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Synthesis and Reactivity of Difluoroaromatic Compounds Containing Heterocyclic Central Groups

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Abstract—The reaction of trichloroacetaldehyde with fluorobenzene, followed by a series of transformations, gave 4-fluorobenzil and 4,4'-difluorobenzil which were used in the synthesis of new difluoroaromatic compounds with a heterocyclic central group. The ^{1}H, ^{13}C, and ^{19}F NMR spectra of the newly synthesized difluoroaromatic compounds were studied. The charge densities on the carbon atoms attached to fluorine were calculated in terms of the PM3 and AM1 semiempirical approximations. A correlation was found between the charge on C(F) and the corresponding ^{13}C and ^{19}F chemical shifts. Using this correlation, the reactivity of difluoroaromatic compounds in nucleophilic substitution reactions was estimated.

Difluoroaromatic compounds having electron-withdrawing groups (such as CO, SO_2, etc.) attract much interest as monomers for the synthesis of aromatic polyethers [1–4]. In the recent years, considerable attention was given to compounds containing other, specifically heterocyclic activating groups [5]. On the other hand, the electronic structure of difluoroaromatic compounds and the effect of the central fragment on the electron density distribution in their molecules have been studied insufficiently.

In the present work we used semiempirical quantum-chemical methods and NMR spectroscopy to examine the effect of central heterocyclic fragments on the electron density distribution in difluoroaromatic compounds. Insofar as the reaction center in such compounds is usually the aromatic carbon atom linked to fluorine (C^4-F), our attention was mainly focused on the variation of electron density on the C^4-F bond.

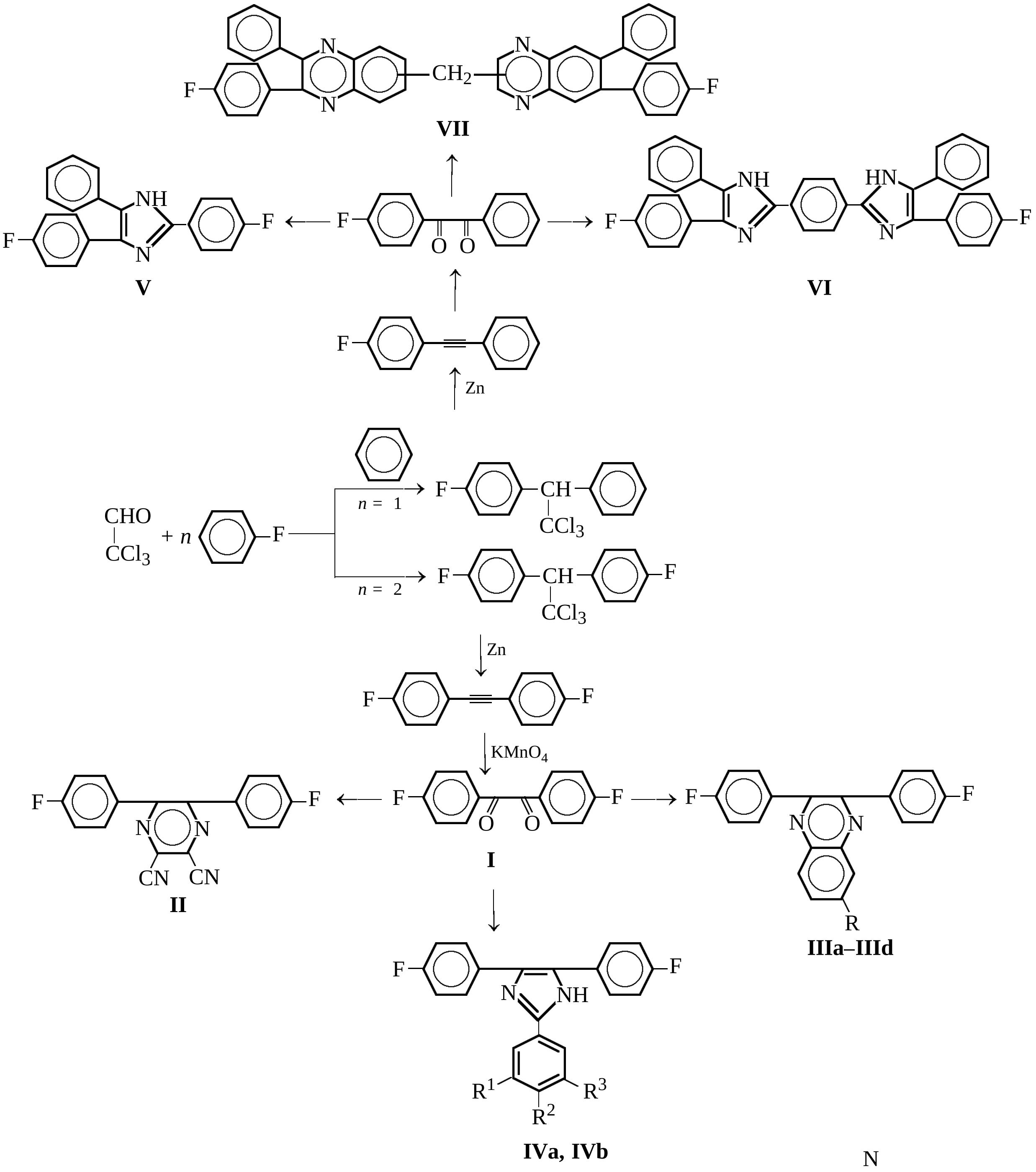
By analogy to the synthesis of bromoaromatic compounds [6], one of the simplest synthetic routes to compounds possessing quinoxaline-2,3-diyl, 2,3-dicyanopyrazine-5,6-diyl, and 2-arylimidazole-4,5-diyl fragments as central moieties seems to include preparation and subsequent transformations of 4-fluorobenzil and 4,4'-difluorobenzyl [7] (Scheme 1). 4-Fluorobenzil was synthesized by reaction of trichloroacetaldehyde with fluorobenzene and benzene, and 4,4'-difluorobenzil was obtained by reaction of trichloroacetaldehyde with 2 equiv of fluorobenzene [8] and subsequent transformations of the products, 1,1,1-trichloro-2-(4-fluorophenyl)-2-phenylethane and 1,1,1-trichloro-2,2-bis(*p*-fluorophenyl)ethane, into 4-fluorodiphenylacetylene and 4,4'-difluorodiphenylacetylene [9], respectively. The latter were then oxidized [10] to 4-fluorobenzil and 4,4'-difluorobenzyl.

