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Theoretical Study of the Synthesis of Aromatic Polyethers by the Nucleophilic Aromatic Substitution between Fluoro Aromatic Compounds and Phenoxides

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ABSTRACT: The electronic parameters of a series of mono- and difluoro aromatic compounds have been calculated by the quantum semiempirical method PM3. From these calculations, a relationship has been established between the charge on the aromatic carbon ipso to the fluorine and the reactivity of these compounds with hard nucleophiles, such as phenolate ions, to give aromatic ethers. A good correlation can also be established between charge on C_{ipso} and the ^{13}C and ^{19}F NMR chemical shifts, used previously to measure the reactivity of fluorine compounds in the above indicated reaction.

Introduction

The nucleophilic aromatic substitution of dihalo compounds (usually difluorides) with bisphenols salts has been shown to be a very useful route for the synthesis of poly(aryl ethers).[1-3] The presence of electron-withdrawing groups in the dihalides activates these compounds toward nucleophilic substitution and allows the obtention of high molecular weight polymers. Recently, Carter et al. have shown that NMR spectroscopy can be used to evaluate the reactivity of difluorides that could be used as potential monomers, because of the capacity of the NMR spectroscopy to measure the electronic density at the site of the reaction.[4-6] ^{19}F chemical shifts proved to be the best NMR parameters to measure the reactivity, due to (a) the higher chemical shift range of this nucleus and (b) the high sensitivity of ^{19}F NMR spectroscopy and the ease of detection.

However, the drawback of this method is the necessity to synthesize the potential monomer to register the NMR spectrum and to decide whether it can be used for polymerization or not. In addition, the nucleophilic attack of the phenolate ions takes place at the C_{ipso}, and therefore, the reaction must be controlled by the properties of this atom and not by those of the fluorine. Therefore, the calculation of the electronic properties of the C_{ipso}, as a function of the type of electron-withdrawing substituent, should allow determination of, *a priori*, the reactivity of a fluoro compound versus a nucleophilic reactant.

Molecular orbital theory has been used to give interesting information about structures, energies, and other properties of known and unknown molecules.[7,8] The evolution of molecular orbital methods has resulted in two main categories, ab initio and semiempirical. Semiempirical methods use a vaguely rigorous quantum mechanical formulation combined with the use of empirical parameters obtained from comparison with experiment, and unlike ab initio methods, their accuracy is limited to the accuracy of the experimental data used in obtaining the parameters.[9,10] However, the advantage of these methods over ab initio calculations is that they are several orders of magnitude faster while enough accuracy is maintained for most organic systems,[11] therefore allowing quantum chemical calculations for quite large systems.

Consequently, in this paper we have calculated, by semiempirical methods, the electronic parameters of a series of mono and difluorides to discover if they can be related with their reactivity. As the ^{19}F NMR chemical shifts seem to give a good idea of this reactivity, we have tried to relate the calculated electronic parameters with the experimentally measured chemical shifts, to know if it is possible to obtain a good relationship between calculated and experimental values. While the current work was under revision, a paper by Hay et al.[12] appeared on the synthesis of new poly(phenylquinoxalines) by nucleophilic substitution of fluorine. In this paper, some limited calculations appeared on the relationship between the charge density at the C–F carbon atoms and the reactivities of monomers toward nucleophilic substitution of fluorine. These authors used the Huckel method, which is the fastest and simplest semiempirical method but also the least accurate because of the neglect of electron–electron interactions.

Experimental Section

Theoretical Calculations. Semiempirical calculations were done by using the original parameters of the program PM3,[13] based on the restricted Hartree–Fock (RHF) method, included in MOPAC version 6.0.[14] This semiempirical method appears to allow a better description of the lone-pair/lone-pair repulsion in various heterocyclic compounds. Thus, the calculation of hypervalent molecules and heterocyclic compounds has been improved with respect to other semiempirical calculations.[15] The program ran on a VAX 9210 computer of the Computer Center of CSIC (Madrid, Spain).

Initial geometries were obtained by molecular mechanics (MM+) by means of the program Hyperchem version 3.[16] The results of this optimization were employed as input data for the semiempirical calculations. The same program was used to visualize the structures obtained after MOPAC minimization.

Geometries were optimized in internal coordinates. The optimization was stopped when Herbert or Peter tests were satisfied in the Broyden–Fletcher–Goldfarb–Shano (BFGS) method.[15] The PRECISE option was applied during the optimization process. The calculations were carried out with full geometry optimization (bond lengths, bond angles, and dihedral angles). The geometry of the Meisenheimer complexes was achieved by minimization of the gradient below 0.1 kcal/mol per Å.

Characterization. ^{19}F, ^{1}H, and ^{13}C NMR spectra were recorded on Varian XL-300 equipment operating at 282.23, 300,

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and 75.43 MHz, respectively, using DMSO-d_6 as solvent. Tetramethylsilane (TMS) was used as the internal reference for ^{1}H and ^{13}C NMR spectra, while $CFCl_3$ was used as the external reference for ^{19}F spectra.

Elemental analyses were done at Centro Nacional de Química Orgánica (CSIC, Madrid, Spain). Melting points were measured by differential scanning calorimetry (DSC) taking the onset as the melting point.

