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Review

KINETICS OF NUCLEOPHILIC SUBSTITUTION REACTIONS OF POLYFLUOROAROMATIC COMPOUNDS

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SUMMARY

This treatment summarises experimental data on the kinetics of nucleophilic substitution reactions in the polyfluoroaromatic series. The review discusses the effects of substituent, solvent, and nucleophilic reagent on the rate and orientation of the nucleophilic aromatic substitution. The additivity of ring fluorine effect on the reactivity of a substrate is considered. The review gives quantitative estimation of the reactivity of polyfluorinated bicyclic and nitrogen-containing heterocyclic compounds and discusses the rate-determining effects. The data on the reaction of the fluorine anion with polyfluoroaromatic compounds are reviewed.

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INTRODUCTION

During their 30 years history polyfluoroaromatic compounds became an object of extensive research, including the development of preparative and industrial synthetic procedures, and studies on their applications [1-7]. Much less developed were the works on quantitative determination of the dependence between the structure and reactivity of these compounds [4]. Some kinetic studies have been carried out to facilitate the choice of conditions for the synthesis of polyfluoroaromatic compounds [1,5].

The growing interest in polyfluoroaromatic compounds, indicated by the far larger list of works than cited above, and advances in physical organic chemistry suggest the future intensive development of the chemistry of polyfluoroaromatic compounds. We believe it necessary to direct the efforts of researchers to solution of fundamental problems of the chemistry of polyfluoroaromatic compounds, investigation of the mechanism of fluorine effect on the aromatic system, studies of rate-determining stages of the reactions, and the search for calculation methods of control over chemical processes, using the available data on correlations between the reaction rate, the structure of polyfluoroaromatic substrate, and the type of reagent.

This review attempts to analyse the modern state of quantitative description of the reactivity of polyfluoroaromatic compounds in their typical reactions - those of nucleophilic substitution, with extensive overview of Soviet works inaccessible for worldwide audience.

Fluorine is characterised by the high electron affinity, due to which fluorine introduction into the benzene ring results in significant changes in the electronic structure and reactivity of aromatic compounds. Introduction of several fluorine atoms into the ring essentially increases the positive charge on ring carbon atoms, which makes the nucleophilic substitution reactions ($S_{N(Ar)}$ reactions) the most typical ones for polyfluoroaromatic compounds[5]. From the very start, researchers of polyfluoroaromatic compounds were interested in the quantitative relationship between the number of ring fluorine atoms and the reactivity of polyfluoroaromatic substrate : whether one should expect a specific behaviour of these compounds due to substitution of all ring hydrogens by fluorine, or their behaviour will simply be governed by the additivity effect. In the latter case the reactions of compounds C_6F_5X should proceed in a similar way as the reactions of other benzene derivatives containing one or two sufficiently strong electron-accepting substituents comparable in their electronic effect with the overall effect of five fluorine atoms. Further studies showed the substitution effect to be not as simple as that.' Along with some similarities of polyfluoroaromatic compounds with activated monofluorobenzenes, there are examples of essential differences, which may result from differences in the effect of ring fluorine or other electron-accepting substituents on the electronic structure of the benzene ring, or by the 'neighbour' effects - the presence of two fluorine atoms in ortho-positions to substituent and reaction centre, and the ensuring sterico-electronic effects.

TABLE 1

Comparison of the reactivity of nucleophilic reagents with polyfluoroaromatic compounds C_6F_5X

X	Nucleophile	Solvent	T, °C	k, l/mol·sec	k_{rel}	E, kcal/mol (lg A)	Ref.
F	CH_3OLi	CH_3OH	50	$2.5 \cdot 10^{-4}$	1	21.9 (11.2)	13
	CH_3OK			$3.3 \cdot 10^{-4}$	1.3	22.6 (11.8)	
	CH_3ONa			$5.4 \cdot 10^{-4}$	2.2	21.4 (11.0)	
F	C_2H_5ONa	C_2H_5OH	50	$5 \cdot 10^{-4}$	1	20.7 (10.7)	14
	$n\text{-}C_3H_7ONa$	$n\text{-}C_3H_7OH$		$9.3 \cdot 10^{-4}$	1.9	21.1 (11.2)	
	$n\text{-}C_4H_9ONa$	$n\text{-}C_4H_9OH$		$1.2 \cdot 10^{-3}$	2.4	21.3 (11.5)	
	$n\text{-}C_5H_{11}ONa$	$n\text{-}C_5H_{11}OH$		$9.3 \cdot 10^{-4}$	1.9	21.4 (11.4)	
F	NaN_3	CH_3OH	50	$5.1 \cdot 10^{-8}$	1	-	15
	$C_5H_{10}NH$	CH_3OH		$8.3 \cdot 10^{-7}$	16	15.5 (4.4)	16
	NaOH	H_2O- dioxan		$1.3 \cdot 10^{-6}$	26	23.2 (9.8)	17
	CH_3ONa	CH_3OH- dioxan		$190 \cdot 10^{-4}$	$35 \cdot 10^4$	19.7 (11.6)	17
F	NH_3	H_2O- dioxan	92	$2.4 \cdot 10^{-8}$	1	-	18
	$C_5H_{10}NH$	dioxan		$4.6 \cdot 10^{-5}$	$1.9 \cdot 10^3$	12.1 (2.9)	16
	NaOH	H_2O- dioxan		$8.1 \cdot 10^{-5}$	$3.4 \cdot 10^3$	23.2 (9.8)	17
	C_6H_5SNa	C_2H_5OH	61	$1.2 \cdot 10^{-4}$	1	-	19
	C_2H_5ONa	C_2H_5OH		$7 \cdot 10^{-4}$	5.8	-	19
	$C_5H_{10}NH$	DMSO	100	$7.1 \cdot 10^{-3}$	140	12.5 (5.2)	14
	$C_6H_{12}NH$	DMSO		$2.6 \cdot 10^{-3}$	52	11.2 (4.2)	14

F	$O(CH_2CH_2)_2NH$	DMSO	100	$8.7 \cdot 10^{-4}$	17	12.4 (4.2)	14
	$n\text{-}C_4H_9NH_2$			$4.4 \cdot 10^{-3}$	90	12.5 (5.0)	
	$(C_2H_5)_2NH$			$3.4 \cdot 10^{-4}$	7	13.1 (4.2)	
	$(n\text{-}C_4H_9)_2NH$			$5 \cdot 10^{-5}$	1	14.0 (3.9)	
CF_3	NH_3	H_2O- dioxan	92	$6.7 \cdot 10^{-4}$	35	-	18
	$4\text{-}CH_3C_6H_4NH_2$	dioxan		$1.9 \cdot 10^{-5}$	1	14.2 (3.3)	20
	$C_5H_{10}NH$	dioxan		$5.4 \cdot 10^{-2}$	$2.8 \cdot 10^{3}$	6.8 (2.8)	16
	CH_3ONa	CH_3OH		31	$1.6 \cdot 10^{6}$	17.4 (11.9)	21
	NaN_3	CH_3OH	50	$2.1 \cdot 10^{-4}$	32	-	15
	$4\text{-}CH_3C_6H_4NH_2$			$6.5 \cdot 10^{-6}$	1	16.4 (5.1)	20
	$C_5H_{10}NH$			$5.9 \cdot 10^{-3}$	$9 \cdot 10^{2}$	7.0 (2.5)	16
	CH_3ONa			1.36	$2 \cdot 10^{5}$	17.4 (11.9)	21
*	NH_3	H_2O- dioxan	25	$6.8 \cdot 10^{-4}$	1	-	22
	$C_5H_{10}NH$	dioxan		5.6	$8.2 \cdot 10^{3}$	-	23

* Pentafluoropyridine

1. The mechanism of $S_{N(Ar)}$ reactions in the polyfluoroaromatic series

For the aromatic nucleophilic substitution reactions, a two-step mechanism involving the intermediate σ-complex formation has been proposed [8-11], and as polyfluoroaromatic compounds represent one of the groups of aromatic compounds, it is reasonable to suggest the two-step mechanism for their nucleophilic reactions too. This supposition is supported by some kinetic data, in particular the data on base catalysis of these reactions [12].

Despite significant advances in the development of experimental equipment for recording fast processes, the achieved level is not enough for the direct recording of intermediate σ-complexes, and this problem is left for the future.

A typical feature of polyfluoroaromatic compounds in the $S_{N(Ar)}$ reactions is their polyfunctionality, i. e. a nucleophile can substitute the fluorine atom located ortho, meta, or para to substituent X other than fluorine [5]. Evidently, this is the reason for the fact that at the initial stage of investigations on these compounds, most works were focused on orientation of substitution in the polyfluorinated ring, which was shown to depend on some effects (the nature of substituent X, reagent, medium polarity), by varying which one can make the desired orientation predominant [1,5,7].

Let us consider some effects on the rate of nucleophilic substitution reactions.

1.1. The nucleophilic reagent effect in the nucleophilic aromatic substitution reactions of compounds C_6F_5X

The rate of $S_{N(Ar)}$ reactions is substantially affected by the nature of nucleophilic reagent. Table 1 shows that in the reactions with polyfluoroaromatic compounds the most reactive nucleophiles are the charged ones : alkaline metal alkoxides of aliphatic alcohols and thiophenoxides. The uncharged reagents - amines - usually have lower reactivities.

What is the role of metal cation in the reagent? The kinetic measurements for the reaction of hexafluorobenzene with lithium, sodium, and potassium methoxides in methyl alcohol, a strong solvating solvent, have shown the latter reagents to be slightly different in their reactivity, the reaction rate constant on passing from lithium methoxide to sodium methoxide increasing only by a factor of 2 : $CH_3OLi < CH_3OK < CH_3ONa$, which does not coincide with the basicity sequence of these reagents.[1] However, variation of organic anion and solvent may substantially change the reactivity relationship of these nucleophiles.[1] Thus, in aprotic bipolar solvents, such as acetonitrile, potassium pentafluorophenoxide is much more (1.5 - 2 orders) reactive with pentafluoropyridine than lithium pentafluorophenoxide.

What is the role of counterion (reagent anion) ? The nature of alkyl radical in one - type reagents, for example, in alkoxides of n-aliphatic alcohols $C_1 - C_5$, produces a small effect on the reaction rate constants, which increase from methoxide to butoxide by a factor of 2.5. Substitution of oxygen by its analogue - the sulphur atom - in the reagent molecule has a greater effect. Thus sodium ethoxide in the reaction with pentafluorobenzene in ethyl alcohol proved to be 6 times more reactive than sodium thiophenoxide. The least reactive reagent among the charged nucleophiles studied was sodium azide, which in the reaction with hexafluorobenzene in methyl alcohol was 16 times less reactive than the uncharged reagent - piperidine, 26 times less reactive than sodium hydroxide, and 4-5 orders less reactive than sodium methoxide : $NaN_3 < C_5H_{10}NH < NaOH \ll CH_3ONa$.

Among the uncharged reagents, aromatic amines are the least reactive with polyfluoroaromatic compounds. In the reaction with octafluorotoluene in dioxane, p-toluidine is 40 times less reactive than ammonia.[1] Thus, in the $S_{N(Ar)}$ reactions of compounds C_6F_5X, the "nucleophilicity" series of the reagents are as follows :

$4\text{-}CH_3C_6H_4NH_2 < NH_3 < C_5H_{10}NH \ll CH_3ONa$

$4\text{-}CH_3C_6H_4NH_2 < NaN_3 < C_5H_{10}NH \ll CH_3ONa$

These "nucleophilicity" data may be effectively used for preparative purposes.

Another important problem closely connected with 'reagent nucleophilicity' is the correct choice of solvent for kinetic studies. The solvent should dissolve well the reagents, provide homogeneous condition for the reaction, be stable in the reaction conditions, and give no by-products. We shall give some practical examples showing the undesirable processes that may result from the incorrect choice of a solvent.[1] Thus attempted synthesis of pentafluorophenol from hexafluorobenzene by its reaction with alkaline metal hydroxides in aqueous alcohol leads to quite a different product - alkyl pentafluorophenoxide. This product is formed as a result of the equilibrium reaction of hydroxides with alcohols leading to the formation of alkoxy anions, which are 3-4 orders more reactive than the hydroxy anion and react with the substrate, shifting the equilibrium towards formation of the by-product - C_6F_5OAlk. To provide the homogeneous medium for the reactions with alkaline metal hydroxides in the series of disubstituted halobenzenes, J.Bunnett successfully used aqueous dioxane [24]. Therefore, when choosing a solvent for the reaction of a polyfluoroaromatic compound with a nucleophile, one should exclude the possibility of side-reactions of nucleophile with solvent and formation of more reactive nucleophiles. Such faults have also been observed in treatment of polyfluoroaromatic compounds with uncharged nucleophiles. Thus, attempted synthesis of the perfluoroindane amino-derivative by treatment of perfluoroindane with aqueous-alcoholic ammonia unexpectedly led to 5-ethoxynonafluoroindane as the main product [25]. Its formation is the result of the presence of the ethoxy anion in the mixture, which is formed in solvation of ammonia by ethanol. As the ethoxy anion is 4-5 orders more reactive than ammonia, it is constantly consumed for the reaction with the substrate, as a result of which $C_2H_5O^-$ is constantly regenerated in the mixture up to complete binding of the substrate. On passing to piperidine, which is more reactive than ammonia, the yield of the alkoxy-derivative decreases. Thus in the reaction of piperidine with hexafluorobenzene in alcohol, the total yield of anisole and phenol comprises only 3-4% [26]. The effect of amine on the yield ratio of amino and alkoxy derivatives in the reactions of amines with p-nitrofluorobenzene in alcohol has been investigated by H. Suhr [27]. The conclusions made in this work seem to be applicable to the similar reactions of polyfluoroaromatic compounds. Some side-reactions have been reported, especially in the reactions of polyfluoroaromatic compounds with low-reactive nucleophiles in DMF. Thus we have found that treatment of hexafluorobenzene with potassium pentafluorophenoxide in DMF as described in [28], gave, along with the target product - decafluorodiphenyl ether, a pronounced amount of N,N-dimethylamino-pentafluorobenzene, which seems to be the result of the reaction of hexafluorobenzene with dimethylamine, a more reactive nucleophile than potassium pentafluorophenoxide, formed from DMF in alkaline medium. Due to this, it is preferable to use other aprotic bipolar solvents - acetonitrile, sulpholane, or DMSO.

How do steric effects influence the nucleophilicity of reagents? The kinetic studies of the reaction of hexafluorobenzene with amines in DMSO have shown steric effects to be much more important for amines of one type than the basicity. This gave a series of relative nucleophilicity of amines : piperidine > n-butylamine > hexamethyleneimine > morpholine > diethylamine > di-n-butylamine [14]. Diethylamine is a good example to illustrate the influence of steric factors on the reactivity of amines : it is three orders more basic than morpholine and one order less reactive. The more rigid bonding of nitrogen with the frame in the morpholine molecule is possibly more sterically favourable for the attack of amine on a substrate than the two freely-rotating radicals in the diethylamine molecule. This reactivity series of amines may be used for the preparative purposes.

1.2. Substituent effect on the rate of nucleophilic substitution reactions of fluorine-containing benzene derivatives

The very first kinetic studies of substitution nucleophilic reactions in the polyfluoroaromatic series involved investigations on the effect of a substrate, substituent, solvent, reagent, fluorine positions in the ring, and fluorine ortho to the reaction centre and substituent, on the reaction rate. Table 2 lists the Arrhenius parameters, rate constants for some reactions of polyfluoroaromatic compounds C_6F_5R with sodium methoxide, and the electronic effects of 4F + p-R and p-R substituents in the polyfluorinated ring.

Monofluorobenzene is a low reactivity compound, which reacts with nucleophilic reagents only under drastic conditions. Sequential introduction of the 2nd, 3rd, 4th and 5th fluorine atoms in the ring leads to a remarkable increase in the reactivity of a substrate [30]. Thus hexafluorobenzene is 8 orders more reactive than fluorobenzene in the reaction with sodium methoxide. The electronic effect of ring fluorine atoms substantially depends on their position relative to the reaction centre. Thus the ratio of rate constants of the reactions of isomeric m-, o- and p-difluorobenzenes with sodium methoxide in methanol at 100°C [30] is 48:8:1, i. e. the strongest electron acceptor is meta-fluorine, ortho-fluorine is 6 times weaker, and the weakest acceptor is para-fluorine : m-F > o-F > p-F . Weakening of the electron-accepting effect of ortho- and para-fluorine atoms seems to result from the fact that these are the resonance positions in which

TABLE 2

Arrhenius parameters, relative rate constants for the reactions of some C_6F_5R and RArF compounds with sodium methoxide in methanol and the electronic effects of 4F + p-R and p-R substituents in the polyfluorinated ring

R	$k \cdot 10^5$ l/mol·sec	k_{rel} (50°C)	lg k (50°C)	E, kcal/mol	Ref.	lg A	σ^{-*}	σ_p^-
							4F + p-R	p-R
$N(CH_3)_2$	0.776	0.093	-5.11	23.5	29	10.8	0.916	-0.147
H	8.1	0.98	-4.09	22.9	29	11.4	1.061	0
	8.3	1	-4.08	22.6	13	11.2	1.063	0
	8.7	1.05	-4.06	20.2	17	9.6	1.066	0
F	45	5.4	-3.35	22.4	29	11.8	1.167	0.104
	34	4.1	-3.47	21.4	13	11.0	1.150	0.087
COO^-	24	2.9	-3.62	19.1	29	9.3	1.129	0.066
Br	166	20	-2.78	19.2	17	10.2	1.249	0.186
Cl	174	21	-2.76	19.9	29	10.7	1.251	0.188
C_6F_5	$9.2 \cdot 10^3$	$1.1 \cdot 10^3$	-1.04	18	**	11.0	1.497	0.434
CF_3	$5.37 \cdot 10^4$	$6.5 \cdot 10^3$	-0.26	13.1	29	8.6	1.609	0.546
	$3.8 \cdot 10^5$	$6 \cdot 10^4$	0.58	16.3	17	11.6	1.729	0.666
	$1.35 \cdot 10^5$ ****	$1.6 \cdot 10^4$	0.13	17.4	21	11.9	1.664	0.601

CN	$4 \cdot 10^6$	$4.8 \cdot 10^5$	1.6	14.8	17	11.6	1.874	0.811
NO_2	$2.6 \cdot 10^7$	$3.2 \cdot 10^6$	2.42	14.9	29	12.5	1.991	0.928
$4\text{-}NO_2C_6H_4F$	$2.6 \cdot 10^2$	30	-2.59	20.1	***	11.0	-	1.27
$2\text{-}NO_2C_6H_4F$	$1.74 \cdot 10^2$	21	-2.76	19.9	***	10.7	-	1.251

* Calculated by us, using the data of [13,17,21,29] , from the Hammett equation $\sum \sigma_i^- = \sigma_{4F+p-R}^- = \frac{1}{\rho} \lg \frac{k}{k_o}$, where k_o and k are the rate constants for the reactions of compounds C_6H_5F and C_6F_5R with sodium methoxide in methanol at 50°C. According to [41], the correlation parameters for the reaction series RC_6H_4F + CH_3ONa (CH_3OH, 50°C) are : $\rho = 7.0$, $-\lg k_o = 11.52$. The σ_p^- values for p-R realised in this reaction series have been determined by us from the equation :

$$\sigma_p^- = \sigma_{4F+p-R}^- - \sigma_{4F+p-H}^-$$

** our data

*** See ref.[9] in [29]

**** See ref.[8] in [21]

the fluorine atom donates the electron density to the benzene ring to the greatest extent via the conjugation effect.