The structure of the products was confirmed by elemental analyses and NMR and IR spectra (Tables 1 and 2). By analogy with [11], we tried to estimate the reactivity of the newly synthesized difluoroaromatic compounds. For this purpose, we performed PM3 and AM1 quantum-chemical calculations of the charge densities q_{C-F} on the C(F) carbon atoms which are reaction centers in nucleophilic substitution. We also measured the chemical shifts of the carbon and fluorine atoms in the ^{13}C and ^{19}F NMR spectra.

The results (Table 3) show that electron-withdrawing substituents act to reduce the electron density on the fluorine atom and carbon atom attached thereto. As the electron-acceptor power of the substituent increases, the reactivity toward nucleophiles increases. The observed increase of the charge density on C^4(F) is consistent with that expected on the basis of general concepts of the substituent effect in aromatic compounds [12]. A satisfactory correlation is observed between the charges on the carbon and respective fluorine atoms (Table 3).

The tendency in the variation of electron density on the aromatic C^4(F) atom, predicted by the calculations, is supported by the ^{13}C and ^{19}F NMR data. The ^{13}C–F resonances in the spectra of **I**–**VII** linearly

Scheme 1.



III, R = H (**a**), CH_3 (**b**), Br (**c**), COOH (**d**); **IV**, $R^1 = R^3 = H$, $R^2 = Br$ (**a**); $R^1 = R^3 = OCH_3$, $R^2 = H$ (**b**).

shift downfield as the charge density on C^4 increases (Table 3). An analogous pattern is typical of the ^{19}F NMR spectra of these compounds. A satisfactory correlation exists between the ^{13}C and ^{19}F chemical shifts and calculated charge densities on C^4 (Table 3). Both calculation methods predict similar trends in the variation of electron density on the carbon atom attached to fluorine.