Materials. All materials were commercially available and used as received unless otherwise noted. The solvents were obtained from Aldrich in the highest purity available and purified, when necessary, by conventional methods. 4-Fluorobenzoyl chloride was obtained by refluxing 4-fluorobenzoic acid (0.1 mol) with thionyl chloride (0.3 mol). The excess of thionyl chloride was stripped off, and the residue was vacuum distilled. The yield was 86%. The Eaton reagent, a mixture of phosphorus pentoxide and methanesulfonic acid, was obtained by dissolving 10 g of the first in 90 g of the second, as cited elsewhere.[17]

Phenyl 4-Fluorobenzoate (1d). A 100 mL flask blanketed by nitrogen was charged with phenol (0.01 mol), trimethylamine (0.01 mol), 4-(dimethylamino)pyridine (0.0001 mol), and 20 mL of chloroform. To this solution was added 4-fluorobenzoyl chloride (0.01 mol) in 5 mL of chloroform. The mixture was stirred at room temperature for 30 min and at 50 °C for 1 h. Then, the solvent was removed on a rotary evaporator. The crude product was purified by sublimation giving a crystalline powder. The yield was 90%; mp = 57 °C. Anal. Calcd for $C_{13}H_9O_2F$: C, 72.22; H, 4.20. Found: C, 72.15; H, 4.22.

4-Fluorobenzanilide (1e). A 50 mL flask blanketed by nitrogen was charged with aniline (0.01 mol), trimethylamine (0.01 mol), and 20 mL of chloroform. To this solution was added 4-fluorobenzoyl chloride (0.01 mol) in 3 mL of chloroform. The mixture was stirred at room temperature for 2 h. Then, the solvent was removed on a rotary evaporator. The crude product was purified by recrystallization from toluene, giving a white crystalline powder. The yield was 75%; mp = 186 °C. Anal. Calcd for $C_{13}H_{10}NOF$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.16; H, 4.53; N, 6.72.

4′-Fluorobenzanilide (1f). This compound was obtained from 4-fluoroaniline and benzoyl chloride under the same conditions as for 4-fluorobenzanilide. The product was purified by recrystallization from toluene, giving a light blue crystalline powder. The yield was 82%; mp = 185 °C. Anal. Calcd for $C_{13}H_{10}NOF$: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.32; H, 4.59; N, 6.71.

4,4′-Difluorobenzanilide (2c). This compound was obtained from 4-fluoroaniline and 4-fluorobenzoyl chloride under the same conditions as for 4-fluorobenzanilide. The crude product was purified by recrystallization from toluene, giving a pearl crystalline powder. The yield was 90%; mp = 186 °C. Anal. Calcd for $C_{13}H_9NOF_2$: C, 66.95; H, 3.89; N, 6.01. Found: C, 66.92; H, 3.94; N, 6.12.

1,3-Bis(4-fluorobenzoyl)benzene (2d). 1,3-Bis(4-fluorobenzoyl)benzene was synthesized using the method described by Hergenrother.[18] The compound was recrystallized from toluene. The yield was 80%; mp = 174 °C. Anal. Calcd for $C_{20}H_{12}O_2F_2$: C, 74.53; H, 3.75. Found: C, 74.19; H, 3.87.

2-(4-Fluorophenyl)benzoxazole (3a). A 250 mL flask blanketed by nitrogen was charged with 4-fluorobenzoic acid (0.01 mol) and 2-aminophenol (0.01 mol). A 40 mL portion of Eaton reagent solution was added into the flask while the mixture was stirred at room temperature for 15 min. The temperature was slowly raised to 120 °C and the reaction was maintained for 12 h. The dark solution was poured into a solution of NaOH in water (0.5 mol/L), and the resulting precipitate was filtered off and treated with a 0.1 N solution of NaOH up to pH of 3. The solid was separated by suction and thoroughly washed with water. Once dried, it was sublimed at reduced pressure. The yield was 74%; mp = 101 °C. Anal. Calcd for $C_{13}H_8NOF$: C, 73.23; H, 3.78; N, 6.57. Found: C, 73.01; H, 3.82; N, 6.67.

2-(4-Fluorophenyl)benzothiazole (3b). It was synthesized from 4-fluorobenzoic acid and 2-aminothiophenol under the same conditions as for 2-(4-fluorophenyl)benzoxazole. Once dried, it was sublimed at reduced pressure. The yield was 82%; mp = 100 °C. Anal. Calcd for $C_{13}H_8NSF$: C, 68.10; H, 3.52; N, 6.11; S, 13.98. Found: C, 67.88; H, 3.55; N, 6.23; S, 13.45.

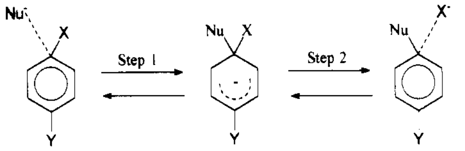

Figure 1. Scheme of the nucleophilic aromatic substitution with formation of the intermediate Meisenheimer complex.

2-(4-Fluorophenyl)benzimidazole (3c). This compound was synthesized from 4-fluorobenzoic acid and *o*-phenylenediamine under the same conditions as for 2-(4-fluorophenyl)benzoxazole. The product was recrystallized from ethanol. The yield was 75%; mp = 251 °C. Anal. Calcd for $C_{13}H_9N_2F$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.16; H, 4.41; N, 13.39.

5-Amino-2-(4-fluorophenyl)benzoxazole. This compound was synthesized from 4-fluorobenzoic acid and 2,4-diaminophenol under the same conditions as for 2-(4-fluorophenyl)benzoxazole. Once dried, it was sublimed at reduced pressure twice. The yield was 68%; mp = 251 °C. Anal. Calcd for $C_{13}H_9N_2OF$: C, 68.42; H, 3.97; N, 12.27. Found: C, 68.14; H, 4.09; N, 12.02.