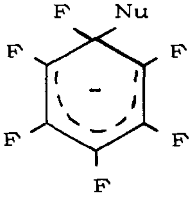
By contrast with p- and m-F, the activating effect of o-F considerably depends on the nature of the reaction centre [31,32] and varies over a wide range. Thus in the dissociation reactions of benzoic acids and phenols, the dissociation constant ratios of isomers para : meta : ortho are 1:8:20 and 1:5:17 respectively, i. e. ortho-fluorine here is the strongest electron acceptor as compared to para- and meta-fluorines.

1.3. The additive effect of benzene fluorine atoms on the reactivity of a substrate

The additive effect of ring fluorine atoms as substituents on the reactivity / pK_a / of polyfluorobenzoic acids was first established by Koptyug and Petrov [33], somewhat later similar results were obtained by Filler [34]. These works stimulated studies on fluorine effect in other types of transformations, in particular, in the reactions of polyfluorobenzenes with sodium methoxide. The ortho-fluorine effect in polyfluorobenzenes has been shown to differ by $\pm$ 0.02 σ^- units [30], the additivity effect of all ring fluorine atoms on the reaction centre showing itself within such accuracy. The calculated reactivity of polyfluorobenzenes in the reaction with sodium methoxide [30] is in good agreement with the experimental data of [35,36]. Using another Scheme of calculations based on the additivity effect of separate fluorine atoms, R. Bolton and J. Sandall showed for 12 fluorobenzenes reacting with sodium methoxide in methanol-DMSO [37] (Tables 3 and 4) a good agreement between the calculated and experimental data. Effective use of additive schemes for estimation of the reactivity of polyfluorobenzenes demonstrated in [30] and [37] calls for the further development of additive schemes for calculating the reactivity of polyfluoroaromatic compounds.

In determining the σ_p^- value for the fluorine atom in the polyfluorinated ring with four fluorine atoms which are substituents in the $S_{N(Ar)}$ reactions of compounds C_6F_6 and C_6F_5R according to the Hammett equation, we have used a different approach as compared with some earlier researchers of nucleophilic substitution reactions of hexafluorobenzene, e.g. Yakobson <u>et al.</u> [13], J.Burdon et al.[29]. The approach is as follows. The k_2 value for the reaction of hexafluorobenzene with nucleophile is substituted into the Hammett equation in calculating the σ_p^- value for p-fluorine, without correction for the statistical factor equal to 6, which is due to the stepwise character of the $S_{N(Ar)}$ process and to the fact that the determining contribution to the σ_p^- value is made precisely by the second stage of the process (the transition stage). As in the transition stage A of the $S_{N(Ar)}$ reaction for hexafluorobenzene we have only one substituted group and only one para-substituent F_{para}, the statistical factor for the transition state is equal to 1, the quantitative effect of all other substituent fluorine atoms being different : $F_{meta} > F_{ortho} > F_{para}$ ($\sigma_p^- = 0 - 0.10$; $\sigma_m = 0.337$, $\sigma_o = 0.2$).

$$\sigma_p^- = \frac{1}{\rho} \lg k / k_o$$



A

The use of statistical factor equal to 6 is understandable in comparing hexafluorobenzene with compounds of the series RC_6H_4F. However, here also division of the k_2 value by 6 is illegal, as in the transition state of the σ-complex molecule A there is only one substituted group, and the other fluorine atoms function as substituents determining the level of substrate reactivity, which are different in their effect on the reaction centre (see above).

In the $S_{N(Ar)}$ reactions of polyfluoroaromatic compounds, the additivity of effects of 4 fluorine atoms and a substituent in the benzene ring is realised for many substituents ranging from strong electron donors to strong electron acceptors. This is indicated, in particular, by the correlation dependences between lg k of the reaction rates and the σ_p (σ_p^-) constants of substituents found in some works [42,44]. The analysis of the σ_p^- values realised in these reactions and in the reactions with a similar mechanism of

TABLE 3

Kinetics of the reactions of polyfluorobenzenes with sodium methoxide in DMSO:methanol (9:1) at 25°C [37] and the $\sum \sigma_i$ values of substituents

Compound	Site of attack	k_2, l/mol·sec			$\sum \sigma_i$		σ_{o-F}
		experim. [37]	Calcd. acc. to [37]	Calcd. from the Hammett equation	Calcd. from experim.	Calcd. from addit.	from experim. data
C_6F_6	C-1	7.4	7.45	11	1.191	1.214	0.229
C_6HF_5	C-3	1.66	1.63	1.15	1.031	1.154	0.178
1,2,3,4-$C_6H_2F_4$	C-1	$3\cdot10^{-4}$	$2\cdot10^{-4}$	$7\cdot10^{-4}$	0.584	0.637	0.190
	C-2	$3\cdot10^{-2}$	$1.8\cdot10^{-2}$	$1.5\cdot10^{-2}$	0.86	0.817	0.26
1,2,3,5-$C_6H_2F_4$	C-1	$4.3\cdot10^{-2}$	$5.4\cdot10^{-2}$	$7.4\cdot10^{-2}$	0.881	0.914	0.207
	C-2	$4\cdot10^{-4}$	$4\cdot10^{-5}$	$1.5\cdot10^{-4}$	0.6	0.54	0.27
	C-5	-	-	$3.8\cdot10^{-3}$	-	0.734	-
1,2,4,5-$C_6H_2F_4$	C-1	$6.7\cdot10^{-4}$	$4.6\cdot10^{-4}$	$7.4\cdot10^{-4}$	0.632	0.637	0.235
1,2,3-$C_6H_3F_3$	C-1	$3.8\cdot10^{-4}$	$3\cdot10^{-4}$	$2.7\cdot10^{-4}$	0.598	0.577	0.261
	C-2	$8.6\cdot10^{-5}$	$5\cdot10^{-5}$	$4.3\cdot10^{-4}$	0.508	0.48	0.254

1,2,4-$C_6H_3F_3$	C-1	$4\cdot10^{-6}$	$6\cdot10^{-7}$	$2.7\cdot10^{-6}$	0.324	0.300	0.263
	C-2	$4.3\cdot10^{-4}$	$1.5\cdot10^{-4}$	$2.7\cdot10^{-4}$	0.600	0.577	0.263
	C-4	$4\cdot10^{-6}$	$6\cdot10^{-7}$	$2.7\cdot10^{-6}$	0.324	0.300	0.263
1,3,5-$C_6H_3F_3$	C-1	$1.35\cdot10^{-3}$	$1.36\cdot10^{-3}$	-	-	0.674**	-
1,2-$C_6H_4F_2$	C-1	$1.2\cdot10^{-6}$	$1.68\cdot10^{-6}$	$1\cdot10^{-6}$	0.252	0.240	0.252
1,3-$C_6H_4F_2$	C-1	$7.3\cdot10^{-6}$	$5\cdot10^{-6}$	$5.3\cdot10^{-6}$	0.360	0.337	-
1,4-$C_6H_4F_2$	C-1	$2\cdot10^{-8}$	$2\cdot10^{-8}$	$4.9\cdot10^{-8}$	0.006	0.06	-
C_6H_5F	C-1	$1.4\cdot10^{-8}$	-	-	-	-	-

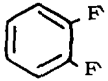
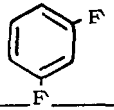
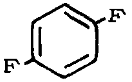
NOTES : * Calculated using σ_p, σ_{m-F} from [40,39]

** The lg k values of the reaction rate of a substrate and $\sigma_m = 0.337$ have been used as reference points in the calculation of ρ for the reaction series $RC_6H_4F + CH_3ONa$; lg $k_o = -7.74$ and $\rho = 7.23$ (25°C, Nu = CH_3ONa, DMSO:CH_3OH = 9:1).

TABLE 4

Kinetics of the reactions of polyfluorobenzenes $C_6H_nF_{6-n}$ with sodium methoxide in methanol at 50°C [38] and the σ constant values of substituents

Compound	Site of attack	$k \cdot 10^6$, l/mol·sec				$\sum \sigma_i$		σ_{o-F}
		50°C		58°C		50°C		50°C
		from the Hammett equation	experim. acc. to [38]	from the Hammett equation	experim. acc. to [36]	calcul. from additivity	calcul. acc. to [36,37,38]	experim. data
C_6F_6	C-1	360	340 [13]	960	774	1.154	1.151 (1.141)	0.209
C_6HF_5	C-1	12		36		0.944		
	C-2	1.6		4.8	302	0.817	1.07 (1.081)	0.198
	C-3	140	105	370		1.094		
1,2,3,4-$C_6H_2F_4$	C-1	$5.4 \cdot 10^{-2}$		0.17	5.7	0.607	0.826)	0.244
	C-2	0.6	1.8	1.9		0.757		
1,3,4,5-$C_6H_2F_4$	C-1	4.7		14		0.884		
	C-2	$6.9 \cdot 10^{-3}$	4.9	$2.3 \cdot 10^{-2}$	10.6	0.48	0.887 (0.869)	0.213
	C-5	0.42		1.3		0.734		
1,2,4,5-$C_6H_2F_4$	C-1	$5.4 \cdot 10^{-2}$	-	0.17	0.103	0.607	(0.574)	0.177
1,2,3-$C_6H_3F_3$	C-1	$2 \cdot 10^{-2}$	-	$6.8 \cdot 10^{-2}$	-	0.547	-	-
	C-2	$2.6 \cdot 10^{-3}$		$9.1 \cdot 10^{-3}$		0.42		

1,2,4-$C_6H_3F_3$	C-1 C-2 C-4	$2.3 \cdot 10^{-4}$ $2 \cdot 10^{-2}$ $1.8 \cdot 10^{-3}$	- - -	$8.7 \cdot 10^{-4}$ $6.8 \cdot 10^{-2}$ $6.5 \cdot 10^{-3}$	- - -	0.27 0.547 0.397
1,3,5-$C_6H_3F_3$	C-1	$1.6 \cdot 10^{-1}$	-	$5 \cdot 10^{-1}$	-	0.674
	C-1	$8.9 \cdot 10^{-5}$	-	$3.4 \cdot 10^{-4}$	-	0.21
	C-1	$6.9 \cdot 10^{-4}$	-	$2.5 \cdot 10^{-3}$	-	0.337
	C-1	$7.9 \cdot 10^{-6}$	-	$3.2 \cdot 10^{-5}$	-	0.06
C_6H_5F	C-1	-	$3 \cdot 10^{-12}$**	-	$1.2 \cdot 10^{-11}$**	0

NOTES : * The $\sum \sigma_i$ values have been calculated using the following σ values for the fluorine atom : m-F 0.337 [39, 40]; p-F 0.06 and o-F 0.21 [30]. The lg k values of rate for the reactions of polyfluorobenzenes, have been calculated using the $\sum \sigma_i$ values calculated from the additivity and $\rho = 7.0$, $\lg k_o = -11.52$ for the reaction series $RC_6H_4F + CH_3ONa$ (in CH_3OH) [41].

** Calculated from the Arrherius equation E = 37.85 kcal/mol, lg A = 13.74 (estimated by us from the averaged data of S.M. Shein [41]).

transfer of the electron effect through the ring, for example, in the dissociation reactions of 4-R-substituted tetrafluorophenols [45], shows that in the absence of pronounced steric and electronic interactions of p-R with o-F of the ring, the electron effects of substituents in the non-fluorinated and polyfluorinated rings are close, reaching $\sigma_p^- = 0.8 - 1.0$ – the accepting ability of a substituent corresponding to the p-CN group. On passing to stronger acceptors, such as p-NO_2 and NO, the value of effective σ_p^- in the polyfluorinated ring markedly decreases as compared with substituent effects in the series of compounds RC_6H_4X.

The authors of [45], who studied the dissocation of 4-R-substituted 2,3,5,6-tetrafluorophenols, have shown the dependences $pK_a - \rho$, σ_p^- for the 4-R-substituted tetrafluoro- and 4-R-substituted phenols to have practically the same ρ value, which suggests that the transfer of substituent electronic effect via the 1,4-tetrafluorophenylene and 1,4-phenylene groups is practically the same. Having analysed the ^{13}C NMR spectra of aromatic and polyfluoroaromatic derivatives, the authors of [46] have come to a similar conclusion that the symmetric substitution of the aromatic ring by such strong electron-accepting substituents as fluorine atoms practically does not change the electron transmittance of the ring.

1.4. Quantitative description of the $S_{N(Ar)}$ reactions of polyfluoroaromatic compounds using the Hammett equation

The correlation between lg k of the rates of $S_{N(Ar)}$ reactions of compounds C_6F_5R and the electronic properties of substituent p-R was noted by the very first researchers of the reaction kinetics of these compounds: for sodium methoxide, this was noted by J.Burdon and his co-workers [29], and by K.C.Ho and J.Miller [17,47] for sodium pentafluorophenoxide, by Ch.Tamborski and R.Pasquale [64]. However, having failed to obtain good correlations lg k – ρ, σ_p, these researchers did not publish any further reports on that matter. There naturally arose a question: why, having a clear-cut symbate correlation between lg k of the rates of $S_{N(Ar)}$ reactions and σ_p of substituents R, one cannot obtain a good correlation? Must we use only the σ_p and σ_p^- values of a given series of compounds to obtain good correlation in this series? But creation of different σ_p (σ_p^-) scales, each for a separate series of compounds, discredits the very idea of the correlation analysis, namely: the universal character of σ_p constants, their independence on the reaction series, and applicability of standard σ_p (σ_p^-) values for predicting the reactivity of a wide range of aromatic compounds with a high degree of precision.

The first data on the use of the Hammett equation for the quantitative description of nucleophilic substitution reactions of polyfluoroaromatic compounds were published by S.M.Shein and his co-workers [41] , who calculated correlation dependences using the standard values of σ_p(σ_p^-) constants and the kinetic data on the reactions of C_6F_5R with sodium methoxide obtained by Burdon [29] , Ho and Miller [17,47] , and somewhat later, their own kinetic data on the reactions of these compounds with piperidine [44] Before calculating the correlations lg k - ρ , σ , S.M.Shein carried out preliminary analyses, having chosen only the reactions which correspond to this dependence and rejected those whose rate lg k substantially deviated from the correlation scheme. However, even with such strict selection, the correlations obtained were, according to Jaffe's criteria [39] , only 'satisfactory' [44] . It took some time to clear out the factors governing electronic effects of substituents in the polyfluorinated ring and learn to overcome the difficulties of using the Hammett equation in the polyfluoroaromatic series, due to which the number of works on this subject is still confined to 7 [41,44,42,48,21,30,49]. We give here some of these results (see Table 5).

The Hammett equation proved to be a convenient and useful analytical instrument to estimate the electronic effect of different substituents in the polyfluorinated ring and to investigate the specific nature of these compounds.

1.5. Estimation of the electronic effects of 4F+p-R, p-R substituents and separate fluorine atoms in the polyfluorinated ring using Hammett equation

Using the additivity of the electronic effects of separate fluorine atoms in the ring, we calculated the overall electronic effects of 4 fluorines and substituents p-R 4F+p-R (σ^-_{4F+p-R}) , ortho-fluorine (σ^-_{o-f}) and para-R substituents (σ^-_{p-R}).

For the calculation we used the Hammett equation in H.H.Jaffe's modification [39] for polysubstituted benzene derivatives.