Comparison of the ^{13}C and ^{19}F chemical shifts of difluoroaromatic compounds with those found for typical activated monomers, such as difluorobenzil

Table 1. Yields, melting points, and elemental analyses of difluoroaromatic compounds **I–VII**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	F	N		S	N	F	N
I	70	121–123	68.31	3.35	15.69	11.21	$C_{14}H_8F_2O_2$	68.29	3.24	15.43	11.37
II	50	254–256	67.81	2.48	11.63	17.25	$C_{18}H_8F_2N_4$	67.93	2.53	11.94	17.60
IIIa	97	134–136	75.38	3.81	12.05	8.61	$C_{20}H_{12}F_2N_2$	75.46	3.79	11.93	8.79
IIIb	91	159–161	75.39	4.21	11.40	8.19	$C_{21}H_{14}F_2N_2$	75.89	4.24	11.43	8.42
IIIc	89	168–170	66.23	3.15	11.21	11.32	$C_{20}H_{11}F_2N_3O_2$	66.11	3.05	10.45	11.56
IIId	95	261–263	69.35	3.23	10.69	7.42	$C_{21}H_{12}F_2N_2O_2$	69.61	3.33	10.48	7.73
IVa	86	266–268	61.09	3.09	9.14	6.75	$C_{21}H_{13}BrF_2N_2$[a]	61.33	3.18	9.24	6.81
IVb	81	225–227	70.11	4.63	9.75	7.21	$C_{23}H_{18}F_2N_2O_2$	70.40	4.62	9.68	7.13
V	87	192–194	75.49	4.21	11.35	8.35	$C_{21}H_{14}F_2N_2$	75.89	4.24	11.43	8.42
VI	83	> 400[b]	78.44	4.42	6.81	10.05	$C_{36}H_{24}F_2N_4$	78.52	4.39	6.90	10.17
VII	90	213–215	80.49	4.41	6.35	9.01	$C_{41}H_{26}F_2N_4$	80.37	4.27	6.20	9.14

[a] Found Br, %: 19.09. Calculated Br, %: 19.42. [b] Decomposes without melting.

