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Effects of fluorine substitution in the catechole ring. An *ab-initio* MO theoretical study

M. Hodošček and T. Šolmajer

Boris Kidrič Institute of Chemistry, POB. 30, 6115 Ljubljana, Yugoslavia, and,
LEK-Pharmaceutical and Chemical Industry, 61000 Ljubljana, Yugoslavia

Molecular orbital calculations on 2,5- and 6F substituted catechol rings were performed in order to get insight into the electronic structure of these biologically very important molecules. σ and π charge distributions, dipole moments, localized orbitals and the effect of fluorine substituent on OH activity were computed for both neutral and anionic species. The resulting theoretical acidities compare well with experimental data while the charge distributions and electron density plots are in accord with classical concepts of theoretical organic chemistry.

Key words: Fluorocatechols—dipole moments—localized orbitals—acidity

1. Introduction

In applying the concepts of physical organic chemistry we are usually not concerned with absolute quantities but with the changes brought about by changes in molecular structure in homologous series. This approach has been implemented in the present work in an attempt to describe the changes in properties of the catechol ring imparted by the fluorine substituent at sites 2, 5 and 6. Recently synthesized analogs of catecholamines are of importance for the pharmacology of adrenergic receptors and the elucidation of mode of binding and selectivity to subtypes [1-3]. The ability to accumulate a negative charge and in giving up a proton can be thought of as a measure of the hydroxyl group acidity [4]. The acidity in turn appears to be the key feature in distinguishing the different H-bonding proton-donor abilities, and probably the biological activity at adrenergic receptors [3, 5]. Our previous papers [6-9] have dealt with the molecular electrostatic potential (MEP) and conformational properties of these and similar

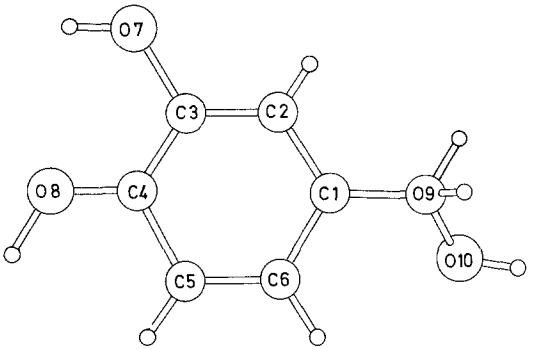


Fig. 1. 1-methylenehydroxy-catechol (in the text abbreviated to (C). CH_2OH substituent stands for catecholamine side chain

molecules. It has been demonstrated [9] that the conformational effect of interacting 2 or 6 substituted fluorine with the side chain β (OH) group (Fig. 1) is negligible. Marked differences in MEP induced by 6 and 2F substitution, respectively, originate in the static electron density distributions [10–14] therefore Mulliken population analyses, dipole moments, localized molecular orbitals [15–18], ionization potentials were computed.

The fluorine substituent interacts with the aromatic ring by withdrawing σ electrons and donating π electrons. The amount of shielding [19] of the 3,4(OH) groups oxygen atoms seems to be dependent on the position of the F substituent. The interesting feature is certainly the means by which the σ and π interactions of the fluorine substituent influence the catechol ring π^* orbitals [20–22].

2. Methods

Ab initio MO computations were done by using a slightly modified version of Gaussian 80 system [23, 24]. Standard model geometries [25] and the basis set STO-3G were used as previously [6–9]. In position 1 a CH_2OH substituent was put to mimick the side chain of the biologically important compound noradrenaline (Fig. 1). the optimized value for the C–O length (1.28 Å) in the catechoxide and substituted catechoxide anions was taken and used throughout. Localized molecular orbitals (LMO) were obtained by a modified Boys procedure [15] and the orbital electron densities plotted. These LMO are in most cases identical to those generated by the more time consuming Edmiston-Ruedenberg method. Convergence was reached when the rms change beween two successive iteration cycles was less than 10^{-4}. Electron density as described by minimal basis set constrains the electrons to a region too close to the nucleus [26] therefore extended standard basis set (431G) calculations of the electron density were carried out to overcome this difficulty. Interaction energies between the substituents and the OH and O^- groups at C4 are given by the energy of isodesmic reactions [19, 22].