TABLE 5

Correlation of rate constants of the reactions of substituted pentafluorobenzenes C_6F_5R with nucleophilic reagents vs. substituent σ_p^- constants

Reagent	Solvent	T, °C	ρ	r	s	-lg k_o	Ref.
pyperidine	n-hexane	50	5.4	0.989	0.33	7.10	44
		100	4.8	0.990	0.27	6.15	
	dioxane	50	4.9	0.992	0.29	5.66	44
		100	4.4	0.994	0.22	4.58	
	methanol	50	5.8	0.986	0.41	6.57	44
		100	4.8	0.991	0.27	4.98	
CH_3ONa	methanol	50	5.3	0.993	0.34	3.89	41
		100	4.7	0.994	0.29	1.94	
		50	6.9	0.999	0.08	2.34	41
CH_3ONa*	16% methanol 84% dioxane	100	6.1	0.998	0.18	0.51	
sodium pentafluorophenoxide	N,N-DMAA	106	5.7	0.986	0.34	-	44

* Correlation with σ_m^- constants

$\lg k/k_o = \rho \sum \sigma_i$, where k is the rate constant of the reaction of polyfluorobenzene, e.g. C_6F_5R , with a given nucleophile at a given temperature; k_o , the rate constant of the reaction of unsubstituted fluorobenzene (C_6H_5F) with the same nucleophile and of the same temperature; ρ , the reaction constant defining the relative sensitivity of this reaction toward the introduction of a substituent into the benzene ring at a given temperature (Table 6); $\sum\sigma_i$, the overall electronic effect of all substituents in the ring on the reaction centre, in σ units, shown (in compounds C_6F_5R) by the 4F+p-R substituents : $\sum\sigma_i = \sigma^-_{4F+p-R} = 2\,\sigma^-_{o-F} + 2\,\sigma_{m-F} + \sigma^-_{p-R}$ where σ^-_{o-F} is the electronic effect of ortho-fluorine; σ_{m-F} , the electronic effect of meta-fluorine, equal to 0.337 [39] ; and σ^-_{p-F} , the electronic effect of para-fluorine (see below). The electron-accepting effect of 2 meta- and 2 ortho-fluorines is determined from lg k of the reaction rate of pentafluorobenzene, according to the Hammett equation(see above): $\sigma^-_{4F+p-H} = \frac{1}{\rho} \lg k/k_o$. From the σ^-_{4F+p-H} value, the ortho-constant of fluorine is then calculated, which is realised in the given reaction : $\sigma^-_{o-F} =$ ($\sigma^-_{4F+p-H} - 2x0.337$):2 . The electronic effects of p-R-substituents are found from the difference of overall electronic effects of C_6F_5R and C_6F_5H : $\sigma^-_{4F+p-R} - \sigma^-_{4F+p-H}$.

Let us consider the electronic effects of para-, meta-, and ortho-fluorine atoms in the ring in the $S_{N(Ar)}$ reactions.

para-Fluorine. Despite the strong inductive effect of fluorine $\sigma_I =$ +0.51 , the fluorine atom para to the group being substituted in the ring (which, for the reactions of polyfluorobenzenes, is fluorine itself) shows itself as a weak electron acceptor, as in resonance para- and ortho-positions, it strongly donates electron density to the ring due to the conjugation effect. Though their table para-constant value for fluorine according to the Hammett equation [39,40] , found from the dissociation of para-fluorobenzoic acid, is +0.062 , the analysis of other reaction series shows that the electronic effect of para-fluorine "drifts" from one series to another, and this drift seems to be due to the effect of the nature of the reaction centre on the resonance ability of fluorine . For the reactions of polyfluorobenzenes with nucleophilic reagents, the σ^-_p value for fluorine varies in the range of 0.01 to 0.10 σ units, which corresponds with the resonance component $\sigma_R = -0.50$ and -0.41. In the polyfluorinated ring, para-fluorine as substituent is the weakest electron acceptor of all other

TABLE 6

The ρ and lg k_o values of reference reactions, used to calculate the σ_p^- values

Series	Reference reaction	T, °C	ρ	-lg k_o	Ref.
I	$C_6F_5R + CH_3ONa \longrightarrow 4\text{-}RC_6F_4OCH_3 + NaF$	50			48
	CH_3OH : dioxane = 1:5	50	5.73	2.4	
	CH_3OH	50	6.9	4.08	
	CH_3OH	20	7.34	5.65	
II	$C_6F_5R + NaN_3 \longrightarrow 4\text{-}RC_6F_4N_3 + NaF$				15
	CH_3OH	50	8.0	8.52	
III	$C_6F_5R + C_2H_5ONa \longrightarrow 4\text{-}RC_6F_4OC_2H_5 + NaF$				48
	C_2H_5OH	61	7.0	3.14	
IV	$C_6F_5R + C_6H_5SNa \longrightarrow 4\text{-}RC_6F_4SC_6H_5 + NaF$				48
	C_2H_5OH	61	6.55	3.91	
V	$C_6F_5R + 2\ C_5H_{10}NH \longrightarrow 4\text{-}RC_6F_4NC_5H_{10} + NaF$				48
	dioxane	25	6.46	6.13	
	dioxane	50	6.39	5.51	
	DMSO	50	8.65	3.33	
	CH_3OH	20	6.43	7.55	
VI	$C_6F_5R + 2\ NH_3 \longrightarrow 4\text{-}RC_6F_4NH_2 + NaF$				18
	dioxane-H_2O	92	5.54	6.55	
VII	$C_6F_5R + C_6F_5ONa \longrightarrow 4\text{-}RC_6F_4OC_6F_5 + NaF$				44
	N,N-DMAA	106	7.22	7.66	

halogens. Comparison of rate constant values for hexafluorobenzene (k_1) and pentafluorobenzene (k_2) shows that in the reactions with charged nucleophiles (sodium methoxide and pentafluorophenoxide) k_1 exceeds k_2 by a factor of 5, whereas with uncharged nucleophiles (piperidine), by a factor of 1.2 - 1.8. In estimating the p-F effect in hexafluorobenzene, different authors disagree in the question of statistical factor. Some authors divide the reaction rate constant of hexafluorobenzene by the statistical factor equal to 6. We never do this, considering that at the moment of reagent attack the electronic effect of fluorine atoms is great, being different in the ortho-, meta-, and para-positions. Dividing the reaction rate constant of hexafluorobenzene by the statistical factor, we artificially decrease its reactivity and underestimate the real para-fluorine effect on the reaction centre. As a matter of fact, the fluorine atoms in hexafluorobenzene are not identical in their electronic effect on the reaction centre, which should be taken into account in considering the effect of fluorine as substituent.

Meta-fluorine. Only for the meta-position to the reaction centre the electronic effect of fluorine seems to be remarkably preserved from one series to another, notwithstanding the changed nature of the reaction centre : the σ_{m-F} value found from the dissociation of benzoic acids absolutely coincided with that found from the dissociation of phenols. In all calculations of the nucleophilic substitution reactions of polyfluorobenzenes we used the table value of $\sigma_{m-F} = +0.337$ [39,40], which corresponds to $\sigma_R = -0.173$.

Ortho-fluorine. The activating effect of ortho-fluorine substantially depends on the nature of the reaction centre and varies over a very wide range- from +0.13 to 0.93 [31,32]. Therefore it is not surprising that all the attempts to establish a standard value of ortho-constant for ortho-fluorine failed. Nevertheless, within one type of transformation, e. g. in the reactions of polyfluorobenzenes with sodium methoxide, as shown in [30], the ortho-constant value varies in the range of $\pm$ 0.02- 0.03 σ units, i. e. within approximation of correlation studies, and may be accepted as constant for the given type of transformation. On passing from the reactions of polyfluorobenzenes with sodium methoxide to those with piperidine in dioxan, the σ^-_{o-F} value increased to +0.27 [21]. Table 3,4 lists the σ_{o-F} values for different reaction series.

TABLE 7

Electronic effects of p-R = Hal substituents in the polyfluorinated benzene ring, in various $S_{N(Ar)}$ reactions (Nu = CH_3ONa, C_6F_5ONa, $C_5H_{10}NH$), p-Hal = F, Cl, Br. The reactivity of the respective C_6F_5R compounds

R	T, °C	Nucleophile	Solvent	k, l/mol·sec	k_R/k_H	lg k	E, kcal/mol (lg A)	Ref.	σ_p^- (C_6F_5R)	σ_p from diss. of benzoic acids
F	50	$C_5H_{10}NH$	DMSO	$5.5\cdot10^{-4}$	1.2	-3.26	12.8 (5.4)	42	0.01	
	50	$C_5H_{10}NH$	dioxan	$5.2\cdot10^{-6}$	1.7	-5.28	12.1 (2.9)	16	0.04	
	50	$C_5H_{10}NH$	CH_3OH	$8.3\cdot10^{-7}$	2.0	-6.08	15.5 (4.4)	16	0.05	
	50	CH_3ONa	CH_3OH	$3.4\cdot10^{-4}$	4.1	-3.47	21.4 (11.0)	13	0.087	0.062
	106	C_6F_5ONa	N,N-DMAA	-	5.5	-	-	44	0.1	
	50	CH_3ONa	CH_3OH	$4.46\cdot10^{-4}$	5.4	-3.35	22.4 (11.8)	29	0.104	
	50	CH_3ONa	CH_3OH-dioxan	$2.1\cdot10^{-2}$	5.3	-1.68	19.7 (11.6)	17	0.11	
	50	NaN_3	CH_3OH	$5.5\cdot10^{-8}$	18	-7.26	-	15	0.16	
Cl	50	$C_5H_{10}NH$	dioxan	$1.2\cdot10^{-5}$	3.9	-4.91	11.4 (2.8)	16	0.09	
	50	$C_5H_{10}NH$	CH_3OH	$1.7\cdot10^{-6}$	4.1	-5.78	18.3 (6.6)	16	0.1	
	50	$C_5H_{10}NH$	DMSO	$6\cdot10^{-3}$	13	-2.22	9.2 (4.0)	42	0.13	0.227
	50	CH_3ONa	CH_3OH	$1.74\cdot10^{-3}$	21	-2.76	19.9 (10.7)	29	0.188	
	106	C_6F_5ONa	N,N-DMAA	-	32	1.51	-	44	0.21	
I	50	CH_3ONa	CH_3OH-dioxan	$3.9\cdot10^{-2}$	9.6	-1.41	18.6 (11.2)	17	0.15	0.18
Br	50	CH_3ONa	CH_3OH	$1.71\cdot10^{-3}$	5.7	-2.78	19.2 (10.2)	17	0.186	0.232
	50	CH_3ONa	CH_3OH-dioxan	$6.4\cdot10^{-2}$	16	-1.19	18.3 (11.2)	17	0.19	
	106	C_6F_5ONa	N,N-DMAA	-	39	1.59	-	44	0.22	

Table 7 lists the σ^-_p values for the reactions of C_6F_5R with nucleophilic reagents. These values, especially for Cl, Br, and I, proved to be lower than the respective σ_p values for the dissociation of benzoic acids. This may be due to the high ability of halogens in the resonance para-position to donate electrons to the polyfluorinated ring by the conjugation effect. In this case, the weakest electron acceptor by the sum of inductive and mesomeric effects is the fluorine atom. A stronger electron acceptor is the para-I atom, which is second in the strength of electronic effect to p-Br and p-Cl.

1.6. Calculation of experimental conditions for the $S_{N(Ar)}$ reactions of compounds C_6F_5R using the Hammett equation

1.6.1. Reference reactions.

To avoid a complicated experiment, which may involve essential amounts of expensive C_6F_5R compounds, it is possible to perform a minimal kinetic experiment for approximate estimation of experimental conditions, including the Hammett lg k vs. ρ, σ correlation scheme. It is most convenient to use the following two correlation variants (Table 6).

1.6.2. Inter-series correlation

The reactions of compounds C_6F_5R (or $4\text{-}RC_6F_4F$) with nucleophilic reagents are regarded as a continuation and constituent part of a similar correlation for substituted monofluorobenzenes : $RC_6H_4F + NuX \longrightarrow RC_6H_4Nu + XF$. To plot such a correlation scheme with extrapolation to the reactions of C_6F_5R, it is necessary to have the kinetic data for 3 reference reactions : 2 reactions of RC_6H_4F and at least one reaction of C_6F_5R (usually with R = H). In principle, these may be any reactions, but for the greatest precision of subsequent calculations it is desirable that they should cover a wide σ^-_p range for substituent p-R; for example, with p-R = H (the reaction with unsubstituted fluorobenzene, for which lg k of its rate is the reference point on the lg k vs. ρ, σ correlation scheme, where $\sigma^-_{p\text{-}H} = 0$), and with R = NO_2 (the reaction with p-nitrofluorobenzene, for which lg k of its rate is the second reference point on the correlation scheme, for which the second coordinate $\sigma^-_{p\text{-}NO_2} = 1.27$). The necessity of the third point,

i. e. lg k of the rate of the reaction of C_6HF_5 with nucleophile is called for by the fact that the σ^-_{4F+p-H} value is unknown beforehand, with several exceptions, due the indefinite character of ortho-fluorine electronic effect. After the σ^-_{4F+p-H} value has been determined experimentally, the σ^-_{4F+p-R} values are calculated, which define the total electron-accepting effect of all ring substituents of compounds C_6F_5R, and which may be tentatively estimated as the sum of the effects : $\sigma^-_{4F+p-H} + \sigma^-_{p-R}$. Then the values are plotted on the correlation scheme, which provides lg k of the rate of a given reaction, and the 'k' value is used to determine time and concentrations for this reaction.

1.6.3. Intra-series correlation

Only separate reactions of the series of C_6F_5R are considered : $C_6F_5R + NuX \longrightarrow 4\text{-}RC_6F_4Nu + XF$. To plot such a correlation scheme, which will be further used to determine conditions for the reactions of various C_6F_5R, it is necessary to have the kinetic data of at least 2 reference reactions. For example, for the reaction of C_6HF_5, for which lg k of the rate = lg k_o is the reference point on the correlation scheme, $\sigma^-_{p-H} = 0$; and for the reaction of $(C_6F_5)_2$ or $C_6F_5CF_3$, lg k of the rate is the second reference point. The second coordinate for these reactions is represented by the σ^-_p values, which for the p-C_6F_5 group are 0.43 ± 0.02 ,, and for the p-CF_3 group, 0.61 ± 0.02 σ units. As a second reference point one may choose lg k of the rates of other reactions. After the scheme has been plotted, and given the σ^-_p value substituent R in C_6F_5R, for whose reaction with nucleophile we want to calculate conditions, we find lg k of the rate from the scheme for the reaction at a given temperature. Given the "k" value, and varying the concentrations of substrate and reagent, we find the minimal time of synthesis. An advantage of the second calculation variant is the smaller amount of preliminary kinetic measurements.

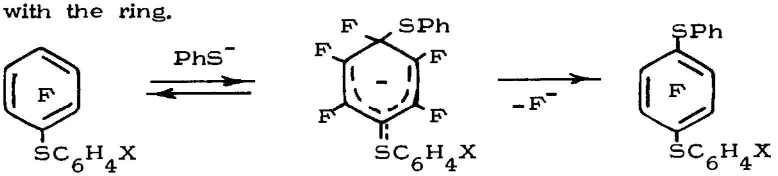
The above methods were used by us to calculate conditions for the synthesis of various polyfluoroaromatic compounds.

Despite some difficulties in applying the Hammett equation to the $S_{N(Ar)}$ reactions in the polyfluoroaromatic series, its wider use is recommended for estimating the quantitative regularities of the reactivity of polyfluoroaromatic compounds and for planning the synthetic experiments in this field.

We hope the data on the electronic effects of substituents in the polyfluorinated ring and the calculation methods reviewed here will help to solve this problem.

2. The behaviour of sulphur- and selenium-containing substituents in the polyfluorinated aromatic ring

The remarkably high activating ability of sulphur-containing substituents in the polyfluorinated ring in the nucleophilic substitution reactions was first reported by J.Birchall and R.Haszeldine with co-workers [19]. On the basis of known table σ_p values, one could suggest the decreased rates of $S_{N(Ar)}$ reactions of compounds C_6F_5R, where R contained the divalent sulphur, as compared with the reactions of pentafluorobenzene with nucleophilic reagents. However, the kinetic studies of the reactions of C_6F_5R with sodium ethoxide and thiophenoxide showed quite opposite results (Table 8). To explain such an unusual activating effect of sulphur-containing groups, the authors suggested a mechanism involving stabilisation of the intermediate σ-complex at the expense of double bonding of sulphur with the ring.



In [48], further reactivity studies have been reported for compounds C_6F_5YR (Y = S, Se; R = CH_3, C_6H_5, CN, $CF(CF_3)_2$, CF_2H, C_6F_5), and for that purpose the authors carried out the kinetic measurements of the reactions of these compounds with sodium methoxide and piperidine. The use of nucleophiles of varied reactivity allows to perform kinetic measurements for fluoroaryls of varied reactivity. In [48], some interesting results have been reported on the effect of sulphur-containing substituents on the reactivity of aromatically bound fluorine and on transmission of the electronic effect via the polyfluorinated ring.