Table 2. NMR spectral parameters of compounds **II–VII**

Comp. no.	Chemical shifts δ, ppm ($CDCl_3$)		
	^1H	^{13}C	^{19}F
II	7.59–7.55 m (2H), 7.30–7.26 m (2H)	164.54 (Ar–F), 162.06 (Ar–F), 15378, 132.18, 132.09, 131.82, 129.78, 115.87, 115.65, 113.86	–108.38
IIIb	8.03–8.00 d (1H, *J* 84 Hz), 7.91 s (2H), 7.60–7.58 d (2H, *J* 8.8 Hz), 7.49–7.45 m (4H), 7.05–7.00 m (4H), 2.59 s (3H, CH_3)	164.24 (C–F), 164.19 (C–F), 161.76 (C–F), 161.72 (C–F), 151.85, 151.10, 141.10, 140.64, 139.52, 135.00, 134.97, 132.39, 131.65, 131.62, 131.56, 125.54, 128.48, 127.79, 115.40, 115.19, 21.75 (CH_3)	–111.79
IIIc	9.00 s (1H), 8.51–8.49 d (1H), 8.26–8.24 d (1H), 7.59–7.54 m (4H), 7.11–7.06 m (4H)	164.91 (C–F), 164.83 (C–F), 162.41 (C–F), 162.33 (C–F), 154.81, 154.21, 147.91, 143.33, 139.78, 133.97, 133.94, 133.91, 133.87, 131.91, 131.82, 131.80, 131.71, 130.57, 125.35, 123.31, 115.74, 115.52	–109.61, –109.89
IIId	8.59 s (1H), 8.28 d (1H), 8.18–8.15 d (1H), 7.54–7.51 m (4H), 7.25–7.21 m (4H)	166.67 (C=O), 164.44 (C–F), 164.39 (C–F), 161.94 (C–F), 161.69 (C–F), 153.81, 153.18, 142.37, 139.75, 134.82, 132.28, 132.22, 132.14, 130.76, 129.69, 129.31, 115.43, 115.21	–111.03, –111.213
IVa	12.77 s (1H, NH), 7.96–7.94 d (2H), 7.64–7.62 d (2H), 7.49–7.45 m (4H), 7.22–7.11 m (4H)	163.16 (C–F), 160.62 (C–F), 150.50, 150.12, 137.12, 135.81, 135.09, 134.56, 132.64, 127.06, 120.77	–114.39, –112.48
IVb	12.42 s (1H, NH), 7.56–7.41 m (4H), 7.22 s (2H), 7.21–7.09 m (4H), 6.49 s (1H), 3.88 s (6H, CH_3)	163.11 (C–F), 160.67(C–F), 150.91, 137.26, 135.29, 120.92, 120.71, 108.74, 106.24, 60.80, 35.98	–112.67, –114.31
V	12.66 s (1H, NH), 8.14–7.13 m (13N)	163.40 (C–F), 162.26 (C–F), 160.91 (C–F), 159.70 (C–F), 144.70 (4), 136.12, 134.95, 131.59, 130.90, 130.46, 128.88, 128.81, 128.61, 128.34, 128.13, 127,74, 127.35, 127.26, 127.03, 126.96, 126.48, 115.62, 115.41, 115.03, 114.82, 35.40	–112.49, –113.00, –115.02
VI	12.79 s (2H, NH), 8.25–7.06 m (26H)	163.51 (C–F), 160.25 (C–F), 145.11, 131.41, 130.62, 130.12, 128.68, 128.42, 128.22, 128.05, 127.53, 127.42, 127.15, 127.03, 126.85, 126.23, 115.42, 115.22, 35.86	–113.06
VII	8.12–8.08 m (2H), 8.04–8.02 m (2H), 7.69–7.66 m (2H), 7.51–7.48 m (8H), 7.34–7.31 m (6H), 7.03–6.97 m (4H), 4.47 s (2H, CH_2)	164.24 (C–F), 161.76 (C–F), 153.36, 152.89, 152.36, 151.91, 142.35, 142.33, 141.19, 141.14, 140.05, 139.99, 139.78, 134.95, 134.92, 131.69, 131.61, 129.60, 129.35, 129.25, 128.79, 128.76, 128.46, 128.36, 128.27, 128,25, 115.33, 115.11, 42.08 (CH_2)	–112.08

and difluorobenzophenone, and nonactivated fluorobenzene provides information on their reactivity and makes it possible to estimate the relative reactivity in the series of quinoxalines **IIIa**–**IIId**. The ^{19}F chemical shifts for the more reactive monomer, 2,3-bis-(4-fluorophenyl)-6-nitroquinoxaline (**IIIc**), are δ_F –109.61 and –109.89 ppm (two different resonances appear since the molecule is unsymmetrical). The less reactive 2,3-bis(4-fluorophenyl)quinoxaline (**IIIa**) is characterized by a δ_F value of –111.95 ppm. The ^{19}F chemical shift of 2,3-dicyano-5,6-bis(4-fluorophenyl)-pyrazine (**II**) is equal to –108.38 ppm. In keeping with our previous data [11], difluoroaromatic compounds with δ_F larger than –110 ppm are activated to nucleophilic substitution to a sufficient extent. This means that compounds **IIIc** and **II** are sufficiently reactive to obtain polymers therefrom. When δ_F ranges from –110 to –112 ppm, more severe conditions are necessary to effect polymerization. The chemical shifts δ_F of compounds **IIIa**, **IIIb**, **IIId**, and **VII**, which are activated due to the presence of quinoxaline fragment, indicate that these compounds can be involved in nucleophilic aromatic substitution, in keeping with the data of [13]. Difluoroaromatic compounds with δ_F values equal to or lower than –112.77 ppm (fluorobenzene) do not undergo polymerization. Actually, our attempts to obtain polymeric products from imidazole derivatives **IVa**, **IVb**, **V**, and **VI** were unsuccessful. Presumably, the imidazole ring is a stronger electron donor than benzene.