2-(4-Fluorophenyl)-6-[(3-hydroxybenzoyl)amino]benzoxazole (4a). A 50 mL flask was charged with 5-amino-2-(4-fluorophenyl)benzoxazole (0.01 mol), 4-hydroxybenzoic acid (0.01 mol), triphenyl phosphite (0.012 mol), 2 mL of pyridine, and 20 mL of DMA. This mixture, blanketed by nitrogen, was heated at 100 °C for 3 h. Then, the solution was poured into a mixture of 75 mL of water and 10 mL of methanol. The solid was filtered off and washed thoroughly with hot water. The crude product was purified by recrystallization from *N*-methylpyrrolidone (NMP)/H_2O (1/2), giving a white crystalline powder. The yield was 80%; mp = 256 °C. Anal. Calcd for $C_{20}H_{13}N_2O_3F$: C, 68.96; H, 3.76; N, 8.04. Found: C, 68.83; H, 3.94; N, 8.15.

2-(4-Fluorophenyl)-6-[(4-hydroxybenzoyl)amino]benzoxazole (4b). It was synthesized under the same conditions as for 2-(4-fluorophenyl)-6-[(3-hydroxybenzoyl)amino]benzoxazole, using 3-hydroxybenzoic acid instead of 4-hydroxybenzoic acid. The crude product was purified by recrystallization from NMP/H_2O (2/3), giving a white crystalline powder. The yield was 70%; mp = 243 °C. Anal. Calcd for $C_{20}H_{13}N_2O_3F$: C, 68.96; H, 3.76; N, 8.04. Found: C, 68.12; H, 3.96; N, 8.17.

2-(4-Fluorophenyl)-6-[(4-fluorobenzoyl)amino]benzoxazole (4c). A 50 mL flask blanketed by nitrogen was charged with 5-amino-2-(4-fluorophenyl)benzoxazole (0.01 mol), trimethylamine (0.01 mol), and 20 mL of *N,N*-dimethylacetamide (DMA). To this solution was added 4-fluorobenzoyl chloride (0.01 mol) in 3 mL of DMA. The mixture was stirred at room temperature for 1 h and at 40 °C for 1 h. Then, the solution was poured into 75 mL of water. The solid was filtered off and washed thoroughly with hot water. The product was purified by recrystallization from toluene giving a white powder. The yield was 90%; mp = 259 °C. Anal. Calcd for $C_{20}H_{12}N_2O_2F_2$: C, 68.37; H, 3.73; N, 7.97. Found: C, 68.02; H, 3.78; N, 8.06.

Theoretical Background

Aromatic nucleophilic substitution has been intensively studied.[19–21] Although formally similar to the aliphatic nucleophilic substitution, the differing reactivity patterns require that this area be considered separately.[22] In general, aromatic nucleophilic substitution proceeds via three main mechanisms. S_N1, addition–elimination, and elimination–addition.[23] More recently, metal-catalyzed[24,25] and radical reactions (S_NAr1)[26,27] have been also established, particularly with substrates that are less reactive through the first three mechanisms. The addition–elimination (S_NAr) mechanism is by far the most important among the nucleophilic aromatic substitutions (Figure 1). It uses one vacant π^* orbital as the initial point of attack by the nucleophile. This allows bonding of the nucleophile to the aromatic ring without displacement of the existing substituents as opposed to the classical reaction mechanism of S_N2 reactions.[25] Thus, this reaction will be the result of the overlapping of the nucleophile's HOMO with the halo aromatic compound's LUMO. The process disrupts the aromatic π system, and therefore, nucleophilic aromatic substitution is usually an energetically demanding reaction, even when electron-attracting substituents are present.

The existence of an intermediate state (Meisenheimer complex)[28] has been established and it has even been isolated.[29] The existence of this intermediate causes the presence of two transition states, the rate of step 1 depends on nucleophile–electrophile bond formation while the rate of step 2 depends on the electrophile–leaving group bond cleavage.

The first step is usually rate determining. This means that, contrary to what happens in a typical S_N2 process, in the S_NAr mechanism the Ar–X bond is not broken in the rate-determining step. Regarding halogen derivatives, the global reaction rate is F $\gg$ Cl > Br > I, and the rates differ by a factor of about 300 between the fluorine and the rest of them.[30] The fact that fluoro derivatives are the most reactive halo compounds is good evidence that this mechanism is different from the S_N2 mechanism.

This order is the result of the polar effect of the halogen. The stronger bond dipole associated with the more electronegative halogen decreases the charge density on the ipso carbon and favors the addition step, thus increasing the general rate of reaction. Furthermore, the more electronegative the halogen is, the more stabilized the transition state will be. The presence of electron-withdrawing groups will raise the electron deficiency on the carbon ipso to the halogen, stabilizing the transition state as well.

However, the theoretical study of any chemical reaction has to consider other electronic parameters besides coulombic interactions between atomic positions charged with different sign.

On a chemical reaction, the incipient interaction of a reactant with another is initially a small perturbation. To such small perturbation should correspond small energy changes, which can be evaluated by perturbation expansion of the energy. This perturbation energy is expected to give a reliable indication of the energy in the initial stages of the reaction.[31] By using a quantum mechanical theory, an expression can be derived for the perturbation energy (ΔE) gained or lost when the orbitals of one reactant overlap with those of another.[32-35]