Comparison of rate constants of the reactions of C_6F_5SR and its analogue from the series of 4-R-substituted monofluorobenzenes with sodium methoxide in methanol at 100°C (the former constants have been calculated from the data of Table 8, the latter ones are reported in [52]) shows that introduction of 4 fluorines into the

TABLE 8

Kinetics of the reactions of pentafluoro-substituted benzene derivatives C_6F_5YR with nucleophilic reagents and the σ_p^- values of substituents YR in the polyfluorinated benzene ring

YR	Reagent	Solvent	T, °C	k, l/mol·sec	$k_{rel.}$	lg k	σ_p^-	Ref.
H	C_2H_5ONa	C_2H_5OH	61	$7\cdot10^{-4}$	1	-3.15	0	19
SCH_3				$1.25\cdot10^{-2}$	18	-1.9	0.18	
H	CH_3ONa	CH_3OH:dioxan 1 : 5	50	$4\cdot10^{-3}$	1	-2.4	0	17
$SeCH_3$				$2.1\cdot10^{-2}$	5.2	-1.68	0.13	48
H	CH_3ONa	CH_3OH	50	$8.3\cdot10^{-5}$	1	-4.08	0	13
SeC_6H_5				$3\cdot10^{-3}$	36	-2.52	0.23	48
$SCHF_2$ **				$2.1\cdot10^{-1}$	2500	-0.70	0.49	49
H	$C_5H_{10}NH$	dioxan	25	$7.2\cdot10^{-7}$	1	-6.13	0	16
SC_6F_5				$6.9\cdot10^{-4}$	$9.6\cdot10^{2}$	-3.16	0.46	48
SCN				$1\cdot10^{-2}$	$1.4\cdot10^{4}$	-2.0	0.64	48
$SCF(CF_3)_2$				$2.7\cdot10^{-1}$	$3.8\cdot10^{5}$	-0.57	0.83	
SO_2F				9.7	$1.35\cdot10^{7}$	+0.99	1.10	
H	C_6H_5SNa	C_2H_5OH	61	$1.22\ 10^{-4}$		-3.92	0	19
SCH_3				$8.08\ 10^{-3}$		-2.09	0.18*	
SC_6H_5				$1.53\ 10^{-1}$		-0.81	0.31	
SC_6H_4Cl-4				$7.25\ 10^{-1}$		-0.14	0.38	
$SC_6H_4CH_3$-4				$9.3\ 10^{-2}$		-1.03	0.29	

* From the Yukawa-Tsuno equation [43,50,51], see in [48]; ** Acc. to [49] E = 16.0 kcal/mol, lg A = 10.15

benzene ring raises the reactivity of a substrate by 6 orders, which corresponds to increase of the total electron accepting ability of ring substituents approximately by 1.06 σ units. Among the sulphur-containing substituents mentioned above there were practically no electron donors. The electron accepting ability of substituents increases with that of the group directly bonded to sulphur, and with sulphur valency in the following order : $CH_3S < C_6H_5S < C_6F_5S < SCN < SCF(CF_3)_2 < SO_2F$. The electronegative character of sulphur being higher than that of selenium, all sulphur-containing substituents in the polyfluorinated ring show a higher electron-accepting ability than their selenium-containing analogues : $CH_3Se < CH_3S$; $C_6H_5Se < C_6H_5S$ (Table 8). The data of Table 8 show no essential difference between the σ_p^- values for compounds $4\text{-}RSC_6H_4X$ and C_6F_5SR, which is only possible in case of similar conductances of the electronic effects of sulphur-containing substituents in the benzene and polyfluorinated rings. This distinguishes sulphur-containing substituents from the nitrogen-containing ones of type NR_2 and $N(CH_2)_n$, which suffer steric inhibition of conjugation with the ring [42]. It is interesting to note that S. Oae [53] obtained similar results as in [48] on the absence of steric inhibition for the conjugation of bulky sulphur-containing substituents with the ring in the presence of bulky groups in ortho-positions, in the case of another reaction series dissociation of sterically hindered phenols. Such a situation is only possible if the electronic effect of sulphur-containing substituents is determined predominantly by the inductive effect. Indeed, the analysis of σ_p^- values of sulphur-containing substituents in the polyfluorinated ring shows that they are determined for 80-94% by the sum of the inductive effects of SH and the R group, which is part of the SR substituent. This allowed to compare the $\sigma_{p\text{-}RS}^-$ values with the values of the inductive effects of R groups to find quite a satisfactory correlation : $\sigma_{p\text{-}RS}^- = 0.74\ \sigma_I(R) + 0.24$ ($r = 0.994$, $s = 0.025$, $n = 4$) This correlation also allows tentative estimation of σ_p^- values for other, earlier uninvestigated, substituents in the polyfluorinated ring.

The electronic effects of sulphur-containing substituents are considered in many works, including spectral studies - in particular, the ^{19}F NMR determination of σ_p for a wide range of compounds $4\text{-}RSC_6H_4F$ [54]. However the σ_p values obtained may not be used to predict the reactivity of compounds where the σ_p^- values are required. At the same time, the results reported in [54] gave rich material for the analysis of factors governing the electronic effect of sulphur-containing substituents. Thus the higher valency of the sulphur atom in the 4-RS-substituent leads to increase of all the components of the electronic effect : σ_I, σ_R and σ_p. Table 8 shows that a similar tendency is observed for the sulphur-containing substituents in the polyfluorinated ring. On passing from substituent 4-CH_3S containing divalent sulphur to 4-SO_2F where sulphur is hexavalent, the electron accepting ability of substituent increases by 0.9 σ units. To clear out the reasons for such dramatic increase in the electron accepting ability of sulphur-containing substituents, one should consider the electronic structure of these compounds, and analyse their spectral data and the mechanism of the reaction of substituent with the reaction centre. Depending on the nature of the reaction centre, and on the type of dominating electron effect (inductive or mesomeric) in the given reaction, the 4-CH_3S group may show itself, judging by the σ_R value, as a strong or weak electron donor. Thus in the dissociation reactions of benzoic acids the σ_R value of the para-thiomethoxyl substituent is -0.25, whereas with the changed nature of reaction centre on passing to the dissociation reactions of phenols and nucleophilic substitution, the electron donating ability of substituent is considerably decreased : $\sigma_R = -0.07$ to -0.02 [55], Table 8. If most of 4-RS(Se) substituents exhibit the predominantly inductive mechanism of interaction with the ring the 4-RO substituents undergo the mesomeric donor-type interaction of oxygen unshared electron pair with the π-system of the benzene ring : $\sigma_p^- = -0.27$, $\sigma_R = -0.52$ [55]. Thus the X-ray spectral studies have shown that the unshared electron pair of oxygen of the alkoxy substituent in compounds C_6H_5OR is practically completely transferred to the π-system of the ring, whereas in their thio-analogues the unshared electron pair is localised for 75-80% on the sulphur atom [46].

3. The reactivity of pentafluorobenzenes with substituents CH_2R, CHR_2, $CH{=}CHR$, CR_3, $C{\equiv}CR$

In [49] we have studied the reactivity of compounds C_6F_5R containing the above substituents as R, in the reactions with sodium methoxide and piperidine, and calculated the electronic effects of substituents R realised in these reactions. The results are summarised in Table 9.

CH_3 Group. This substituent acts as an electron donor, probably, for all positions of the polyfluorinated ring. The reactivity of pentafluorotoluene in the reaction with sodium methoxide has been considered in [5,21,49] . The reaction has been shown to proceed 25 times as slow as a similar reaction of pentafluorobenzene (Table 9). The CH_3 group might be suggested to be an analogue of another electron-donating group, CH_3O , in its effect in the polyfluorinated ring. However these groups have been found to produce different effects on the isomer ratio of the methoxylation products of compound C_6F_5R . The CH_3 group is exclusively a para-orientant, whereas the CH_3O group directs nucleophile to all positions of the polyfluorinated ring : ortho:meta:para = 16:32:52 [59] , i.e. it reacts with the ring by a different mechanism than the CH_3 group. A surprising fact is the absence of ortho-substitution products and insignificant (only 3%) yield of the meta-substitution products of pentafluorotoluene [58] . The absence of data on k_{ortho} and k_{meta} does not allow the quantitative estimation of the CH_3 electronic effect on the ortho- and meta-positions of the polyfluorinated ring. In view of the absence of ortho-substitution products above 1% , one can suggest the CH_3 group to strongly deactivate the ortho-position. The reason for such deactivation is not clear to us as yet. Literature contains rather contradictory data on the ortho-constant value for that substituent [32] . The σ_o value is known to vary from -0.19 to $+0.29$, depending on the reaction series. The rate constant for the reaction of methoxylation of ortho-position to the CH_3 group in $C_6F_5CH_3$ is presumably 2 orders of magnitude lower than in the nucleophilic attack at the para-position, i.e. the σ_o value for the CH_3 group in the polyfluorinated ring is ~ 0.20 σ units(or more) lower than for the para-position, being equal to -0.40 σ units or below. As for the electronic effect of the CH_3 group on the para-position of the polyfluorinated ring in the nucleophilic substitution reactions [42] , the calculations from the Lg k values of the $S_{N(Ar)}$ reaction rates showed it to be close to the value reported in literature for other reaction series [55] : $\sigma_p^- = -0.20$.

CH_2R Groups. We have not found any literature data on the kinetics of the $S_{N(Ar)}$ reactions of pentafluorobenzenes containing these groups in the ring with R=OH and $R=OCH_3$. On the basis of literature [55] σ_p values for these groups calculated from the dissociation of benzoic acids, one can suggest the nucleophilic constants for these substituents in the polyfluorinated ring for the $S_{N(Ar)}$ reactions to be within 0 to +0.10 σ units.

TABLE 9

The reactivity of compounds C_6F_5R in the $S_{N(Ar)}$ reactions and the electronic effects of 4F+ p-R, p-R substituents in the polyfluorinated ring (R = CH_3, CH_2R, CHR_2, CR_3, CH=CHR, C≡CR)

R	T, °C	Reagent	Solvent	$k\cdot10^5$ l/mol·sec	k_R/k_H	lg k	E kcal/mol (lg A)	σ^- 4F+p-R	σ^- p-R	σ_p from diss. of benzoic acids	σ_I [56]
H	20	CH_3ONa	CH_3OH	0.22	1	-5.65	22.6 (11.2)	1.060	0	0	0
	50	"	"	8.3	1	-4.08	[13]	1.063	0		
CH_3	50	"	"	0.31	0.037	-5.51	20.8 (8.56) [49]	0.859	-0.204	-0.16	-0.05
CH_2F	50	"	"	530	64	-2.27	17.7 (9.7) [49]	1.321	0.258	0.10 [57]	0.13 [57]
CHF_2	50	"	"	9600	1156	-1.02	15.8 (9.66) [49]	1.500	0.437	0.32 [57]	0.26 [57]
CF_3	50	"	"	$1.35\cdot10^5$	$1.6\cdot10^4$	0.13	17.4 (11.9) [21]	1.664	0.601	0.53	0.43
CF_3	20	$C_5H_{10}NH$	$C_5H_{10}NH$	180	$6.4\cdot10^4$	-2.74	7.0 (2.5) [16]	-	0.60		
CCl_3	20	"	"	270	$9.6\cdot10^4$	-2.57	11.35 (5.89) [49]	-	0.62	0.46	0.41
H	20	"	"	$2.8\cdot10^{-3}$	1	-7.55	16.7 (4.9) [16]	-	0	0	0

$CH(OC_2H_5)_2$	50	CH_3ONa	CH_3OH	$1.6\cdot10^4$	$1.9\cdot10^3$	-0.80	22.8 (14.63) [49]	1.531	0.468	-0.05	0.18
$CH=CH_2$	50	"	"	110	13	-2.96	23.1 (12.64) [49]	1.223	0.16	-0.08	0.08
$CH=NC_6H_5$	50	"	"	$2.8\cdot10^4$	$3.4\cdot10^3$	-0.55	19.76 (12.8) [49]	1.567	0.504	0.42	-
$CH=N(O)C_6H_5$	50	"	"	$2\cdot10^4$	$2.4\cdot10^3$	-0.70	16.3 (10.3) [49]	1.546	0.483	-	-
CN	50	"	"	$4\cdot10^6$	$4.8\cdot10^5$	1.6	14.8 (11.6) [17]	1.874	0.811	-0.70	0.57
$C\equiv CC_6F_5$	20	"	"	3200	$1.5\cdot10^4$	-1.5		1.580	0.52	-	-

CH_2F Group. Upon substitution of H atoms in the CH_3 group of pentafluorotoluene by the F atoms, the reactivity of a substrate in the $S_{N(Ar)}$ reactions considerably increases (Table 9). The p-F atom in the benzene ring and the fluorine atom separated from the ring by the bridge $-CH_2-$ group behave in a different way towards the reaction centre in the ring. Thus the ring p-F atom is known to be a strong electron acceptor by the inductive effect $\sigma_I=+0.51$, and at the same time, a strong electron donor by the conjugation effect $\sigma_R= - 0.45$. The p-F atom strongly deactivates the para-position, and, to a less extent, ortho- and meta-positions of the polyfluorinated ring to nucleophilic substitution by the conjugation effect. The CH_2F group in the polyfluorinated ring shows electron-accepting effect by the inductive $\sigma_I =+0.12$ and resonance $\sigma_R = +0.14$ mechanisms of interaction with the polyfluorinated ring (Table 9). The σ_p values for that substituent , found from the dissociation of benzoic acid and by ^{19}F NMR , are mutually in good agreement [55,60,57] , but they are lower (by 0.14 σ units) than the σ_p^- value for that substituent calculated by us from lg k of the rate of methoxylation of $C_6F_5CH_2R$, as the σ_p values do not allow for the additional conjugation of substituent with the reaction centre in the transition state [39,40] .

CHR_2 Groups. An interesting example of a substituent whose accepting ability in the polyfluorinated ring is strongly activated as compared to the non-fluorinated one is $CH(OEt)_2$, which is a weak donor in the benzene ring $\sigma_p = -0.05$, and a strong acceptor in the polyfluorinated one $\sigma_p^- = + 0.47$ (see Table 9). Due to its steric interaction with o-F in the polyfluorinated ring this bulky group is, presumably, completely withdrawn out of conjugation and its interaction with the reaction centre proceeds exclusively by the inductive mechanism.

Substitution of the H atom by F in the CH_2F group markedly activates the accepting ability of substituent, which for the CHF_2 group in the polyfluorinated ring, in the $S_{N(Ar)}$ reactions, is 0.18 σ units higher. In fact this value is much smaller than would be expected upon introduction of such a strong acceptor as fluorine into this group.

CR_3 Groups. CF_3 Group. Likewise, substitution of the H atom by F in the CHF_2 group increases the electron-accepting ability of substituent by only 0.16 σ units (see Table 9), this increment being exclusively at the expense of activated induction component.

Comparison of the σ_R and σ_I components of the electronic effect for all the above-considered fluoroalkyl substituents shows that at least ~ 70% of their electronic effect is determined by the induction component, the resonance contribution amounts to only ~ 30%. The analysis of perennial discussion on the character of electronic interaction of the CF_3 group with the ring [57,60-63] shows that the resonance contribution of this substituent is supposed to be largely determined by the character of reaction centre.

The discussions on the mechanism of CF_3 electron effect transfer intermittently break out again [63] . Thus R.D.Chambers and his co-workers [18] studied the kinetics of the reaction of C_6F_5R (R = CF_3, CF_2CF_3, $CF(CF_3)_2$, and $C(CF_3)_3$) with ammonia, and made a conclusion about the absence of negative hyperconjugation in the case of CF_3 group (Table 10). This opinion was then disputed in ref. [21] , which studied the kinetics of the reaction of perfluorinated methylbenzenes and benzocycloalkenes with sodium methoxide and piperidine. The authors of [21] reported substantial decrease of the accepting ability of the o-CF_3 group, which they attributed to the negative hyperconjugation effect in the transition state. There are alternative viewpoints reducing the electronic behaviour of the o-CF_3 group to steric effects, namely , to sterico-electronic hindrance for the nucleophilic attack due to interaction of o-CF_3 dipoles with electron pairs or the charged part of the attacking nucleophile [64] .

The activating effect of the CF_3 group in the polyfluorinated ring has been studied in detail (see Table 11). Substitution of this group for H in pentafluorobenzene or for F in hexafluorobenzene increases the reactivity of a substrate by several orders, depending on the character of nucleophile. This is indicated by the data on the reactivity of C_6F_5R compounds with C_6F_5ONa [64] , sodium methoxide [17,21,29,58] , piperidine [16] , sodium azide [15] , para-toluidine [20] , and hydroxylamine [65] . Further substitution of fluorine in the octafluorotoluene ring by the CF_3 groups does not produce such a dramatic effect on the reactivity, possibly except for much more reactive perfluoro-ortho-xylene and perfluoromesitylene; and on passing to perfluoro-para-xylene, the reactivity of a substrate even decreases [21] . The reason is in the fact that only in the case of CF_3 substitution for p-F the reactivity increase is maximal, whereas in the rest cases, due to the small difference between the electronic effects of o-F and o-CF_3 , m-F and m-CF_3 , the

TABLE 10

Kinetics of the reactions of C_6F_5R compounds with ammonia in aqueous dioxan at 92°C [18]

		R			
		CF_3	CF_2CF_3	$CF(CF_3)_2$	$C(CF_3)_3$
$k \cdot 10^3$ l/mol·sec		0.67	1.44	1.0	1.73
lg k		-3.17	-2.84	-3.0	-2.76
σ_p^- *		0.61	0.67	0.64	0.69
σ_p ** acc. to [57,60]	A	0.62	0.69	0.68	0.71
	B	0.49	0.52	0.52	0.55
	C	0.41	-	0.53	0.27
σ_I acc. to [57,60]		0.40	0.41	0.48	0.55

NOTES : * Calculated from the Hammett equation $\sigma_p^- = \frac{1}{\rho} \lg \frac{k}{k_o}$ for the given reaction series $C_6F_5R + NH_3$, 92°C, water dioxane. The k_o value was estimated by analogy with the reactions of C_6F_5R with piperidine [16] for which the ratio $k_{C_6F_5CF_3}/k_{C_6HF_5} = 2.4 \cdot 10^3$ is known. By our estimate, $k_o = 2.8 \cdot 10^{-7}$ l/mol·sec, lg k_o = -6.55, the ρ value is estimated as 5.54, having assumed the value $\sigma^-_{p-CF_3} = +0.61$ as a standard (reference point). ** Where A, B, C are the ways of determining the σ_p value of the substituent by [57,60]: A - from the pK aniline ions, B - from the chemical shifts of δ^F by the ^{19}F NMR method, C - from the pK of benzoic acids.

increase is minimal or even negative, as for perfluoro-para-xylene. Nevertheless, perfluorodi- and - trimethylbenzenes are highly activated compounds, which allows easy substitution of their first two fluorines in the ring by a nucleophile [21] .