The ^{13}C chemical shifts of difluoroaromatic compounds (difluorobenzophenone, difluorobenzil) which successfully react with nucleophiles, range from δ_C 164.5 to 166.7 ppm, whereas nonactivated fluorobenzene is characterized by a δ_C value of 162.29 ppm [13]. The chemical shifts of C(F) for compounds **II**, **IIIa**–**IIId**, and **VII** having pyrazine and quinoxaline central fragments appear in the region of ~163 ppm, and they are capable of undergoing nucleophilic substitution [13]. Compounds **IVa**, **IVb**, **V**, and **VI** are characterized by δ_C values lower than 162.29 ppm; therefore, they are inactive in nucleophilic substitution reactions (Table 3).

Table 3. ^{13}C and ^{19}F chemical shifts and charge densities q_{C-F} on the C^4(F) atoms in compounds **I**–**VII**

Comp. no.	Chemical shifts δ, ppm		q_{C-F}	
	^{19}F	^{13}C	PM3	AM1
I	–101.440	166.700	0.103	0.130764
II	–108.380	163.460	0.085	0.112495
IIIa	–111.950	163.090	0.074	0.102290
IIIb	–111.791	162.995	0.073	0.103308
	–112.000	162.955	0.072	0.102050
IIIc	–109.609	163.659	0.081	0.109814
	–109.890	163.576	0.080	0.108328
IIId	–111.030	163.214	0.077	0.106334
	–111.213	163.163	0.077	0.105043
IVa	–112.476	161.910	0.071	0.099024
	–114.393	161.889	0.065	0.092427
IVb	–112.668	161.890	0.069	0.097683
	–114.309	160.780	0.064	0.091039
V	–112.493	162.154	0.071	0.100559
	–113.000	160.982	0.068	0.090139
VI	–113.06	161.880	0.065	0.090081
VII	–112.077	163.002	0.0718	0.0995

EXPERIMENTAL

The initial compounds and solvents were purified by known methods. The ^{1}H (400 MHz), ^{13}C (100.61 MHz), and ^{19}F (188.3 MHz) NMR spectra of solutions in $CDCl_3$ ($c \approx 0.4$ M) were recorded on Bruker AMX-400 and Bruker AC-200 spectrometers, respectively. Semiempirical quantum-chemical calculations were performed using the PM3 and AM1 methods with full geometry optimization.

2,3-Dicyano-5,6-bis(4-fluorophenyl)pyrazine (II). A mixture of 0.85 g of diaminomaleonitrile, 1.64 g of 4,4'-difluorobenzil, 10 ml of acetic acid, and 50 ml of butyl acetate was heated for 1 h under reflux with stirring. The solvent was distilled off, and the residue was recrystallized from ethyl alcohol to obtain 1.06 g (50%) of compound **II** as bright yellow crystals with mp 254–256°C.

2,3-Bis(4-fluorophenyl)quinoxaline. A flask equipped with a gas-inlet tube (for argon supply) was charged with 3.18 g of compound **I**, 1.08 g of *o*-phenylenediamine, 45 ml of chloroform, and 5 ml of methanol. The mixture was left to stand for 24 h at room temperature under argon, and the solvent was distilled off on a rotary evaporator. The residue was recrystallized from ethyl alcohol to obtain 3.05 g (98%) of compound **IIIa** as colorless crystals with mp 134–136°C. Compounds **IIIb**–**IIId** and **VII** were synthesized in a similar way. Their yields, melting points, and analytical and spectral data are given in Tables 1 and 2.

2-(4-Bromophenyl)-4,5-bis(4-fluorophenyl)imidazole (IVa). A mixture of 1.23 g of 4,4'-difluorobenzil, 0.925 g of 4-bromobenzaldehyde, 2.69 g of ammonium acetate, and 50 ml of acetic acid was heated for 7 h under reflux with stirring. The mixture was then cooled and poured into water. The precipitate was filtered off, thoroughly washed with water, and dried for 10 h at 100°C under reduced pressure. Yield 1.79 g (87%), colorless crystals, mp 266–268°C. Compounds **IVb**, **V**, and **VI** were synthesized in a similar way. Their yields, melting points, and analytical and spectral data are given in Tables 1 and 2.

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