This equation, known as the Fukui–Klopman–Salem equation, has the following form:

$$\Delta E = -\sum_{ab} (q_a + q_b)\,\beta_{ab}S_{ab} + \sum_{k<1} \frac{Q_kQ_l}{\epsilon R_{kl}} + \sum_{r}^{\text{occ}} \sum_{s}^{\text{unocc}} - \sum_{s}^{\text{occ}} \sum_{r}^{\text{unocc}} \frac{2(\sum_{ab} c_{ra}c_{sb}\beta_{ab})^2}{E_r - E_s}$$

where q_a and q_b are the electron populations in the atomic orbitals a and b; β and S are the resonance and overlap integrals; Q_k and Q_l are the total charges on atoms k and l; ϵ is the local dielectric constant; R_{kl} is the distance between the atoms k and l; C_{ra} is the coefficient of atomic orbital a in molecular orbital r, where r refers to the molecular orbitals on one molecule and s refers to those on the other; and E_r is the energy of molecular orbital r. The first term accounts for the interaction between filled orbitals. In our study, we can consider, at first approximation, that this term will be the same for the reaction of a specific nucleophile and any fluoro aromatic compound. The second term is simply the electrostatic repulsion or attraction between charged centers. This term is obviously very important when ions or polar molecules are reacting. The third term represents the interaction of the filled orbitals with all the unfilled ones of correct symmetry. It has a bonding effect, and its value depends on the energy separation between orbitals. Thus, the most important interactions should be the HOMO–LUMO ones, because of their lower energy separation. When a chemical process is controlled by this term, it is said that this reaction is orbital controlled; when the process is controlled by the second term, it is said that the reaction is charge controlled. Obviously, there can be mixing of both controls.

Table 1. Electronic Parameters of Halobenzenes and 4-Nitrohalobenzenes

compd	charge (C_{ipso})	E_{LUMO}	compd	charge (C_{ipso})	E_{LUMO}
fluorobenzene	0.0647	0.0271	4-fluoronitrobenzene	0.1277	−1.4143
chlorobenzene	−0.1236	0.0629	4-chloronitrobenzene	−0.0793	−1.3563
bromobenzene	−0.1086	0.0361	4-bromonitrobenzene	−0.0697	−1.3889
iodobenzene	−0.1292	0.1115	4-iodonitrobenzene	−0.0986	−1.3061

Although the derivation of this equation involves several approximations, it works very well in many organic reactions and permits accurate establishment of, quantitative differences of reactivity.[35]

Results and Discussion

We have calculated, by PM3, the electronic parameters of a series of halobenzenes and 4-nitrohalobenzenes. As can be seen in Table 1, three main features can be pointed out.

(1) The charge of the carbon bound to the halogen is positive when that halogen is fluorine and negative for the rest of the compounds.

(2) The presence of the electron-withdrawing substituent decreases the electronic density on the carbon ipso to the halogen (C_{ipso}), the decrease being in the order F > Cl > Br > I. The charge on this carbon remains negative when it is bound to Cl, Br, or I.

(3) The presence of electron-withdrawing groups lessens the LUMO energy, increasing the soft behavior of the compounds. These are very interesting results because they can explain the differential reactivity of halo compounds in S_NAr and also their reaction mechanism. They seem to point out that both orbital and charge terms have to be considered. Thus, when the electrophiles are chloro, bromo, or iodo derivatives, with or without electron-withdrawing substituents, the reaction is controlled by the orbital term because the coulombic interaction between a negative charge and a slightly negative center has to give an endoergic effect. Therefore, the reaction against a hard nucleophile will be highly hindered, and these halo compounds will only react with soft nucleophiles,[23] that is, compounds with high values of energy of the HOMO.

When the compound is a fluoro aromatic derivative without electron-attracting groups, the charge term will be only slightly favorable. Thus, the compound could react with soft nucleophiles. With compounds with low values of HOMO energy, hard nucleophiles, the reaction will only be possible under severe conditions, high temperatures and long reaction times.

When there are electron-withdrawing groups present, the higher charge deficiency on the ipso carbon makes easier the reaction with hard nucleophiles, because the charge controlled term on the equation becomes more important. In that way, the activated fluorine compounds can react with either soft or hard nucleophiles under mild conditions.

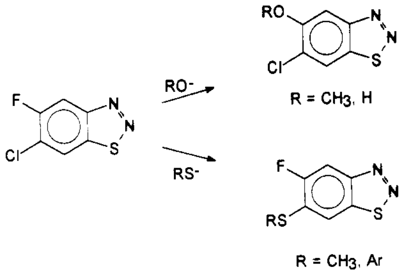

Figure 2. Scheme of the reaction of 5-fluoro-6-chloro-1,2,3-benzothiadiazole with *soft* and *hard* nucleophiles.

Therefore, soft nucleophiles, such as the thiophenolate ion, can react with no activated halo compounds. On the other hand, hard nucleophiles, such as the phenolate ion, react under mild conditions only with fluoro compounds with electron-attracting groups on the ortho or para position respect to the halogen.

An interesting result that can clarify the mechanistic study of the S_NAr is the reaction depicted in Figure 2. This reaction is highly specific.[36] Thus, when the nucleophile is soft, substitution on the carbon ipso to the chlorine occurs, while, when the nucleophile is hard, the substitution takes place on the carbon bound to the fluorine. A PM3 calculation for this compound gave a negative value for the charge on the carbon ipso to the chlorine (−0.150 e) and a positive value (0.063 e) on the carbon ipso to the fluorine. However, the LUMO was centered on the carbon bound to the chlorine. This result justifies totally the regioselectivity experimentally observed and proves that, when the nucleophile is hard, the reaction is mainly led by the charge term.

The reaction of phenoxides and fluoro aromatic compounds that we are studying is the typical reaction between a hard nucleophile and a medium–hard molecule. Therefore, it should be mainly controlled by the electrostatic attraction between the negative charge borne on the oxygen and the positive charge that exists on the carbon ipso to the fluorine. Thus, at a first approximation, the electronic parameter that controls the differential reactivity among fluoro aromatic compounds will be the charge's difference between them.

Therefore, we have done a theoretical study of a large series of *p*-substituted fluoro aromatic compounds, most of them synthesized by us and some previously reported by Carter et al.,[4] by means of the quantum semiempirical method PM3.

In Figure 3 is shown the structure of the whole series of compounds studied (compounds marked with an asterisk are those reported by Carter et al., whereas the compound 3-[(4-fluorophenyl)sulfonyl]-2,2,3,3-tetrafluoropropanol (**1g**) has been reported by Feiring et al.[37,38] as one of the strongest electron-withdrawing groups).