$$XC_6H_3(OH)_2 + C_6H_5OH \rightarrow C_6H_4(OH)_2 + XC_6H_4OH \quad (1)$$

$$XC_6H_3(OH)O^- + C_6H_5OH \rightarrow C_6H_4(OH)O^- + XC_6H_4(OH) \quad (2)$$

where X is a fluorine substituent at positions C2, C5 and C6, respectively. The

difference in interaction energies for OH and O^- group gives the effect of the substituent X on relative gas phase acidity of OH.

3. Results and discussion

3.1. Charge distribution and ionization potentials

The results of the Mulliken population analyses for the series are given in Table 1. The comparison of the q_σ and q_π (total σ and π charges of substituents OH and F donated (accepted) to (from) the ring) indicates that fluorine is interacting with the aromatic ring by withdrawing σ electrons and donating π electrons. Both σ and π donating abilities of the 4-(OH) group in unsubstituted catechol ring increase considerably on deprotonation of the OH group. From moderate π donor ($q_\pi = -0.086$) and a strong σ acceptor in OH there is a change to strong π donor ($q_\pi = -0.464$) and very moderate σ acceptor ($q_\sigma = -0.027$) in O^-. Similar to the shielding effect in substituted phenols [19] in the case of F-substitution a rather large σ accepting contribution about $q_\sigma = 0.20$ is noted and small π charge donation ($q_\pi = -0.07$) at the site of the halogen substitution is computed. Correspondingly, the q_σ contribution at the OH group is diminished and q_π slightly enlarged the only exception being orto placed 5F substituent where the q_π effect is negative. These results may be rationalized by considering the molecular orbital energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals, presented along with total electron energies of the series in Table 2. The LUMO π orbital energies of the F-substituted catechols are lowered the shift being largest in the case of 6F substitution while in the case of 5F substituent the LUMO of 5-fluorocatechol (5-FC) is between the 2-fluorocatechol (2-FC) and 6-fluorocatechol (6-FC) LUMO orbital energies. Electron withdrawal brought about by fluorine substitution seems to be the cause of this orbital energy lowering in the case of meta-substituted 2-FC and 6-FC and vice versa for 5-FC the π donation of OH and O^- groups is diminished due to the higher lying LUMO orbital. To summarize, by examination of charges in Mulliken σ and π charge distribution and LUMO energy levels of the series we see that the lower

Table 1. Mulliken charges (a.u.) for (i) substituted catechols ($Y1$ – OH at C3 and $Y2$ = OH at C4), (ii) substituted catechoxide anions ($Y1 = O^-$ and $Y2$ = OH)

	X	$q_r(Y1)$	$q(Y2)$	$q(X)$	$q(Y1)$	$q(Y2)$	$q(X)$
(i)	H	0.185	0.171	—	−0.086	−0.093	—
	2F	0.182	0.162	0.204	−0.088	−0.090	−0.075
	5F	0.175	0.202	0.202	−0.083	−0.095	−0.072
	6F	0.182	0.169	0.203	−0.089	−0.091	−0.077
(ii)	H	−0.027[a]	0.224	—	−0.464	−0.074	—
	2F	−0.025	0.215	0.243	−0.468	−0.070	−0.066
	5F	−0.04	0.220	0.242	−0.457	−0.075	−0.059
	6F	−0.027	0.222	0.241	−0.472	−0.073	−0.070

[a] $q = -0.063$ and $q = 0$ for a hydrogen atom in benzene [22]

Table 2. Calculated total energies and energies of HOMO and LUMO orbitals for fluorine substituted catechols, and catechxide ions