<u>p-CF_2CF_3 Group.</u> Upon substitution of one F atom in the CF_3 group, having a strong inductive effect in the ring σ_I =+0.51 , by the CF_3 group, having a 0.1 σ units weaker inductive effect, the electron-accepting ability of substituent increases from σ_p^- =+0.61

for the CF_3 group to +0.67 for p-CF_2CF_3 . The latter value is close to the one found for that group by Sheppard [60] from the dissociation of anilinium ions in the benzene series.

p-$CF(CF_3)_2$ Group . Upon substitution of another fluorine atom in the p-CF_2CF_3 substituent by the CF_3 group , the electron-accepting nature of substituent even somewhat decreases : the $\sigma_p^- = +0.64$ value for that group is 0.03 σ units smaller than for the p-CF_2CF_3 group and 0.04 σ units smaller than the σ_p^- value for the some substituent found from the dissociation of anilinium ions in the non-fluorinated benzene ring (see Table 10). Possibly a certain decrease in the accepting ability of substituent is due to steric effects in the polyfluorinated ring . The nucleophilic attack at the ortho-position to this group in the polyfluorinated ring has been found to be sterically inhibited [21] : the reaction of perfluoro-para-isopropyltoluene with sodium methoxide gives only 14% of the product of substitution at the ortho-position to the $CF(CF_3)_2$ group, and 86% - at the ortho-position to a less bulky CF_3 group .

$C(CF_3)_3$ Group . Substitution of a third fluorine atom in the CF_3 group by the CF_3 group have led , despite the increased size and steric interactions with o-F of the polyfluorinated ring , to the pronounced increase of accepting ability as compared the CF_3 and even p-CF_2CF_3 group (as shown by the kinetic data for the reaction of $C_6F_5C(CF_3)_3$ with ammonia) (see Table 10) . The reason for that phenomenon is unclear as yet .

CCl_3 Group . According to the kinetic data for the reaction of $C_6F_5CCl_3$ with piperidine , this group is similar in its electronic effect to its fluorine analogue - the CF_3 group (Table 9) .

$CH_2{=}CH$ Group . The nucleophilic constant σ_p^- value for that group, calculated from lg k of the rate of the reaction of pentafluorostyrene with sodium methoxide , considerably differs from σ_p , obtained for that group from the dissociation of benzoic acids . This group is electron donor in the benzene ring , whereas in polyfluorinated ring , in the $S_{N(Ar)}$ reactions , it is a weak electron acceptor with the σ_p^- value that only slightly differs from the σ_I value for that substituent , indicating a complete withdrawal of this group from conjugation with the polyfluorinated ring , presumably , due to steric interaction with o-F of the ring .

$C{\equiv}C{-}R$ Groups . Introduction into the ring of the $-C{\equiv}C-$group having a strong inductive electron-accepting effect $\sigma_I = +0.30 \div +0.35$

TABLE 11

Kinetic data for the reactions of perfluoromethylbenzenes with sodium methoxide in methanol and with piperidine in dioxan

Compound	Reagent	T, °C	$k \cdot 10^3$ l/mol·sec	E, kcal/mol	Ref.	lg A	$k_{rel.}$	$\sum \sigma_I$
C_6F_6	CH_3ONa	25	0.02	21.4	13	11.0	1	1.167
	$C_5H_{10}NH$	50	0.0053	12.1	16	2.9		
$C_6F_5CF_3$	CH_3ONa	25	137 (5.6*)	17.4	21	11.9	$6.9 \cdot 10^3$(280*)	1.662
		50	1350					(1.483*)
	$C_5H_{10}NH$	50	16	6.8	16	2.8		
4-$CF_3C_6F_4CF(CF_3)_2$	CH_3ONa	25	36 (5.9**)	14.6	21	9.3	$1.8 \cdot 10^3$	1.587
		35	90					
		50	280					
	$C_5H_{10}NH$	50	0.097	5.71	21	0.13		
		82	0.22					
		100	0.32					
4-$CF_3C_6F_4CF_3$	$C_5H_{10}NH$	50	0.099	8.41	21	1.7		
		82	0.32					
	CH_3ONa	20	40	15.4	21	10.1	$2.9 \cdot 10^3$	1.613
		25	57					
		35	140					
		50	400					

3-$CF_3C_6F_4CF_3$	CH_3ONa	25	320	-		-	$1.6 \cdot 10^4$	1.646
	$C_5H_{10}NH$	25	3.7	7.5	21	3.1		
		50	10					
		82	28					
2-$CF_3C_6F_4CF_3$***	$C_5H_{10}NH$	25	33	8.2	21	4.5		
		50	100					
	CH_3ONa	25	1700	-		-	$8.5 \cdot 10^4$	1.802
1.3.5-$(CF_3)_3C_6F_3$	CH_3ONa	25	2400	-		-	$1.2 \cdot 10^5$	1.821
	$C_5H_{10}NH$	25	2.3	8.41	21	3.5		
		50	6.3					
		82	22					

NOTES : * Nucleophilic attack at the 2-position.

** Nucleophilic attack at the 3-position (ortho-substitution to the heptafluoroisopropyl group 14%).

*** Nucleophilic attack at the 4-position.

[56] considerably activates the polyfluoroaromatic substrate to the nucleophilic substitution reactions [5,66]. Literature gives no data on the σ_p (σ_p^-) value for the $C{\equiv}CC_6F_5$ group, but gives these for its closest analogue - for the $C{\equiv}CCF_3$ group : $\sigma_p = 0.51$, $\sigma_1 = 0.31$ [56]. Kinetic measurements for the reaction of $C_6F_5C{\equiv}CC_6F_5$ with sodium methoxide gave us the σ_p^- value = 0.56 of the same order. In the analysis of kinetic data, there arose the problem of separating the initial and successive reactions. At the initial stage the nucleophilic substitution reaction proceeds in the ring, but later on the product formed at this stage, which has a similar reactivity as the substrate, also interacts with nucleophile, forming the symmetric 4,4'-dimethoxy-derivative. These processes may be separated by extrapolating the meaning reaction rate constants to zero time when there is no contribution of a successive process.

CH=NAr, group. Upon substitution of the $=CH_2$ fragment in the $CH{=}CH_2$ substituent by the $=NC_6H_5$ fragment, the length of conjugated chain considerably increases, as well as the electronic effect of the substituent, and the possibility of charge delocalisation along the chain bonded with the =CH group directly attached to the polyfluorinated ring. As a consequence, the $CH{=}NC_6H_5$ substituent shows considerably increased electron-accepting ability as compared to the vinyl group, from $\sigma_p^- =$ 0.14 to $\sigma_p^- = 0.53$. The latter value is naturally higher than the σ_p value = 0.42 [55,56], obtained from the dissociation of benzoic acids.

4. Quantitative estimation of the reactivity of fluorine-containing diphenyls, bicyclic and heterocyclic compounds

With the grown availability of polyfluorinated diphenyls, bicyclic and heterocyclic compounds, researchers grew interested in the quantitative estimation of the reactivity of these compounds in their typical reactions - those of nucleophilic substitution.

The basic problem here was the exact determination of the position of nucleophilic attack, which was successfully solved using ^{19}F NMR. Variation in the reactivity of aromatic compounds containing a condensed aromatic system as compared with their non-fluorinated analogues was studied long ago, but the kinetic data on the nucleophilic substitution reactions of polyfluorinated bicyclic compounds of such type have been obtained only recently.

4.1. Bicyclic polyfluoroaromatic compounds

The kinetic data for the reactions of bicyclic polyfluoroaromatic compounds with nucleophilic agents are reported in few works [21,58,67] for octafluoronaphthalene, perfluorinated benzocycloalkenes [21,58], and diphenyls [67].

4.1.1. 2-R-Substituted heptafluoronaphthalenes

It has been found for the reaction of octafluoronaphthalene with nucleophilic reagents [5] that nucleophile predominantly attacks the 2 β-fluorine atom, whereas further fluorine substitution by nucleophile takes place at the 6 position. For the 2-substituted heptafluoronaphthalenes, the nucleophilic attack is directed at the 6 position, the electron-accepting substituents accelerating these reactions, and the electron-donating ones retarding them in comparison with 2H-heptafluoronaphthalene [58]. Comparison of the relative rate constant k_R/k_H values in the series of polyfluorinated benzenes and naphthalenes shows the electronic effect transmittance of R to be slightly different in the benzene and naphthalene systeims (see Table 12).

4.1.2. Perfluorinated benzocycloalkenes $C_6F_4(CF_2)_n$, where $n = 2 - 4$

In [21], the kinetics have been measured for the reactions of perfluorinated cycloalkenes with sodium methoxide in methanol and with piperidine in dioxan (Table 13). The reactivity of perfluorobenzocycloalkenes has been shown to increase by a factor of 2 with the increased size of perfluoroalicyclic ring by one CF_2 group : perfluorobenzocyclobutene $<$ perfluoroindane $<$ perfluorotetralin. In this case, nucleophile attacks predominantly the β-fluorine atom of the benzene ring fused with the perfluoroalicyclic ring. Perfluorobenzocycloalkenes have been shown to be the close analogues of perfluoro-ortho-dialkylbenzenes in their reactivity. Thus perfluorobenzocyclobutene shows the similar (only twice as low) reactivity as perfluoro-ortho-xylene.' Perfluoroindane is close in its reactivity to perfluoro-ortho-methylethylbenzene, and perfluorotetralin - to perfluoro-ortho-diethylbenzene. These data have shown that the main contribution to the reactivity of perfluorobenzocycloalkenes is made only by two CF_2 groups directly annealed with the ring.' Extension of the acyclic ring by the CF_2 groups produces a much weaker effect than introduction of the CF_2 group into the aromatic ring.

TABLE 12

Kinetic data for the reactions of some polyfluorinated naphthalenes with sodium methoxide in methanol at 50°C [58]

Compound	$k \cdot 10^4$ l/mol·sec	$k_{rel.}$	C_6F_5R R	$k \cdot 10^4$ l/mol·sec	$k_{rel.}$
1H-heptafluoronaphthalene	4.5	0.05	H	0.83	1
2-H-heptafluoronaphthalene	92	1	Cl	17	20
2-Cl-heptafluoronaphthalene	480	5.2	C_6H_5	1.23	1.5
2-phenylheptafluoronaphthalene	118	1.3	F	3.4	4.1
octafluoronaphthalene	430	4.7	CH_3O	0.066	0.08
2-methoxyheptafluoronaphthalene	28	0.3	C_6F_5	920	1110

Regarding the perfluoroalicyclic ring $-(CF_2)_n-$ fused with the aromatic ring to be a substituent, we have determined the electronic effects of such cycles from the reactivity data for perfluorobenzocycloalkenes in their reaction with sodium methoxide (Table 14). For the cyclic group $-(CF_2)_2-$ the electronic effect on the β-position of the aromatic ring is 1.013 σ units, which is close to the effect of such groups as p-CN and p-SO_2CH_3. Increase of the length of cyclic fragment by one CF_2 group leads to increase of the electron-accepting ability of cyclic substituent by 0.05 - 0.06 σ units.

Substitution of the cyclic fragment $-(CF_2)_4-$ in perfluorotetralin by the cyclic group -CF=CF-CF=CF- leads to a 0.44 σ units decrease of the electron-accepting ability of the cycle; in terms of rate constants this corresponds to the reactivity decrease by three orders. This results both from the decreased number of fluorine atoms and the created possibility for fluorine atoms to donate electron density to the conjugated chain.

The perfluorobenzocycloalkenes considered are highly activated fluoroaryls, which are close in their reactivity to such a highly activated fluoroaryl as 2,4-dinitrofluorobenzene. This means that perfluorobenzocycloalkenes may possibly be used as 2,4-dinitrofluorobenzene analogues, i. e. as effective arylating agents.

4.1.3. Fluorinated diphenyls

The reactions of partially and completely fluorinated diphenyls with sodium methoxide proceed with substitution of exclusively the fluorine atom in the 4-position of the polyfluorinated ring [5,37,69].

TABLE 13

Kinetic data for the reactions of perfluorobenzocycloalkenes and octafluoronaphthalene with sodium methoxide in methanol and with piperidine in dioxan [21]

Compound	Reagent	T, °C	$k \cdot 10^3$, l/mol·sec	E, kcal/mol	lg A	$k_{rel.}$	$\sum\sigma_I^*$
perfluorobenzocyclobutene**	$C_5H_{10}NH$	25	31	8.92	5.04		
		35	57				
		50	97				
		60	160				
	CH_3ONa	25	1300	-	-	$6.5 \cdot 10^4$	1.786
perfluoroindane	CH_3ONa	25	2800	-	-		1.830
	$C_5H_{10}NH$	22	66	9.92	6.1		
		25	69				
		35	150				
		45	220				
		50	260				
perfluorotetraline	$C_5H_{10}NH$	25	170	8.0	5.13		
		50	550				
		82	1500				
	CH_3ONa	25	6600			$3.3 \cdot 10^5$	1.878
hexafluorobenzene	CH_3ONa	25	0.02	-	-	1	1.167

(continued)

TABLE 13 (cont.)

Compound	Reagent	T, °C	$k \cdot 10^3$, l/mol·sec	E, kcal/mol	lg A	$k_{rel.}$	$\sum\sigma_I$*
octafluoronaphthalene***	CH_3ONa	22	1.8	21.92	13.5	$1.4 \cdot 10^2$	
		25	2.8; 2.1 68				
		30	5.5				
		40	15				
		50	47				
	$C_5H_{10}NH$	30	0.27	7.41	1.7	1	
		50	0.51				
		96	2.2				
octafluorodiphenylene	CH_3ONa****	25	2.0****				
octafluoronaphthalene			750				
decafluorophenanthrene			5.8				
octafluorotoluene			100				
decafluorodiphenyl			1.2				

NOTES : * The total electronic effect of substituents in the benzene ring is determined from the Hammett *equation* : $\sum\sigma_i = \frac{1}{\rho} \lg \frac{k}{k_o}$, *where* $\rho = 7.77$, $-\lg k_o = 13.77$ *for the reference reaction* series $RC_6H_4F + CH_3ONa$ (CH_3OH) (extrapolated from the data of [41]).

** With NuX = CH_3ONa yield ratio of $\alpha : \beta$ is 1:2, with NuX = $C_5H_{10}NH$, $\alpha : \beta$ = 1:3[21].

*** α-Isomer content acc. to [58] is less than 20%.

**** Acc. to [68] in methanol.

TABLE 14

The electronic effect of substituents in perfluorobenzocycloalkenes and octafluoronaphthalene estimated from the kinetic data for the reactions with sodium methoxide at 25°C

Compound	Electronic effect of substituents, σ units	
	of all substituents in Ar_FF	of the cyclic fragment on the aromatic β-position
perfluorobenzocyclobutene	1.770	1.013
perfluoroindane	1.830	1.073
perfluorotetraline	1.878	1.121
octafluoronaphthalene	1.440	0.683

From the lg k values of the rates of the reactions of substituted diphenyls $4\text{-}XC_6H_4C_6F_5$ with sodium methoxide calculated in [37] we have calculated the electronic effects of substituents $4\text{-}XC_6H_4$ in the polyfluorinated benzene ring (Table 15). It has been shown that, depending on the electronic nature of X and location in the non-fluorinated ring, the σ_p^- values range from -0.007 for the substituent with X = $p\text{-}CH_3$ to +0.229 σ units with X = $p\text{-}NO_2$. It should be noted that the electronic effect of substituent X on the reaction centre is much weaker in the non-fluorinated phenylene system than in the polyfluorinated ring. The most reactive fluorinated diphenyl is decafluorodiphenyl, which in the reaction with sodium methoxide [69] is three orders more reactive than the half-fluorinated diphenyl $C_6H_5C_6F_5$ [37] (Table 15). The electronic effect value for $p\text{-}C_6F_5$ in the polyfluorinated ring, in the $S_{N(Ar)}$ reactions, has been estimated at 0.41 - 0.44 [69].

5. Electronic effect of substituents containing nitrogen directly bonded with the polyfluorinated ring

NH_2 group. This group is a strong electron donor to the polyfluorinated ring, predominantly to the resonance ortho- and para-positions, due to which these positions are most deactivated to nucleophilic substitution, and the amino group in the polyfluorinated ring is mainly meta-orientant [5] (Table 16). Thus in the reaction of pentafluoroaniline with sodium methoxide, the main product is the product of meta-substitution : ortho : meta : para = 5:79:16 [71]. Considering the isomer ration, the calculation of the σ_p^- value from the lg k values of the overall rate constant for the reaction of pentafluoroaniline with sodium

TABLE 15

Kinetic data for the reaction of substituted diphenyls with sodium methoxide in methanol at 50°C [37,69]

	X							
$XC_6H_4C_6F_5$	H	m-CH_3	4-CH_3	m-CI	m-Br	m-NO_2	4-NO_2	*
$k \cdot 10^4$ l/mol·sec	1.23	1.10	0.72	7.5	5.3	25.6	32	$9.2 \cdot 10^2$
k_{Ar}/k_H	1.0	0.89	0.59	6.1	4.3	20.8	26	$7.6 \cdot 10^2$
lg k	-3.91	-3.96	-4.14	-3.13	-3.30	-2.59	-2.49	-1.04
$\sum \sigma_i = \bar{\sigma}_{4F+p-R}$ **	1.087	1.080	1.054	1.199	1.177	1.276	1.290	1.497
$\bar{\sigma}_p$ ***	0.026	0.019	-0.007	0.138	0.116	0.215	0.229	0.434

NOTES : * Compound $C_6F_5C_6F_5$; ** Calculated from the Hammett equation : $\sum \sigma_i = \bar{\sigma}_{4F+p-R} = \frac{1}{\rho} \lg \frac{k}{k_o}$, where k and k_o are the rate constants of the reaction of unsubstituted diphenyl and unsubstituted fluoroaryl C_6H_5F with sodium methoxide in methanol at 50°C. Acc. to [41], for the reaction series : $RC_6H_4F + CH_3ONa$, methanol, 50°C, lg k_o = -11.52, ρ = 7.0; *** The $\bar{\sigma}_p$ values for phenyl substituents p-XC_6H_4 have been calculated from the equation : $\bar{\sigma}_p = \bar{\sigma}_{4F+p-R} - \bar{\sigma}_{4F+p-H}$, where p-R = p-$XC_6H_4$, the electronic effect of 4 ring fluorine atoms calculated earlier [30,42] for this reaction series is 1.061.

methoxide [17] gives the values of -0.53 and σ_R = -0.63 for the amino group in the polyfluorinated ring.