In Table 2 are shown the results of the PM3 calculations. From the data of this table, several relationships can be observed.

The presence of electron-withdrawing groups causes, as has been already pointed out, a decrease on the electronic density of the carbon atom ipso to the fluorine (para with respect to the electron-withdrawing group) and on the fluorine atoms. Therefore, a linear relationship exists between the charge on the C_{ipso} and the charge on the fluorine (Figure 4).

The maximum effect is produced by the (perfluoroalkyl)sulfonyl (**1g**) and by the NO_2 (**1b**) substituents, which cause a decrease of the electronic density of 0.0724 and 0.0632 e on the carbon atom and of 0.0133 and 0.0130 e on the fluorine, with respect to the reference compound, fluorobenzene (**1a**).

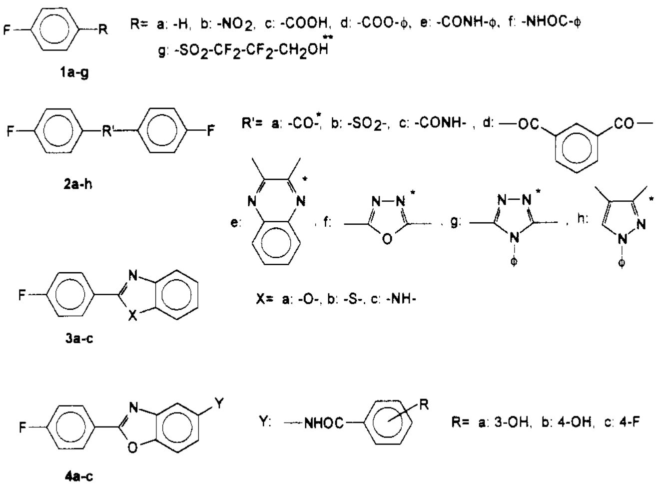

Figure 3. Structure of the series of compounds studied in this work. *Compounds reported by Carter et al.[4-6] **Compound reported by Feiring et al.[37]

Table 2. Electronic and NMR Parameters of a Series of Mono- and Difluoride Derivatives

	charge			δ	
compd	(C_{ipso})	(F)	dist (C–F)	^{13}C	^{19}F
1a	0.0647	−0.0932	1.3436	162.29	−112.77
1b	0.1277	−0.0801	1.3397	165.76	−102.58
1c	0.0998	−0.0869	1.3416	164.93	−106.75
1d	0.1008	−0.0864	1.3415	165.78	−106.00
1e	0.0929	−0.0869	1.3418	164.05	−108.65
1f	0.0424	−0.0937	1.3440	158.31	−118.70
1g[b]	0.1380	−0.0794	1.3392		−98.50
2a[a]	0.0957	−0.0881	1.3420	165.27	−106.01
2b	0.1169	−0.0851	1.3411	165.30	−104.08
2c-CO	0.0948	−0.0861	1.3415	164.04	−108.55
2c-NH	0.0445	−0.0929	1.3438	158.31	−118.60
2d	0.0864	−0.0881	1.3426	164.80	−105.64
2e[a]	0.0735	−0.0913	1.3432	163.10	−111.99
2f[a]	0.0895	−0.0867	1.3419	165.55	−106.81
2g[a]	0.0740	−0.0902	1.3427	163.38	−110.49
$\mathbf{2h_3}$[a]	0.0688	−0.0916	1.3427		−114.88
$\mathbf{2h_4}$[a]	0.0614	−0.0922	1.3432		−114.88
3a	0.0863	−0.0885	1.3421	163.91	−107.36
3b	0.0820	−0.0896	1.3424	163.88	−108.67
3c	0.0753	−0.0897	1.3426	163.04	−110.97
4a	0.0836	−0.0898	1.3425	164.20	−107.35
4b	0.0837	−0.0895	1.3424	164.16	−107.40
4c-Bzox	0.0850	−0.0892	1.3423	164.12	−108.57
4c-Amide	0.0962	−0.0858	1.3414	164.13	−107.36

[a] NMR data taken from refs 3 and 4. [b] NMR data taken from ref 35.

The compound **2c** deserves a comment, because the behavior of the two fluorine atoms and the carbons joined to them depends on the position of the ring with respect to the amide group. When the ring is connected to the CO side (**2c**-CO), a strong decrease on the charge density is observed [related to fluorobenzene (**1a**)] for both carbon and fluorine. However, when the ring is connected to the NH side (**2c**-NH) an increase of the charge density of the carbon can be observed, while almost no effect appears for the fluorine atom. This effect, which can also be seen if we compare compounds **1e** and **1f**, seems to suggest that the electron-donating effect of the NH group affects the carbon atoms of the ring, but has very little influence on the fluorine. However, the great variation on ^{19}F chemical shifts of compounds **1f** and **2c**-NH related to fluorobenzene (see Table 2) indicates that the substituent plays a significant influence on the fluorine and that the calculations do not seem to predict correctly the behavior of the

