i) the formation of a second hydrogen bond between the aminic hydrogen and the nitro group oxygen, as depicted in **A** of Fig. 2; (ii) an attractive interaction between the two nitrogen atoms (of the amine and of the nitro group), as shown in **B** of Fig. 2. The former interaction, which represents the accepted assumption[11] cannot explain why piperidine (a secondary amine) parallels the behaviour of butylamine (a primary amine). The latter interaction was previously observed[12] in solid state by X-ray diffraction of crystals of 2-*N*-(2,4,6-trinitrophenyl)pyridineamine and of other related compounds.

In Table 2, 2-nitro-fluorobenzene and 2-fluoropyridine show



A B

Fig. 2

the same K_c values with respect to butylamine. These data indicate that the K_c values reported here cannot be considered the main result of some specific interactions between the amine and the nitro group. Furthermore, the position of the nitro group has some influence: for butylamine the ratio of K_c values of X-nitro-fluorobenzene: fluorobenzene are: 4.3:1, 2.1:1, and 0.6:1 for X = 3, 2, 4, respectively. The fact that K_c for 4-nitro-fluorobenzene is slightly lower than K_c for fluorobenzene may be explained by the usual electronic effects of the nitro group, if a direct interaction between fluorine (as electron donating atom) and nitro group (as electron accepting group) is conceived. 3-Nitro-fluorobenzene is the most prone to complex with butylamine, in spite of the fact that electronic effects in *meta* and *para* positions are very similar as tested by Hammett σ_m and σ_p values (0.71 and 0.78, respectively)[13] of the nitro group. The most likely explanation is the direct conjugation (fluorine–nitro group) which is stronger in the *para* than in the *meta* position.

^{19}F spectral data obtained adding triethylamine (TEA) to 2-nitro-fluorobenzene show a weak association, which obviously cannot be ascribed to hydrogen bonding. Interactions between nitro-halogenobenzene and tertiary amines were previously observed by us in different systems[7,14] and were attributed to an electron donor–acceptor adduct. Donor–acceptor complexes, of course, may be present also for protic amines, as extensively investigated in previous papers, in particular for aromatic amines.[1,2,7]

We have indicated that the present data mainly refer to hydrogen bonding, but other kinds of interactions may also be involved. In Table 2 one can see that a secondary amine is more prone than a primary one to associate with nitro-fluorobenzenes, as shown by the ratios $K_c^{piperidine}/K_c^{butylamine}$ = 22 and 9 for 2-nitro-fluorobenzene and for 4-nitrofluoro-benzene, respectively. This fact agrees with known kinetic data: in fact in S_NAr reactions, secondary amines are more effective in enhancing k_{obs} values (s^{-1} mol^{-1} dm^3) on increasing the initial concentration of the amine. We previously affirmed that S_NAr catalytic kinetic behaviour is due to the presence of some interactions between substrate and amine in a rapidly established equilibrium preceding the substitution process.[3] Piperidine allows the formation of hydrogen bonding or other non-covalent interactions better than non-cyclic secondary amines because of its cyclic structure. In fact in the case of non-cyclic amines, literature data[15] indicate that butylamine was more prone to afford a complexation with dinitrobenzenes than di- and tri-butyl amines.

In conclusion, the formation of the hydrogen bonding N–H···F may be an aid to the leaving group departure in solvents poorly able to solvate F^- ion, moreover we think that this interaction involves the leaving group in an equilibrium preceding the attack of the nucleophile.

Experimental

All the NMR spectra were recorded on Varian Gemini 300 spectrometer operating at 300.07 MHz for ^1H, 75.46 MHz for ^{13}C and 282.33 MHz for ^{19}F resonance; samples were prepared as 1 ÷ 2 10^{-4} mol dm^{-3} solutions in [$^2H_8$]toluene. Proton and carbon chemical shifts are given in ppm from internal Me_4Si; fluorine shifts are referred to $CFCl_3$. The various spectra were recorded using the following parameters: ^1H spectral width 4.5 kHz, pulse width 7.8 μs (*ca.* 60° flip angle), repetition time 2 s, acquisition time 2 s; ^{13}C spectral width 18 kHz, pulse width 5 μs (*ca.* 30° flip angle), repetition time 5 s, acquisition time 1 s; ^{19}F spectral width 70 kHz, pulse width 8.3 μs (*ca.* 60° flip angle), repetition time 2 s, acquisition time 1.5 s. The signal-to-noise ratio was improved by applying a 2 Hz line broadening factor to the FID prior to Fourier transformation in ^{13}C spectra. The digital resolution was improved to 0.007 ppm by zero-filling to 16 K data points.

All compounds used in this study are commercially available (Aldrich Chemical Co.). Chemical shifts were found to be reproducible to within ±0.1 ppm.

The last addition of the primary or secondary amines to the solutions of the fluoroaromatics produces ^{19}F signal shifts varying from 30 to 75 Hz; the concentration of the fluoro-benzenes holds reasonably constant within a set of spectral determinations. The range of amine concentration used for the evaluation of K_c was between 0.01 and 0.5 mol dm^{-3}. The addition of triethylamine to 2-nitro-fluorobenzene produces a feeble shift of ^{19}F signals, but the reproducibility of the measurement was unsatisfactory. We are able to indicate only a limit value of $K_c \leqslant 0.05$ (mol^{-1} dm^3).

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