<u>$NAlk_2$ and $N(CH_2)_n$ groups.</u> Pentafluorobenzenes C_6F_5R, where R is represented by these groups, unexpectedly appeared to be only 10 to 30 times less reactive than pentafluorobenzene C_6HF_5 in the reactions with sodium methoxide, and much more (2 orders) reactive than pentafluoroaniline. It would seem that substitution of hydrogen atoms in the amino group by the alkyl groups, which usually act as electron donors, must enhance the electron-donating ability of substituents $NAlk_2$ and $N(CH_2)_n$ as compared with the kinetic measurements for the reactions of these compounds with sodium

TABLE 16

Electronic effects of nitrogen-containing substituents in the polyfluorinated ring (nitrogen is directly bonded to the ring) and the reactivity of the respective C_6F_5R compounds

R	T, °C	Nucleophile	Solvent	k, l/mol·sec	k_R/k_H	lg k	E, kcal/mol (lg A)	Ref.	σ_p^- (C_6F_5R)	σ_p from diss. of benzoic acids	σ_I
NH_2	50	CH_3ONa	CH_3OH-dioxan	$3.8 \cdot 10^{-6}$ *	$0.95 \cdot 10^{-3}$	-5.42	23.7 (11.4)	17	-0.53	-0.66	0.1
$N(CH_3)_2$	50	"	CH_3OH	$7.76 \cdot 10^{-6}$	0.093	-5.10	23.5 (10.8)	29	-0.15	-0.60	-
$N(C_2H_5)_2$	50	"	CH_3OH-dioxan	$6.6 \cdot 10^{-4}$	0.165	-3.18	18.6 (9.4)	42	-0.14	-	-
$N(C_4H_9\text{-}n)_2$	50	"		$3.7 \cdot 10^{-4}$	0.092	-3.43	17.2 (8.2)	"	-0.18	-	-
$N(CH_2)_5$	50	"	"	$5 \cdot 10^{-4}$	0.125	-3.3	20.4 (10.5)	"	-0.16	-0.50	-
$N(CH_2)_6$	50	"	"	$1.3 \cdot 10^{-4}$	0.032	-3.88	22 (11)	"	-0.26	-	-
$N(CH_2CH_2)_2O$	50	"	"	$2.1 \cdot 10^{-4}$	0.052	-3.67	21.4 (10.8)	"	-0.22	-	-
$NHNH_2$	50	"	CH_3OH	$7.2 \cdot 10^{-4}$	8.7	-3.14	18.5 (9.4)	49	0.14	-0.55	0.14
$N{=}CHC_6H_5$	50	"	"	$6.6 \cdot 10^{-4}$	8.0	-3.18	-	"	0.13	-0.55	-
N_3	50	"	"	$1 \cdot 10^{-3}$	12	-3.0	19.2 (9.95)	"	0.15	-0.08	0.42
$N(O){=}NC_6F_5$	20	"	"	$2.8 \cdot 10^{-1}$	$1.3 \cdot 10^{5}$	-0.55	-	"	0.70	-	-
$N{=}NC_6F_5$	20	"	"	1.6	$7.2 \cdot 10^{5}$	0.20	-	"	0.80	-	-
NO_2	50	"	"	$2.6 \cdot 10^{2}$	$3.2 \cdot 10^{6}$	2.42	14.9 (12.5)	29	0.94	0.778	0.63
$N{=}NC_6F_5$	20	$C_5H_{10}NH$	"	$1 \cdot 10^{-1}$	$3.7 \cdot 10^{6}$	-1.0	-	49	1.02	-	-
$N{=}NC_6H_5$			"	$3.5 \cdot 10^{-1}$	$1.2 \cdot 10^{7}$	-0.46	-	"	1.10	0.64	-
-N= **	50	"	dioxan	15	$4.8 \cdot 10^{6}$	1.18	8.1 (6.66)	23	1.05	-	-
NO_2	50	NaN_3	CH_3OH	$2.9 \cdot 10^{-1}$	$1 \cdot 10^{8}$	-0.54	-	15	1.0	0.778	0.63
NO	50	"	"	28	$9.3 \cdot 10^{9}$	1.447	-	"	1.24	0.123	-

NOTES : * Considering the ratio o:m:p = 5:79:16 acc. to [71]; ** Nitrogen heteroatom in pentafluoropyridine.

methoxide [17,29,69] have shown its substantial decrease. Introduction of alkyl substituents into the amino group leads to the changed orienting ability of substituents in the polyfluorinated ring - they proved to be para-orientants at least for 70% or more [5,29,69]. A convincing explanation to this was offered by Burdon [72], who suggested that the increased size of substituent R in the polyfluorinated ring leads to the enhanced sterico-electronic interactions of R with o-F of the ring and partial or complete cleavage of conjugation of substituent with the reaction centre. The kinetic measurements and calculations of σ_p^- values for these substituents in the polyfluorinated ring confirm Burdon's hypothesis. Comparison of the electronic effects of substituents $NAlk_2$ and $N(CH_2)_n$ in the series of $p\text{-}RC_6H_4X$ and C_6F_5R has shown that in the polyfluorinated ring these substituents are much weaker electron donors than in the non-fluorinated ring [42]. Still, partial conjugation of such substituents with the polyfluorinated ring is preserved , since on the whole, notwithstanding the inhibition of conjugation, these substituents remain electron donors (Table 16). Increased length of hydrocarbon radical at nitrogen leads to the increased donating ability of substituents, thus reducing the reactivity of $C_6F_5NAlk_2$, and vice versa, the decreased length of the radical leads to the decreased donating ability of substituent and increased reactivity of a substrate. Nevertheless, the observed variations of rate constants for the reactions of $C_6F_5NAlk_2$ with sodium methoxide are not higher than 2- or 3-fold.

$\underline{NHNH_2}$ group. This group is known to be a strong electron donor in the non-fluorinated benzene ring, the main contribution to the electronic effect being via the donor-type conjugation effect : $\sigma_p = -0.55 \div -0.29$, $\sigma_R = -0.69 \div -0.43$, $\sigma_I = 0.14$ (Table 16) [55,73-75]. Therefore pentafluorophenylhydrazine was expected to be close to pentafluoroaniline in its reactivity in the reaction with sodium methoxide, and the electronic effect of the hydrazo group to be of the same order as that of the amino group. The hydrazo group however proved to be predominantly para-orientant in the polyfluorinated ring [5], and pentafluorophenylhydrazine was found to be 3 or 4 orders more reactive than pentafluoroaniline. The σ_p^- value of the hydrazo group was calculated to be 0.14, which is equal to the induction constant of this group, indicating a total absence of donor-type conjugation with polyfluorinated ring.

$\underline{N_3}$ group. This group exhibits a strong inductive effect from 0.36 to 0.42 [55], but by the sum of inductive and mesomeric effects it is a weak electron donor in the dissociation of the respective benzoic acid. In the aromatic nucleophilic substitution reactions, this group, according to J.Miller[75,47], is a weak electron acceptor $\sigma_p^- = 0.15$, $\sigma_R = -0.54 \div -0.44$. On passing to the reaction of pentafluoroazide with sodium methoxide, the σ_p^- value of the N_3 group remains practically the same, 0.154 (Table 16), which is surprising in view of possible increase of sterico-electronic interactions of this group with the polyfluorinated ring, as one would expect pronounced increase of the accepting ability of this substituent in the polyfluorinated ring.

N=CHAr group. In the non-fluorinated ring this group is a strong donor of electron density : $\sigma_p = -0.55$. The kinetic measurements for the reaction of pentafluorobenzene containing this substituent with sodium methoxide[49]have shown that in the polyfluorinated ring this substituent is a weak acceptor with $\sigma_p^- = 0.13$, which indicates complete cleavage of conjugation of this substituent with the polyfluorinated ring (Table 16).

N=NAr group. This group shows itself as a strong electron acceptor, being a para-orientant for nucleophiles. The main contribution to the accepting ability of these groups is made by the -N=N- fragment. The kinetic measurements have been carried out for the reactions of polyfluoroaromatic compounds with such substituents (with Ar = C_6H_5 and C_6F_5 / trans-form) with sodium methoxide and piperidine (Table 16), which allowed to determine the electronic effects of both substituents. Both substituents have been shown to be strong acceptors $\sigma_p^- =$ 0.90 and 0.74 respectively, the substituent containing the non-fluorinated phenyl group being a stronger electron acceptor.

$N(O)=NC_6F_5$ group. This group in the polyfluorinated ring is para-orientant in $S_{N(Ar)}$ reactions, with nucleophile first entering the ring directly bonded with N-oxide group, and then the 2nd ring[5]. We have not found any σ_p (σ_p^-) values for this substituent in literature. One could suggest the electronic properties of this substituent and $N=NC_6F_5$ to be similar. Introduction of an oxide group has been shown (Table 16) to lead to a certain decrease (by 0.10 σ units) of the accepting ability of this substituent down to $\sigma_p^- = 0.64$.

NO_2 and NO groups. The strongest electron-accepting substituents are the NO_2 and NO groups, which strongly activate the ortho- and para-positions of the polyfluorinated ring to the nucleophilic reactions.

The NO_2 group shows a strong ortho-effect, therefore in polyfluoronitrobenzenes, along with para-substitution, we also observe the pronounced ortho-substitution, whose contribution substantially increases with a decrease of medium polarity[76]. Table 16 represents quantitative estimation of the electronic effect of NO_2 and NO groups. It is seen from the Table 16 that the σ_p^- value in the polyfluorinated ring varies in the range of 1.27 to 0.63 σ units and in general is lower than in the non-fluorinated ring. This is possibly due to sterico-electronic interactions of the NO_2 group with o-F of the ring, leading to partial cleavage of conjugation with the reaction centre. R.Bolton and J.Sandall carried out a very interesting study. They measured the kinetics of substitution of p- and o-F in various nitropolyfluorobenzenes by the methoxy anion[77]. Based on these data, we determined the effective (i. e. realised in every concrete substrate) σ_p^- and σ_o^- values for the nitro group depending on fluorine position with respect to it. Thus in 3.4.5-trifluoronitrobenzene, where there are no fluorine atoms in ortho-positions to the p-NO_2 group, the electronic effect of p-NO_2 group does not change (Table 17). However, if we introduce at least one fluorine atom in the ortho-position to the NO_2 group, the electronic effect of NO_2 decreases by 0.1 - 0.2 σ units. Introduction of two fluorine atoms into the ortho-position to the nitro group decreases the electronic effect of the latter on the para-position of the ring by 0.4 σ units (Table 17), as observed, e. g., in 2.4.6-trifluoronitrobenzene. And, though further introduction of fluorine atoms slightly decreases the sterico-electronic effect of two ortho-F atoms on the nitro group (see the electronic effect of ortho- and para-nitro groups in perfluoronitrobenzene), nevertheless this effect is clear-cut and may be attributed in terms of conventional conceptions to sterico-electronic inhibition of conjugation of the nitro group with the benzene ring. The NO_2 group also produces a "reverse" effect on ring o-F in the reactions of polyfluorobenzenes with sodium methoxide. By contrast with other polyfluorobenzenes in these reactions, in nitropolyfluorobenzenes the electronic effect of o-F is 0.05 - 0.06 σ units smaller and amounts to 0.15 σ. The reason for this should possibly be sought in the mechanism of interaction of these substituents with the ring.

The kinetic data on the reactivity of pentafluoronitrosobenzene in nucleophilic reactions are much more scarce. As yet only the rate constant for the reaction with sodium azide in methanol at 50°C has been measured (see Table 18), and an attempt to estimate the rate for the reaction of piperidine in acetonitrile by traditional methods met with serious experimental difficulties. The kinetic data for the reactions of pentafluoronitrobenzene and pentafluoronitrosobenzene with sodium

TABLE 17

Influence of mutual position of the nitro group and fluorine atoms on the electronic effect of ortho- and para-nitro groups and ortho-fluorine (calculated by us from the kinetic data for the reactions of fluoronitrobenzenes with sodium methoxide in methanol at 25°C [77])

$ArNO_2$	$k \cdot 10^3$, l/mol·sec		$\sum \sigma_i$ *		σ^-		
	ortho	para	ortho	para	o-NO_2	p-NO_2	o-F
2-F	0.18	-	1.25	-	1.25	-	-
4-F	-	0.26	-	1.27	-	1.27	-
2,4-F_2	5	3.7	1.432	1.415	1.095	1.078	-
2,5-F_2	0.26	-	1.270	-	1.210	-	-
3,4-F_2	-	3.1	-	1.405	-	1.27	0.14
2,3,4-F_3	110	64	1.601	1.572	1.214	1.085	0.15
2,3,5-F_3	8	-	1.457	-	1.247	-	0.15
2,4,5-F_3	6	141	1.442	1.615	1.045	1.128	0.15
2,4,6-F_3	17	19	1.499	1.505	0.825	0.831	-
3,4,5-F_3	-	66	-	1.573	-	1.273	0.15
2,3,4,5-F_4	190	1520	1.631	1.745	1.084	1.108	0.15
2.3.4.6-F_4	300	340	1.657	1.663	0.833	0.839	0.15
pentafluoro-	1720	40000	1.753	1.924	0.869	0.950	0.15

* Calculated from the Hammett equation in Jaffe's modification [39] for polysubstituted benzenes lg $k/k_o = \rho \sum \sigma_i$, where k is the rate constant for the reaction of fluoronitrobenzene; k_o, for the reaction of fluorobenzene with sodium methoxide in methanol (calculated from lit. data averaged in [41], E = 37.35 kcal/mol, lg A = 13.74).

azide show that the nitroso group in the polyfluorinated ring is a much stronger electron acceptor than the nitro group, exceeding the latter by 0.24 σ units (in terms of reaction rate constants, this is almost 2 orders see Table 18).

For the reactions of pentafluoronitrobenzene and pentafluoronitrosobenzene with more reactive nucleophilic agents than sodium azide, measurement of reaction rates by the traditional titrimetric methods becomes impossible as they are very high. Due to this, other methods were used [78], in particular the conductimetric method, which allowed measurement of the rates for the reactions of such highly reactive

TABLE 18

Reaction kinetics of substituted pentafluorobenzenes with sodium azide in methanol at 50°C [15]

C_6F_5R R	k l/mol·sec	$k_{rel.}$	lg k	σ_p^- *	σ_p [39,40,55,56]	σ_I [55,56]
H	$3 \cdot 10^{-9}$	1	-8.52	0	0	0
F **	$5.5 \cdot 10^{-8}$	18	-7.26	0.16	0,062	0.51
Br	$2.1 \cdot 10^{-7}$	70	-6.68	0.23	0.23	0.44
CF_3	$2.1 \cdot 10^{-4}$	$7 \cdot 10^5$	-3.68	0.61	0.54	0.41
CN	$5.5 \cdot 10^{-2}$	$1.8 \cdot 10^7$	-1.26	0.91	0.66	0.56
NO_2	0.29	$1 \cdot 10^8$	-0.54	1.0	0.778	0.63
NO	28	$9.3 \cdot 10^9$	1.447	1.24	0.12	0.37

NOTES : * Calculated by the Hammett equation $\sigma_p^- = \frac{1}{\rho} \lg \frac{k}{k_o}$. When calculating ρ, as the reference points for constructing the correlation dependence lg k - ρ, σ_p^-, the values of the lg k of C_6HF_5 and C_6F_5Br were chosen for lg k_o and lg k, respectively, for which values the standard values $\sigma_{p-H} = 0$, $\sigma^-_{p-Br} = 0.23$ are assumed.

** Without statistical factor .

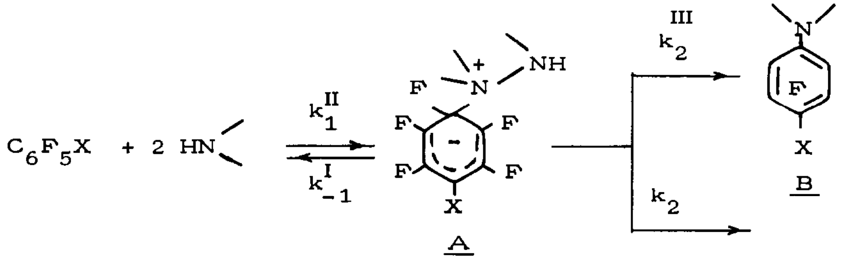
substrates as pentafluorobenzonitrile, pentafluoronitrobenzene, pentafluorobenzosulphofluoride with quite a reactive nucleophile-piperidine (Table 19). The analysis of kinetic data showed the reaction of piperidine with octafluorotoluene to be a limiting case when the reaction is defined by the 2-order equation. The reactions of piperidine with more reactive substrates are specified predominantly by the 3-order equation [78]. Increased order of the reaction on passing from octafluorotoluene to more reactive substrates possibly reflects a change in the limiting stage of the process. This stage turns to be the decomposition of intermediate complex <u>A</u> . In the reactions with charged nucleophiles, the transformation of the anionic σ-complex is fast. In the case of amine as a nucleophile, the decomposition of the intermediate type <u>A</u> zwitter ion by the 1-order reaction seems to be comparatively slow. More effective is the 3-order route involving one more amine molecule. As the 1st stage of the reaction is reversible and the concentration of intermediate <u>A</u> is small, the transformation to product <u>B</u> will only occur on condition that the C_6F_5R molecule reacts with two amine molecules, which determines the 3rd order of the reaction.