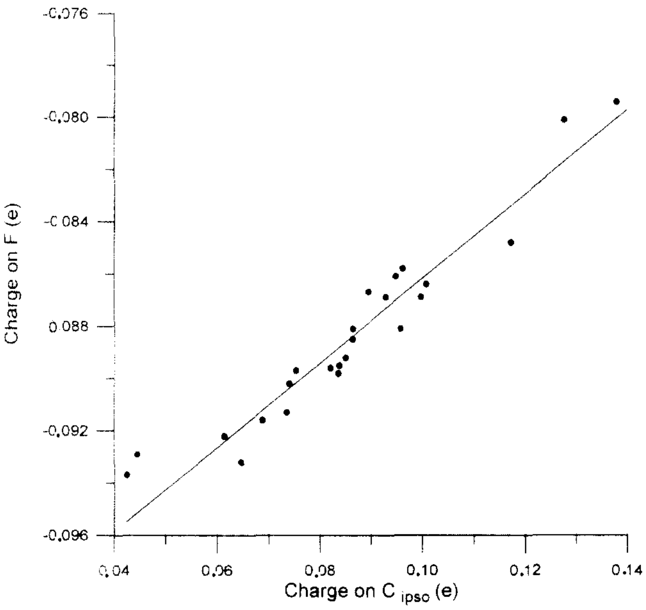

Figure 4. Plot of the charge on the carbon ipso to the fluorine versus the charge on the fluorine.

molecules in this particular case. The effect of the electron-withdrawing groups is always greater on the carbon atom that on the fluorine atom, and therefore, the charge separation increases with the electron-withdrawing capacity of the substituent [$\text{charge}_C - \text{charge}_F = 0.1578$ e for fluorobenzene (**1a**), 0.2079 e for 4-nitrofluorobenzene (**1b**), and 0.2169 e for (perfluoroalkyl)sulfonyl (**1g**)]. Because of that larger charge separation, the C–F bond is more polar and consequently the distance C–F is shorter.

Reaction Intermediate. The Meisenheimer Complex. The formation of the Meisenheimer complexes (MC's) causes a disruption of the π aromatic system. This disruption would have to manifest itself by severe changes in their geometries. Therefore, we have calculated the geometries of several MC's, resulting from the attack of the phenoxide ion to fluoro compounds, and compared them with those of the corresponding reactants.

The distances C–F raised about 0.05 Å with respect to those of the original reactants. Nevertheless, there was no correlation between these bond length increases and the electronic features of the group borne on the para position. These small variations suggest that at this point of the reaction the removal of the leaving group has not started.

The changes in the distances between aromatic carbons were more significant. Thus, the distance C_{ipso}–C_{ortho} strongly increased as a function of the group attached on the para position. The more electron-attracting the group was, the larger the increase and the greater the sp^3 character of the bond. The changes on the distance C_{meta}–C_{para} denoted poorer correlation with the substituent, although that distance raised and so did the sp^3 character of the bond. More interesting is the distance C_{ortho}–C_{meta}. There was always a decrease depending on the substituent, approaching values closer to a typical sp^2 than the initial bond. When this had a high electron-withdrawing effect, the distance reached 1.35 Å. On the other hand, the angle C_{ortho}–C_{ipso}–C_{ortho} of these MC's had value of ca. 113° in all of them. This shows that the carbon ipso of these intermediates has more sp^3 than sp^2 character.

All these geometric changes indicate that the reaction with the nucleophile causes the disruption of the aromatic system, with the appearance of sp^3 character in the C_{ipso}. The tendency of the ring to recover its aromatic character produces the elimination of the fluorine atom, and the obtention of the final product. The obtained geometric parameters are closer to the experimental values than the previously[39] obtained by MNDO.

Table 3. Relative Heats of Formation of the MC's between Different Fluoro Compounds and Phenoxide Anion ($\Delta H_{rel} = \Delta H_{MC} - \sum \Delta H_{reactants}$) and Values Referred to the Fluorobenzene MC

compd	ΔH_{rel} (kcal/mol)	$\Delta H_{rel} - \Delta H_{fluorobenzene\ MC}$	compd	ΔH_{rel} (kcal/mol)	$\Delta H_{rel} - \Delta H_{fluorobenzene\ MC}$
1a	9.04	0.00	**2a**	−20.02	−29.06
1b	−23.05	−32.08	**2h$_3$**	−0.41	−9.44
1e	−11.26	−20.30	**2h$_4$**	10.72	1.68
1f	4.01	−5.02			

In Table 3 are shown the relative enthalpies of the MC's ($\Delta H_{rel} = \Delta H_{MC} - \sum \Delta H_{reactants}$), and the values referred to the enthalpy of the fluorobenzene complex. It is worth noting that the values of ΔH_{rel} are negative if the groups attached para are electron attracting, showing a higher stability of the complex. The differences between **1e** and **1f** and between **2h$_3$** and **2h$_4$**, which we have discussed previously, can also be observed in the Meisenheimer complexes. As shown in Table 3, the MC formed through substitution of position 3 (**2h$_3$**) is slightly more stable that the initial reactants and more stable that the complex of fluorobenzene. On the contrary, the MC formed through substitution of position 4 (**2h$_4$**) is less stable that the reactants and the complex of fluorobenzene. Compounds **1e** and **1f** present the same behavior.

Therefore, these results confirm that either a higher value of the electronic density on the fluorine or a lower value on the C_{ipso} will give way to a higher stability of the corresponding Meisenheimer complex, and hence to a higher reactivity versus a nucleophilic reactant. Furthermore, when the values of electronic densities are close to those of fluorobenzene, the charge on the C_{ipso} is better than the charge on the fluorine to determine the reactivity of the compound. From all the data shown up to now, it can be said that the electronic density on the C_{ipso} is the main parameter in the control of the reactivity of fluoro compounds with phenolate ions. Therefore, as the NMR chemical shifts seem to be related with the reactivity, a direct relationship has to be established between the charge on C_{ipso} and chemical shifts.

Correlation between Electronic Parameters and NMR Chemical Shifts. The fact that nuclei in different environments have different nuclear shielding, and therefore different chemical shifts, makes NMR a powerful probe of the electronic structure of a molecule, which in turn controls its chemistry. As an example, it is well-known that the introduction of a substituent on a benzene ring removes the degeneracy of the NMR signal of benzene by perturbing the ipso, ortho, meta, and para carbons to different extents. This reflects the fact that different sites in a molecule are influenced by different blends of substituent effects, and a parallelism can be established between the electronic parameters of the different atoms and their corresponding chemical shifts.