TABLE 19

Kinetic the reaction of highly activated compounds of the series C_6F_5R with piperidine in acetonitrile [78]

R	T, °C	k^{III}, l^2/mol^2 sec	E, kcal/mol	lg A
CF_3	20	$4.52\cdot10^{-2}$ *	6.5 ± 0.5	3.60
	25	$5.56\cdot10^{-2}$		
	30	$8.22\cdot10^{-2}$		
	40	$11.3\cdot10^{-2}$		
CN	20	$0.42\cdot10^{-3}$	5.4 ± 0.6	7.24
	30	$0.55\cdot10^{-3}$		
	40	$0.75\cdot10^{-3}$		
NO_2	20	$1.44\cdot10^{-3}$	3.6 ± 0.02	6.45
	30	$1.77\cdot10^{-3}$		
	40	$2.14\cdot10^{-3}$		
SO_2F	20	$14.6\cdot10^{-3}$	3.1 ± 0.1	7.08
	30	$17.2\cdot10^{-3}$		
	40	$20.5\cdot10^{-3}$		

* for $C_6F_5CF_3$ by the 2-order equation , l/mol sec



In the kinetic studies of the reactions of C_6F_5R with amines, the nucleophile is frequently used in excess, which allows measurement of the rates of slow reactions and calculate rate constants from the 2-order equation. On passing to highly reactive electrophiles, one should take into account the possibility of sequential and concurrent polysubstitution reactions proceeding at the rates close to the rate of substitution of the 1st fluorine atom.

Due to this the excess of amine is undesirable. Moreover, in the kinetic studies of these reactions, one should take into consideration possible change of the general order of the reaction. The analysis of kinetic data on the reactivity of highly reactive polyfluorinated substrates C_6F_5R with piperidine has shown their rate lg k values to correlate well with the σ_p (σ_p^-) values of substituents R (r=0.994 and 0.998). The correlation between lg k^{III} and σ_p^- indicates localisation of the negative charge on substituent R and thus its promotion of deprotonation of nitrogen by another molecule of amine (in terms of the base catalysis mechanism). In the electrophilic catalysis by amine, a reverse effect should be expected - the presence of correlation between Lgk of the reaction rate with the σ_p^- values for substituents R . At the same time, the preserved correlation upon substitution of σ_p^- by σ_p may indicate that the ability of substituent R to undergo direct polar conjugation with the reaction centre in the polyfluorinated ring is less significant than in the series of non-fluorinated analogues.

6. Electronic effect of oxygen-containing substituents

O^- Group. The oxy group is transformed in alkaline medium to the O^- anion , which is a strong electron donor for the resonance ortho- and para-positions of the polyfluorinated ring, due to which the O^- group is exclusively meta-orientant for the attacking nucleophile [5,17].. The strong deactivating ability of this group is shown by the comparison of rate constants for the reactions of C_6F_5H and $C_6F_5O^-$ (as a sodium or potassium salt) with sodium methoxide : $k_{C_6F_5H}/k_{C_6F_5O^-} = 10^5$ [17] . The absence of exact data on the isomer ratio of products in this reaction did not allow us to estimate the electron effect of the O^- substituent in σ units.

CH_3O and AlkO Groups . The methoxy group in the polyfluorinated ring is the electron donor for all ring positions , whereas in the non-fluorinated ring this group in the meta-position is electron acceptor σ_m =+0.10 [56] , suggesting a specific effect of the polyfluorinated ring on the electron-donating substituent. In the reaction with sodium methoxide , pentafluoroanisole is one order less reactive than pentafluorobenzene. This reaction gives all the three isomers of dimethoxytetrafluorobenzene , with a slight predominance of the para-isomer , in the ratio of ortho:meta:para =16:32:52 [59] . The electronic effect of the methoxy group in the polyfluorinated ring is represented in Table 20.

The electronic effect of AlkO groups containing C_2-C_5 alkyls is obviously similar to that of the CH_3O group, as indicated by the

TABLE 20

Reaction kinetics of substituted pentafluorobenzenes with sodium alkoxide [69]

C_6F_5R R	Reagent	Solvent	T, °C	$k \cdot 10^3$ l/mol·sec	E kcal/mol	lg A
C_2H_5O	C_2H_5ONa		90	0.9	22.8	10.7
		C_2H_5OH	100	2.3		
			120	10.2		
n-C_3H_7O	n-C_3H_7ONa		90	0.8	24	11.4
		n-C_3H_7OH	100	1.9		
			120	10.5		
n-C_4H_9O	n-C_4H_9ONa		70	0.14	23	10.8
		n-C_4H_9OH	90	0.86		
			100	2		
			120	10.2		
n-$C_5H_{11}O$	n-$C_5H_{11}ONa$		90	0.72	23.8	11.2
		n-$C_5H_{11}OH$	100	1.8		
			120	9		
$N(C_2H_5)_2$	CH_3ONa		80	7	18.6	9.4
		CH_3OH: dioxan 1:5	90	14		
			120	110		
			130	180		
$N(C_4H_9\text{-}n)_2$	CH_3ONa		90	7	17.2	8.2
		CH_3OH: dioxan 1:5	100	12		
			110	24		
			120	40		
			130	70		
$N(CH_2)_5$	CH_3ONa		80	7	20.4	10.5
		CH_3OH: dioxan 1:5	90	15		
			100	33		
			110	65		
$N(CH_2CH_2)_2O$	CH_3ONa		80	4	21.4	10.8
		CH_3OH: dioxan	90	9		
			100	20		
$N(CH_2)_6$	CH_3ONa		70	0.8	22	11.2
		CH_3OH: dioxan 1:5	90	6		
			100	13		
			110	32		
			120	52		

(continued)

TABLE 20 (cont.)

C_6F_5R R	Reagent	Solvent	T, °C	$k \cdot 10^3$ l/mol·sec	E kcal/mol	lg A
			130	100		
C_6F_5	CH_3ONa	CH_3OH-dioxan 1:5	23	240	15.6	10.9
			30	490		
			40	1040		
C_6F_5	CH_3ONa	CH_3OH	30	13	18.0	11.1
			40	34		
			50	92		
			60	190		

kinetic data for the reactions of alkoxypentafluorobenzenes with sodium alkoxides (Table 20).

$OCHF_2$ Group . Compounds C_6F_5R with this group as R reacts with sodium methoxide 6 times quicker than pentafluorobenzene and 56 times quicker than pentafluoroanisole [49] , being similar in its reactivity to pentafluoroiodobenzene [17] . In the polyfluorinated ring this group is an acceptor towards all positions, though a weaker one than in the non-fluorinated ring. The reaction rate constants have been assigned in proportion to the yield of every isomeric product. The ratio of the latter has been accepted to be similar as in the reaction of compound $C_6F_5OCF_3$ with similar properties : ortho: meta:para =11:7:82 [79] . By the inductive effect this group is a strong acceptor σ_I =+0.45 [56,57] , being electron donor by the conjugation effect and analogue of the CH_3O group by this effect. Substitution of two H atoms by F in the CH_3O group increases the inductive effect of substituent from +0.23 to 0.45 , and of the σ_p^- value from -0.18 to +0.10.

The data on the reactivity of compounds C_6F_5R (R=COX, $X=O^-$, $N(CH_2)_5$, OR ($R=CH_3$, C_2H_5), CH_3 , CF_3) in the $S_{N(Ar)}$ reactions are summarised in Table 21 . From these data we have calculated the σ_p^- values of substituents for the polyfluorinated compounds in these reactions and compared them whith the σ_p values for the non-fluorinated compounds reviewed in [56] .

COO^- Group . In the non-ionised form this group is rather a strong electron acceptor σ_p = 0.44, σ_I = 0.29 . But in the nucleophilic reactions this group certainly exists only in the ionised form. Ionisation brings about considerable changes of electronic properties: an accepting group may either become an electron donor or its influence is close to electroneutral : $\sigma_p = -0.12 - 0$, $\sigma_I = -0.12 - +0.09$. Comparison of rate constants for the reactions of pentafluorobenzene and pentafluorobenzoic acid with sodium methoxide in methanol shows that the latter in the ionised form reacts 3 times quicker in these conditions , i.e. the COO^- group in the polyfluorinated ring acts as a weak electron acceptor with $\sigma_p^- = +0.066$.

$CON(CH_2)_5$ Group . Literature contains no σ_p and σ_I values for this substituent , but these are available for its N,N-dimethyl analogue : $\sigma_p = +0.36$, $\sigma_I = +0.31$. The properties of these substituents may be suggested to be very close. Comparison of rate constants for the reaction of pentafluorobenzene and N-piperidine of pentafluorobenzoic acid with piperidine in methanol shows the latter substrate to react 340 times quicker, and $\sigma_p^- = +0.36$ for the $CON(CH_2)_5$ group found from Lgk of the rate for this reaction shows this substituent to be a strong electron acceptor, the major contribution made by the inductive mechanism ($\sigma_I \approx +0.31$) .

$COOCH_3$ Group . Compounds C_6F_5R containing the COOR groups as $R = CH_3$, C_2H_5 in the nucleophilic reactions are highly active compounds similar in their reactivity to octafluorotoluene [5,16] . Literature provides no clear-cut σ_p values for this substituent (0.44±0.09) [56] . Such variations are usually attributed to variations in the nature of the reaction centre , solvation or the angle of substituent deviation from the benzene ring plane , leading to the changed contribution of σ_R to the electronic effect of these substituents. In the nucleophilic reactions of C_6F_5COOR ,there may occur not only p-F substitution in the ring but also substitution of the OR part of the substituent by the nucleophile radical (several % of the substrate may react at different reaction centres), as , e.g., in the reaction of carbomethoxypentafluorobenzene with piperidine [16] . In the reaction with piperidine , the activating ability of the $COOCH_3$ group amounts to $\sigma_p^- = +0.57$, and for the CF_3 group , +0.60 . For the p-$COOC_2H_5$ group the activating ability decreases almost by 0.10 σ units , comprising $\sigma_p^- = +0.48$, which may be attributed to increase inhibiting effect of steric factors to the transfer of σ_R with increase of R size .

$COCH_3$ Group . This group is a strong activator for para-halogen in the benzene ring towards nucleophilic substitution , $\sigma_p^- = +0.87$ [56] , being close in its activating effect to the p-CN group. However , as shown by the kinetic studies of the reactivity of pentafluoroacetophenone with piperidine and p-toluidine (see Table 21) , in the poly -

TABLE 21

Kinetic data for the reaction of the compounds C_6F_5R with various nucleophiles

R	T, °C	Nucleophile	Solvent	$k \cdot 10^5$ l/mol·sec	$k_{rel.}$	lg k	E, kcal/mol (lg A)	σ_p	σ_I
H	50	CH_3ONa	CH_3OH	8.3	1	-4.08	22.6 (11.2) [13]	0	0
COO^-	50	CH_3ONa	CH_3OH	24	2.9	-3.62	19.1 (9.3) [29]	-0.05 [56]	-0.12 [56]
H	50	$C_5H_{10}NH$	CH_3OH	0.041	1	-6.39	16.4 (4.9) [16]	0	0
$CON(CH_2)_5$	50	$C_5H_{10}NH$	CH_3OH	14	340	-3.87	10.6 (3.3) [16]	0.36 [56]	0.31 [56]
$COOCH_3$	50	$C_5H_{10}NH$	CH_3OH	360	8870	-2.44	9.9 (4.3) [16]	0.44 [56]	0.32 [56]
$COCH_3$	50	$C_5H_{10}NH$	CH_3OH	$1.4 \cdot 10^3$	$3.4 \cdot 10^4$	-1.87	10.3 (5.1) [16]	0.47 [56]	0.29
CF_3	50	$C_5H_{10}NH$	CH_3OH	590			7.0 (2.5) [16]	0.54	
H	106	C_6F_5ONa	N,N-DMAA	-	1 [48]	0	-	0	0
$COOC_2H_5$	106	C_6F_5ONa	N,N-DMAA	-	2900 [48]	3.46	-	0.45	0.32
H	100	$4\text{-}CH_3C_6H_4NH_2$	CH_3OH	$2.2 \cdot 10^{-3}$	1	-7.66	-	0	0
$COCF_3$	100	$4\text{-}CH_3C_6H_4NH_2$	CH_3OH	66	$3 \cdot 10^4$	-3.18	13.1 (4.49) [20]	0.80 [56]	0.59 [56]
$COCH_3$	100	$4\text{-}CH_3C_6H_4NH_2$	CH_3OH	7	$3.2 \cdot 10^3$	-4.14	15.6 (5) [20]	0.47 [56]	0.29 [56]

fluorinated ring the electron-accepting ability of this substituent is 0.22 σ units lower, which seems to be due to stericoelectronic effects arising from interaction of the COR group with o-F of the ring. Nevertheless, in the polyfluorinated ring this substituent strongly activates substitution of p-F, being close in this to the effect of the p-CF_3 group.

$COCF_3$ Group. With H substituted by F in the $COCH_3$ group, it shows increased electron-accepting ability : from $\sigma_p = 0.47 \pm 0.10$, $\sigma_I = 0.29 \pm 0.05$ to $\sigma_p = 0.80$ and $\sigma_I = 0.59$ [56]. For the polyfluorinated compounds with this substituent, the rate of the reaction with p-toluidine is one order higher than for the respective compounds with the $COCH_3$ group, which comprises 0.18 σ units. In its electron-accepting effect ($\sigma_p^- = 0.86$) in the polyfluorinated ring, the $COCF_3$ substituent is similar to the p-CN group.

7. Nitrogen-containing heterocyclic compounds. The activating effect of ring nitrogen heteroatom

The synthetic aspects of poly(fluoro-, chloro-)pyridines have been covered in detail, starting from 1972, in review [80]. The kinetic data for the reactions of such compounds with nucleophilic reagents have only been obtained during the last decade, by the English researchers [22,81,82].

On the basis of synthetic data analysis, it has been shown in [80] that substitution of the -FC= fragment of the polyfluorinated ring by the nitrogen heteroatom leads to substantial activation of ring fluorine atoms to the nucleophilic substitution reactions, and that in the efficiency of electron-accepting effect the nitrogen heteroatom approximates such strong accepting substituents as the p-CN and p-NO_2 groups. The analysis of σ values of nitrogen heteroatom for different reaction series [83] confirms these conclusions obtained at the quantitative level in [80]. The kinetic data obtained by the English researchers and the σ values of nitrogen heteroatom reported in [83] (Table 22). suggest that in pentafluoropyridine the most activated position is the para- or 4-position, somewhat less activated is the 2-position, and the least activated is the 3-position of the ring towards nucleophilic substitution reactions.

The transfer of electronic effect by substituents in azines has many specific features, and this problem has been treated in review [84]

Table 23 summarises some kinetic data for the reactions of various polyhalopyridines with ammonia and sodium methoxide [36,81],

TABLE 22

σ-Constants for the pyridine ring nitrogen atom [83]

σ (σ^-)			Solvent	Reaction
α	β	γ		
0.75	0.65	0.96	85%-CH_3OH 15%-H_2O	Alkaline hydrolysis of methyl benzoates
1.00	0.59	1.17	100%-CH_3OH	Methanolysis of halogeno-pyridines

TABLE 23

Reaction kinetics of certain polyhalogenopyridines with sodium methoxide (a) in methanol at -7.6°C [36] and with ammonia (b) in a water-dioxan solution at 25°C [81]

Compound	Direction of the attack	a $k \cdot 10^4$ [36] l/mol·sec	b k [81] l/mol·sec
pentafluoropyridine	4	$1.9 \cdot 10^4$	$6.8 \cdot 10^{-4}$
2.3.4.6-tetrafluoropyridine	4	$2.42 \cdot 10^2$ *	$2.2 \cdot 10^{-5}$
	2	3	$5.9 \cdot 10^{-6}$
2.3.4.5-tetrafluoropyridine	4	$6.42 \cdot 10^2$	$2.9 \cdot 10^{-5}$
2.3.5.6-tetrafluoropyridine	2.6	$3.47 \cdot 10^{-1}$ **	
4-chloro-2.3.5.6-tetrafluoro-pyridine	2.6	20.9 **	
4-chloro-2.3.6-trifluoro-pyridine	2	63.7	
2.4.6-trifluoropyridine	4	6.28	$0.7 \cdot 10^{-6}$
	2.6	$5 \cdot 10^{-1}$ **	$0.2 \cdot 10^{-6}$

NOTES : * Separation of k is carried out by the NMR and GLC data.
** Corrected with an account of the statistic factor.

which suggest a high reactivity of these compounds.

Unfortunately, the authors of these works do not compare the reactivity of these compounds and the typical well-studied fluoroaryls, such as 2.4-dinitrofluorobenzene and p-nitrofluorobenzene, which would allow a deeper analysis of halogen electronic effect in the heteroaromatic nucleus.

In the article [70] authors have demonstrated that in the reaction of $Re(CO)_5^-$, $Mn(CO)_5^-$ and $CpW(CO)_3^-$ ($Cp = C_5H_5$) with hexafluorobenzene and pentafluoropyridine, and $CpFe(CO)_2^-$, $Re(CO)_5^-$, $Mn(CO)_5^-$, $CpW(CO)_3^-$, $CpMo(CO)_3^-$ with 2-(pentacarbonylmanganese)-4,6-difluoro-1,3,5-triazine contact ion pairs are markedly more reactive than both solvent-separated ion pairs and free ions.

Introduction of two nitrogen heteroatoms into the polyfluorinated ring, depending on their mutual position, sharply increases or slightly reduces the reactivity of a substrate [82]. On passing from pentafluoropyridine to tetrafluoropyrazine where a second nitrogen atom is para to the first one, the rate constant for the reaction with ammonia decreases 13-fold (Table 24).

TABLE 24

Reaction kinetics of fluorinated azines with ammonia in water-dioxan (60:40) at 25°C [82]

Compound	Direction of the attack	k l/mol·sec	$k_{rel.}$
pentafluoropyridine	4	$2.8 \cdot 10^{-2}$ *	
	4	$6.8 \cdot 10^{-4}$	1
4-chloro-2,3,5,6-tetrafluoropyridine	2	$1.6 \cdot 10^{-6}$	$2.28 \cdot 10^{3}$
tetrafluoropyrimidine	4	1.35	$2 \cdot 10^{3}$
trifluoro-s-triazine	-		$\sim 10^{5}$
tetrafluoropyridazine	4	$2.5 \cdot 10^{-2}$	$3.7 \cdot 10^{1}$
tetrafluoropyrazine	-	$5.1 \cdot 10^{-5}$	$7.46 \cdot 10^{-2}$

* 80°C

On passing from pentafluoropyridine to the diazine with mutually ortho nitrogen heteroatoms, the reactivity of the substrate increases 37-fold. The greatest effect is observed with meta-position of heteroatoms. The respective tetrafluoro-meta-diazine (tetrafluoropyrimidine) is 2000 times more reactive than pentafluoropyridine.

Introduction of a third nitrogen atom into the cycle, e. g. on passing from tetrafluoropyrimidine to symm. trifluorotriazine, as shown in [82], raises the reactivity of the substrate by 2 orders more. The rate of the reaction of the substrate with ammonia increases to such an extent that become difficult to measure [82].

Thus, all polyfluorinated azines are highly reactive compounds, which allows to use them as arylating agents in the very slow $S_{N(Ar)}$ reactions.

The kinetic data on the reactivity of polyfluorinated azines obtained by the English researchers considerably facilitate synthetic planning in this series of compounds.

8. Factors governing the rate of nucleophilic substitution reactions in the polyfluorinated ring

The rate of nucleophilic substitution reactions in the polyfluorinated ring depends on the nature of activating substituent R, nucleophile and solvent. The effect of the two first factors has already been considered above. Let us discuss the medium effect on the rate of $S_{N(Ar)}$ reactions of the polyfluorinated compounds.

8.1. Solvent effect

Medium effect on the rate constant has been studied most completely for the reaction of hexafluorobenzene with piperidine [85,86], whereas for the reaction of piperidine with different C_6F_5R (R = H, F, Cl, C_6F_5, CF_3, and $COCH_3$), only the effect of three solvents has been investigated - hexane, dioxan and methanol [16]. The effect of DMSO has been considered for the reactions of piperidine with C_6F_5R (R = $N(CH_2)_5$, CH_3, H, F, and Cl) [42]. The use of the electroconductivity method allowed to measure the rate constants for the reactions of piperidine with rather reactive compounds C_6F_5R (R = CN, NO_2) [78] catalysed by a strong catalyst for these reactions - acetonitrile. Let us discuss in detail the solvent effect on the rate constant of the reaction of piperidine with hexafluorobenzene.

The lowest rate for this reaction has been reported in the non-polar and non-solvating solvent - n-hexane (ε = 1.9), and the highest - in the highly polar solvent - DMSO (ε = 48.5), the rate constant increasing on passing from n-hexane to DMSO by almost 4 orders (~ 6000 -fold) (Table 25). The other solvents occupy a medium place in the effect on the reaction rate, the dominating solvents among them being the aprotic bipolar solvents - DMF, sulpholan, and DMSO (the strongest catalysts for this reaction), as well as acetonitrile, benzonitrile, and nitrobenzene whose effect is one order weaker than

TABLE 25

Effect of solvents on the velocity constant of the reaction of hexafluorobenzene with piperidine at 140°C [85,86]

Solvent s	(25°C) ε	E kcal/mol	lg A	$k_{rel.}$ * k_s/k_{hexane}
n-hexane	1.9	10.4	0.3	1
dioxan	2.2	14.3	4.0	43
benzene	2.27	13.4	2.6	5
hexafluorobenzene	-	9.4	0.37	4
anisol	4.3	15.2	4.2	20
N,N-dimethylaniline	5.0	10.7	1.9	30
chlorobenzene	5.6	8.9	0.4	12
N-(n-amyl)piperidine	-	15.0	3.6	7
piperidine	5.8	10.2	2.4	160
aniline	7.0	11.7	3.3	220
tetrahydrofuran	7.4	9.1	1.4	60
1.2-dimethoxy ethane	9.5	10.9	2.2	40
t-C_4H_9OH	10.9	19.1	6.0	10
n-C_4H_9OH	17.7	13.7	3.1	12
n-$C_6H_{11}OH$	11.8	14.9	3.3	14
pyridine	12.3	11.7	3.7	500
2-ethoxyethanol	13.7	-	-	54
acetophenone	17.4	11.2	3.0	180
acetone	20.7	9.6	2.0	120
n-C_3H_7OH	20.0	19.9	6.6	19
C_2H_5OH	25.2	14.5	3.7	18
benzonitrile	26	10.3	2.8	370
CH_3OH	32.6	15.5	4.4	25
nitrobenzene	34.8	12.3	3.4	118
CH_3CN	37.4	11.3	2.9	120
CH_3NO_2	38.5	18.0	7.2	800
ethyleneglycol	38.7	8.0	0.7	43
triethyleneglycol	26.5	12.6	3.8	210
N,N-dimethylformamide	37.6	10.9	3.7	1400
sulpholane	44	14.6	5.7	1500
dimethylsulphoxide	48.5	12.5	5.2	6000

* where, in $k_{hexane} = 6.3\ 10^{-6}$ l/mol sec (140°C)

that of the former. More efficient than the latter is pyridine. Among other amines catalysing this reaction, the most efficient are those in which the nitrogen atom is the least screened one. Rather efficient is the reagent itself (piperidine) [12], but its analogue, -N-amylpiperidine, containing a bulky radical at nitrogen, is 20 times weaker as a catalyst for this reaction. Comparison of physico-chemical parameters of 30 solvents whose influence was considered for this reaction shows that the solvent effect on the reaction rate increases with polarity (ε) and its ability to nucleophilic catalysis.

Comparison of the relative effect of the same solvents on the rate constants for the reactions of piperidine with two fluoroaryls with close reactivity one of which is an activated monofluorobenzene and the other - a polyfluoroaryl (hexafluorobenzene)) has shown that the reactions of polyfluoroaromatic compounds with amines are less sensitive to the solvent catalysis, which is typical for the para-substituted halobenzenes [86,87]. Therefore the smaller sensitivity of the reaction of hexafluorobenzene with piperidine to the solvent catalysis as compared to the similar reaction with p-nitrofluorobenzene has been attributed to the ortho-effect of fluorines according to the "built-in" solvation type [86]. Similar tendencies in solvent effect on the rate constant have been observed for the reactions of compounds C_6F_5R with p-toluidine [20]. Due to a considerably lower reactivity of p-toluidine as compared with piperidine, medium effect on the rates of these reactions has been studied only for the reaction of this compound with a highly activated compound - octafluorotoluene. The lowest rate constant has been reported for the non-polar non-solvating solvent - n-hexane, and the highest for DMSO, the k_{DMSO}/k_{hexane} ratio comprising about 30000. These studies have shown that, by varying a solvent, it is possible to accelerate or slow down the reactions of polyfluoroaromatic compounds with uncharged nucleophiles by 3 or 4 orders. Notwithstanding the advances in these studies, important technological problems have not as yet been solved, such as ease and completeness of solvent separation from the reaction products for their recycling, and lowering the energy consumption in solvent regeneration. Therefore we believe that the search for cheap, highly efficient and easy-regenerating solvents will go on.

Generally alcohols (or phenols) are used as solvents for the reactions of C_6F_5R with charged reagents - alkaline metal alkoxides and phenoxides. In these solvents, the cation and anion of the reagent are strongly solvated, therefore, to increase the reaction rate, the solvents should be used with the additions desolvating the reagent anion, which would solvate well the metal cation. The solvents generally used as such additions are the aprotic bipolar solvents - dioxan [17] and DMSO [37], the latter being rather efficient : substitution of 90% of methanol by DMSO raises the rate of the reaction of hexafluorobenzene with sodium methoxide by 5 orders [37]. Similar results were reported in [88] which studied the effect of methanol-DMSO binary system on the rate constant of the reaction of p-nitrofluorobenzene with sodium methoxide. The suggested mechanisms of the catalytic effect of DMSO and dioxan in nucleophilic substitution reactions have been discussed in [89]. The kinetic studies of the reactions of hexafluorobenzene [49] and pentafluoromethylbenzoate with sodium methoxide in binary mixtures of methanol with non-polar solvents indicate participation of ortho-fluorines in this reaction according to the "built-in" solvation type.

During recent years, studies have been carried out on the use of liquid ammonia as an effective catalytic medium for some reactions of fluoroaryls (including the polyfluorinated ones) with charged reagents [90,91]. Liquid ammonia is especially valuable and prospective for the reactions of polyfluoroaromatic compounds where the solvent is simultaneously a reagent.

Liquid ammonia is a polar solvent (ε = 25.4), it dissolves well some salts, hydroxides and alkoxides. Its advantage as a solvent is ease of its separation from the reaction products. It works as a solvent in the temperature range of -77°C (m.p.) to -33.4°C (b.p.). As reported in [90,91], a number of $S_{N(Ar)}$ reactions with charged reagents were carried out in liquid ammonia in very mild conditions and at a high rate. Thus the reactions of ortho- and para-nitrofluorobenzenes with sodium methoxide in liquid ammonia at -70°C have been shown, to proceed 9 orders quicker than in methanol.

The available literature data on the use of liquid ammonia as the reaction medium suggest it to be a prospective solvent for the low-temperature reactions of polyfluoroaromatic compounds with charged reagents.

9. Fluorine : halogen ratio in the $S_{N(Ar)}$ reactions of activated mono- and polyfluorobenzenes

The 2-step character of the nucleophilic aromatic substitution where the process of intermediate complex formation is rate-determining for the whole process [92] is suggested to be the main reason for the higher reactivity of fluoroaryls as compared to similar bromo- and iodoaryls [93]. Let us consider the fluorine : halogen ratio with halogen Cl , taking this to be the rate constant ratio for the nucleophilic reactions of fluoro- and chloroaryls having the same aryl fragment. For the nucleophilic substitution reaction of activated monochloro- and monofluorobenzenes with alkoxides, phenoxides, thiophenoxides and amines, the fluorine to chlorine ratio varies depending on the reagent, solvent and aryl radical structure within 1 to 3 orders [92,93].

It would be reasonable to suggest that on passing from the activated monofluoroaryls to other activated compounds of the aromatic series - namely, to polyfluoropolyhalobenzenes of the type of $C_6F_nHal_{6-n}$ where Hal = Cl, Br, I, the ratio between the nucleophilic substitution rates (fluorine/halogen) will remain within 1 to 3 orders, which indicates the exclusive substitution of fluorine in these compounds.

Indeed, at first Burdon [94], and afterwards Bolton and Sandall [95], showed that in the reaction of pentafluorochlorobenzene, as well as polyfluoropolychlorobenzenes, with sodium methoxide, exclusively the fluorine atom in the ring is substituted, the chlorine atom remaining intact. This suggests the fluorine to chlorine ratio to remain within $\sim 10^2$. On passing from pentachlorofluorobenzene [13], where the replacea group is fluorine, to hexachlorobenzene with chlorine being the replaced group [96], the reaction rate constant decreases by 2 orders. Similarly, it has been shown for polyfluorobromo- and iodobenzenes that the replaced group is exclusively the fluorine atom, whereas bromine and iodine do not react, acting only as the para-orienting electron-accepting substituents [17,29].

10. Interaction of fluorine anion with polyfluoroaromatic compounds

The second step of $S_{N(Ar)}$ reactions of polyfluoroaromatic compounds involving the decomposition of the intermediate σ-complex to end products is regarded to be an irreversible process. But does this apply to all nucleophilic substitution reactions? Some authors attributed some by-products to the reverse reaction initiated by the fluorine anion attack on the reaction product [97,98]. In particular, the reaction of pentafluorophenol with pentafluoropyridine gave '-unexpected' products : 2-(pentafluorophenoxy)-3,4,5,6-tetrafluoro- and 2,6-bis-(pentafluorophenoxy)-3,4,5-trifluoropyridines from bis-(pentafluorophenoxy)-3,5,6-trifluoro- and 2,4,6-tris-(pentafluorophenoxy)-3,5-difluoropyridines.

But these works give no kinetic data for these reactions, which would provide information on the reactivity of the fluorine-anion. The possibility of direct kinetic measurements involving F^- has appeared only recently when alkaline metal fluorides with the radioactive fluorine isotope ^{18}F became available. The kinetic studies on isotope exchange between ^{18}F and pentafluorobenzenes C_6F_5X (X = H, Cl, Br) in DMSO carried out in [99] indicate the 2-step character of the $S_{N(Ar)}$ reaction in the polyfluoroaromatic series and allow to estimate the contribution of the rate of nucleophilic substitution by the fluorine anion (Table 26).

TABLE 26

Reaction kinetics of compounds of the type C_6F_5X with $^{18}F^-$ in DMSO [99]

T, °C X	$k \cdot 10^3$, l/mol·sec 40	50	60	70	90	$k_{rel.}$ at 60°C
H	0.03	0.13	0.47	1.5	-	1
Cl	2.2	6.0	20	60	-	43
Br	1.7	4.2	9.8	25	-	21
F	0.21	0.67	2.0	5.9	42	4.3

Thus comparison of rate constants for the reaction of hexafluorobenzene with sodium methoxide in methanol-DMSO (1:9) [37] and of hexafluorobenzene with potassium fluoride containing the radioactive fluorine isotope, in DMSO [99] shows that at 25°C the rate of the reaction of fluorine anion with the substrate is 2 orders smaller than with sodium methoxide. In fact this difference is larger, as on passing from methanol-DMSO (1:9) to DMSO the rate constant for the reaction of hexafluorobenzene with sodium methoxide increases (if the graphic correlation of lg k vs. the mole proportion to pure DMSO is extrapolated) by at least one order, and the ratio of 'nucleophilicities' $k_{CH_3O^-}/k_{F^-}$ actually increases to 3 orders.

The similar ratio (3 orders) between the nucleophilicities of fluorine anion and sodium methoxide has been obtained for the reactions of the fluorine anion with polychloro(fluoro)benzenes in sulpholane [100,101], and of the same compounds with sodium methoxide. The same results are obtained in comparison of the data obtained by G.Yakobson with co-workers [102] for the reaction of fluorine anion with chloroaryls catalysed by crown ethers with the kinetics data for the reactions of the same substrates with sodium methoxide.

The data presented in [99] indicate the efficiency and informativity of the tracer method in the kinetic studies of nucleophilic reactions in the polyfluoroaromatic series. The data of [97 - 99] allowed to predict conditions for the "reverse" reaction between the fluorine anions and the products of the main reaction : a. low reactivity of the nucleophile comparable with that of F^- ; b. the reaction product is a highly activated substrate easy reacting with nucleophiles; c. the reaction is conducted in a solvent with highly catalytic properties. In this case control of the reaction should be dual : over consumption of the reagents and over accumulation of the reaction products.

CONCLUSION

The reviewed papers show that the aromatic nucleophilic substitution reactions in the series of polyfluoroaromatic compounds attract close attention of fluoroorganic chemists. The results of kinetic studies are very important for understanding the factors determining the rate and mechanism of the $S_{N(Ar)}$ reactions in the polyfluoroaromatic series. Thus the analysis of the products of the reactions of polyfluoroaromatic compounds with a superbase - sodium amide - in liquid ammonia provided evidence for the radical - anion mechanism of these $S_{N(Ar)}$ reactions [103]. Though the lifetime of radical - anions is small, their formation is unambiguously indicated by the analysis of the products of reaction with electrophiles - methyl iodide and the starting compound. These data complement the picture of radical reactions of aromatic compounds with nucleophilic reagents [104].

It has been generally concluded that no qualitative changes in studies on the nucleophilic substitution reactions are possible without investigating changes in the electronic structure of organic molecules in the course of reactions. Unfortunately, there has been no marked progress in this direction. Instead of the one-sided approach involving only accumulation of new experimental data, future efforts in developing polyfluoroaromatic chemistry should combine experimental work with the theoretic studies including the quantum-chemistry calculations. This is still a complex and difficult problem. Thus attempts to explain orientation of the nucleophilic attack in the series of polyhalobenzenes by theoretical calculations led to results which are in poor agreement with experiment. For better understanding of the orienting effect of substituents (R = H, OH, NH_2) under the action of different nucleophiles the author of [105] has carried out MNDO calculations of the heat of formation of various σ-complexes in $S_{N(Ar)}$ reactions. The calculation results however are in poor agreement with the experimentally observed orientation of nucleophile. The reasons seem to be in the approximations, which do not allow for some effects. Thus in the calculations of substituent effect on stabilisation of Meizenheimer complex, the unsubstituted arene system is taken as a basis. The effect of fluorines as substituents, especially those in meta-positions, on molecular orbital energy was not taken into account. Besides, these calculations were carried out for gas phase and do not allow for solvation contribution, though it may be rather significant, as may be seen from the data reviewed here.

Thus there are no radically new approaches to the determination of the nucleophilic attack in the polyfluorinated ring by calculations, except some simple particular cases. New approaches should take into account at once the electronic and solvation effects, and the nature of nucleophile in the process. Solution of this problem remains one of the most interesting and fascinating problems of theoretic organic chemistry.

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