Nuclear shielding is often discussed in the terminology developed by Saika and Slichter:[40]

$$\sigma = \sigma_i^{\text{dia}} + \sigma_i^{\text{para}} + \sum \sigma_j^{\text{inter}}$$

In studies of substituent effects on chemical shifts, it is possible to keep constant the third term in the equation. In addition, substituent-induced changes in the diamagnetic term are often relatively small for all nuclei other than hydrogen, and therefore, the chemical shift is determined mainly by the paramagnetic shielding term,

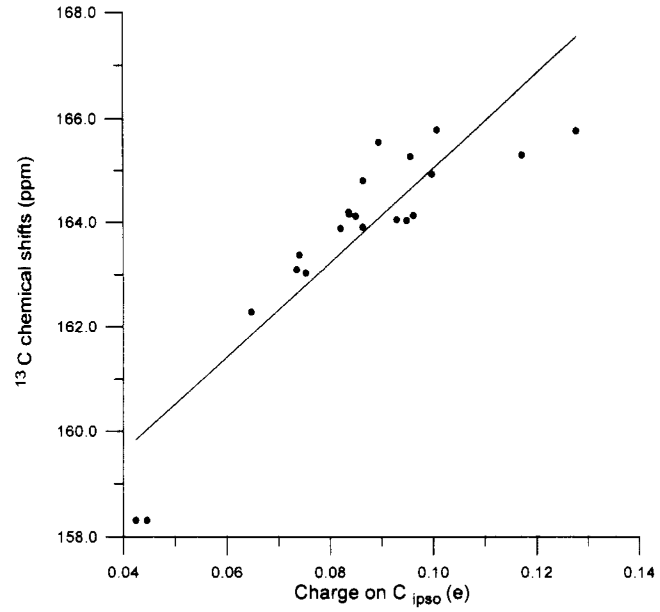

Figure 5. Plot of the charge on the carbon ipso to the fluorine versus its ^{13}C chemical shift.

which can be expressed by the following equation:[41]

$$\sigma_i^{para} = -\frac{e^2k^2}{2m^2c^2}(\Delta E)^{-1}\langle r^{-3}\rangle_{2p}[Q_{ii} + \sum_{i\neq j} Q_{ij}]$$

where Q_{ii} and Q_{ij} represent the electron density and the bond order, respectively, according to molecular orbital theory, ΔE is the mean electronic excitation energy, and $\langle r^{-3}\rangle_{2p}$ is the inverse cube of the distance between a 2p electron and the nucleus.

Several studies[42,43] have determined that, for series of molecules in which ΔE and the bond order terms are reasonably constant, a correlation exists between the ^{13}C chemical shift of one atom and its charge.

$$\Delta\,\delta = K\Delta q$$

It relies upon the dependence of σ_i^{para} upon $\langle r^{-3}\rangle_{2p}$, which is closely related to electron density. In the same sense, variations in the σ_i^{para} term are the dominant cause of ^{19}F chemical shifts in aromatic fluorine compounds, ^{19}F chemical shift values arising in different proportions from π-polarization of the adjacent benzene ring and from direct C–F polarization.[44]

Therefore, we have used the ^{19}F and ^{13}C NMR chemical shifts as a probe to determine experimentally the charge's distribution on the different fluoro compounds.

In Table 2 are shown the available values, either reported previously or measured in this work. To check that both series of results are comparable, we have measured again the spectra of compounds **1a**, **2a**, and **2b**, previously reported by Carter et al.,[4] and found a maximum difference of 0.15 ppm for ^{19}F and 0.10 ppm for ^{13}C, which allows the comparison of both series.

A linear correlation can be established between the ^{13}C chemical shifts and the total charge density on C_{ipso} (Figure 5), similar to that found in previous works.[45,46] However, due to the small range of chemical shifts involved in the representation, the presence of additional effects contributes to a greater dispersion of the data in the correlation.

In a similar way, a good correlation exists between the charge on C_{ipso} and the ^{19}F chemical shifts, as can be seen on Figure 6. The quality of the correlation is better in this case (R^2 = 0.92 versus 0.80 above). This is probably due to the larger range of the ^{19}F chemical shifts (about 20 ppm versus about 8 ppm for the ^{13}C), which makes this experiment a better probe for the study of these effects. As the reactivity of a fluoro compound with a nucleophilic reactant is determined by the charge on the C_{ipso}, the existence of the good correlation between charge on C_{ipso} and ^{19}F chemical shifts justifies the claim of Carter et al. that the ^{19}F NMR chemical shift can be used as a reliable probe to measure the reactivity of fluoro compounds.

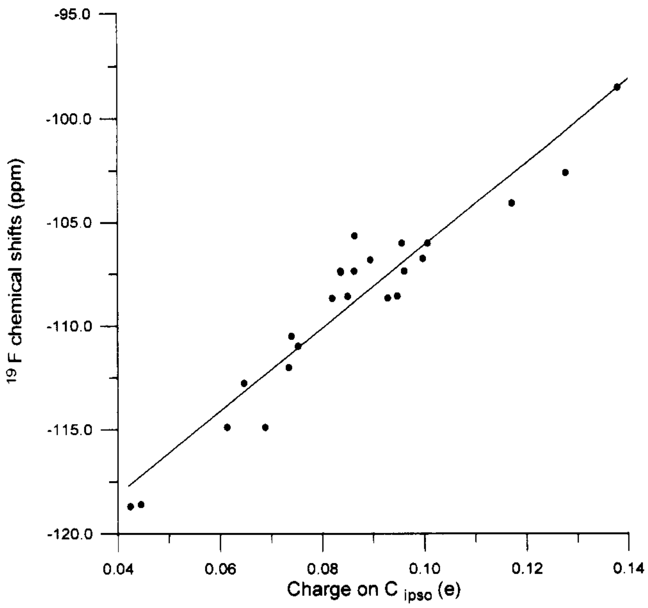

Figure 6. Plot of the charge on the carbon ipso to the fluorine versus the ^{19}F chemical shifts.

Conclusions

The use of quantum semiempirical calculations has allowed us to estimate easily the electronic parameters of fluoro compounds as a function of the type of para substituents. From these parameters it can be said that the reactivity of fluoro compounds with phenolates is controlled mainly by the electronic density on the carbon bound to the fluorine atom, the frontier orbitals playing a minor role.

The charge on the carbon ipso to the fluorine atom can be related with the ^{13}C and ^{19}F NMR chemical shifts, which had been previously claimed as a probe to determine the reactivity of this type of reaction. However, in spite of the good correlation found by Carter et al., it must be considered that the ^{19}F chemical shifts are only indirect probes of the reactivity, because reactivity depends actually on the electronic properties of the C_{ipso}.

Therefore, semiempirical quantum chemical calculations can be used as a fast and accurate method to determine *a priori* the suitability of a new difluoride compound to give high molecular weight polymers by reaction with phenoxides.

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References and Notes

(1) Maiti, S.; Mandal, B. K. *Prog. Polym. Sci.* **1986**, *12*, 111.
(2) Johnson, R. N.; Farnham, A. G.; Clendinning, R. A.; Hale, W. F.; Merriam, C. N. *J. Polym. Sci.: A-1* **1967**, *5*, 2375.
(3) Hedrick, J. L.; Labadie, J. W. *Macromolecules* **1990**, *23*, 1561.
(4) Carter, K. R. *Polym. Mat. Sci. Eng.* **1993**, *69*, 433.

(5) Carter, K. R.; Miller, R. D.; Hedrick, J. L. *Macromolecules* **1993**, *26*, 2209.

(6) Hedrick, J. L.; Tweig, R.; Matray, T.; Carter, K. R. *Macromolecules* **1993**, *26*, 4833.

(7) Clark, T. *A Handbook of Computational Chemistry*; J. Wiley: New York, 1985.

(8) Stewart, J. J. P. *Semiempirical Molecular Orbital Methods* in *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1990.

(9) Stewart, J. J. P. *J. Comput. Chem.* **1985**, *10*, 209.

(10) W. Thiel, *Tetrahedron* **1988**, *44*, 7393.

(11) Dewar, M. J. S.; Storch, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 3898.

(12) Strukelj, M.; Hamier, J.; Elce, E.; Hay, A. S. *J. Polym. Sci.: Part A: Polym. Chem.* **1994**, *32*, 193.

(13) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(14) MOPAC 6.0. *QCPE* **1990**, 455.

(15) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301.

(16) MM+ in *Hyperchem* 3.0, Autodesk Inc.: Sausalito, CA, 1993.

(17) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

(18) Hergenrother, T. M.; Jensen, B. J.; Havens, S. J. *Polymer* 1988, *29*, 358.

(19) Kenner, J. *J. Chem. Soc.* **1914**, *105*, 2717.

(20) Unginade, A. *Chem. Rev.* **1946**, *38*, 405.

(21) Bunnett, J. F. *Q. Rev.* **1958**, *12*, 1.

(22) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.

(23) Paradisi, C. *Nucleophilic Aromatic Substitution* in *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991.

(24) Semmelhack, M. F. *Nucleophilic Addition to Arene Metal Complexes* in *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991.

(25) Carber, D. R.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem.* **1982**, *47*, 1036.

(26) Norris, R. K. *Nucleophilic Coupling with Aryl Radicals* in *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991.

(27) Zoltewicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33.

(28) Orvick, J. A.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2417.

(29) Meisenheimer, J. *Justus Liebig's Ann. Chem.* **1902**, *323*, 205.

(30) Brines, G. P.; Miller, J.; Livern, M.; Lutz, P. G. *J. Chem. Soc.* **1954**, 1265.

(31) Salem, L. *Electrons in Chemical Reactions. First Principles*; J. Willey: New York, 1982.

(32) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3339.

(33) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223.

(34) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 543.

(35) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley: London, 1968.

(36) Davies, J. H.; Haddock, E.; Kirby, P.; Webb, S. B. *J. Chem. Soc.* **1971**, C, 2843.

(37) Feiring, A. E.; Wonchoba, E. R. *J. Polym. Sci.: Part A: Polym. Chem.* **1994**, *32*, 389.

(38) Yagulposkii, L. M.; Ilchenko, A. Y.; Kondrakenko, N. V. *Russ. Chem. Rev.* **1974**, *43*, 32.

(39) Nudelman, S. M.; MacCormack, P. *J. Chem. Soc. Perkin Trans. 2* **1987**, 805.

(40) Saika, A.; Slichter, C. P. *J. Chem. Phis.* **1954**, *22*, 26.

(41) Karplus, M.; Pople, J. A. *J. Chem. Phis.* **1963**, *38*, 2803.

(42) Webb, G. A. *The Multinuclear Approach to NMR Spectroscopy*; Lambert, J. B., Riddell, F. G., Eds.; NATO ASI series, vol C-103, 1983.

(43) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; J. Wiley, New York, 1988.

(44) Craik, D. J. in *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed. Academic Press: London; 1983, Vol. 15.

(45) Nelson, G. L.; Levi, G. C.; Cargioli, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 3089.

(46) Hehre, W. J.; Taft, R. W. in *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; Wiley-Interscience: New York, 1976, Vol. 12.