X[a]	Y1	Y2	*E* a.u.	HOMO[b] a.u.	LUMO a.u.
H	OH	OH	−487.959448	−0.2299	0.2654
				(−0.3058)	(0.1438)
2F	OH	OH	−585.413884	−0.2376	0.2634
				(−0.3212)	(0.1398)
5F	OH	OH	−585.417082	0.2384	0.2632
				(−0.3221)	(0.1389)
6F	OH	OH	−585.414027	0.2261	0.2560
				(−0.3148)	(0.1283)
H	H	OH	−414.124921	−0.244921	0.2638
2F	H	OH	−511.578999	−0.2443	0.2599
5F	H	OH	−511.584905	−0.2499	0.2603
6F	H	OH	−511.578874	−0.2373	0.2530
H	O^-	OH	−478.211029	−0.0108	0.0840
2F	O^-	OH	−584.673358	−0.0194	0.0746
5F	O^-	OH	−584.671300	−0.0174	0.0827
6F	O^-	OH	−584.674304	−0.0214	0.0741

[a] X=additional substituent at the catechol ring, Y1 and Y2 are substituents at C4 and C3.

[b] Values in parenthesis are ionization potentials obtained by extended basis set

π^* energy levels are brought about by lower σ acceptance and greater π donor interaction of the *X* catechol ring substituents. Experimental data [20, 21] stating that π energy levels of planar aromatic systems do not shift appreciably on perfluorination appears to be qualitatively valid here too; photoelectron spectra of the title compounds should confirm these premises.

The dipole moments are presented in Table 3. The calculated dipole moment of 2 FC is largest in the series (3.9 Debye) while 6-FC is found to have a relatively very small dipole moment (0.82 Debye). These results are very similar to those of previous calculations on substituted benzene and phenol rings [19, 22]. In unsubstituted catechol the charge densities show considerable σ withdrawal and π donation from the oxygen *p*-type lone pair into the ring. Changes in substituted catechols (C) arise primarily from charge alternation brought about by σ charge withdrawal at positions of 2 and 6 substituents, respectively. Dipole moments of C and 5-FC molecules lie between these two extremes. Therefore, a crude estimate of the strength of dipolar induced forces which may be instrumental in interaction between substituted catechol ring and environment is given by changes in dipole moments in this series.

3.2. Effect of fluorine on 4-OH acidity

The computed relative acidities of substituted catechols and catechoxide anions are listed in Table 3. The effect of substituent on acidity depends both on σ and π electron properties. The energies of interaction between OH and O^- groups

Table 3. Effect of substituents and the dipole moments of F substituted catechols and corresponding anions

	Catechol [kcal/mol]	Catechoxide [kcal/mol]	Stabilization energy [kcal/mol]	Dipole moment [Debye]			
				x	y	z	Total
H	0.	0.	0.	−2.09	0.79	1.00	2.45
2F	0.22	5.18	4.95	−3.83	0.77	−0.01	3.90
5F	−1.47	0.18	1.66	−0.25	0.79	−2.04	2.20
6F	−0.39	5.84	5.46	−0.28	0.76	−0.08	0.82

(Eq. 1 and 2 of the Methods section, respectively) and the X substituent on the catechol ring are given in the first two columns of Table 3. The interaction energies of the meta positioned F with the ring are largest (in 2-FC 5.18 kcal/mol and in 6-FC 5.84 kcal/mol) indicating that the greater (smaller) π charge donation to the ring as a result of the second substituent the larger (smaller) substituent-ring stabilizing interaction. The effects of substituents on acidities in catechols do not parallel the corresponding situation in catechoxide anions but are largely determined by effects in the anion. In case of 5-FC both σ withdrawal and π donation are smaller; the LUMO orbital is less lowered than in case of 2-FC and 6-FC bringing about smaller overall stabilizing interaction (1.66 kcal/mol). In case of 5-fluorocatechoxide the strong σ acceptance interaction with O^- negative charge overrides the destabilization of the catechol ring (−1.47 kcal/mol). Enhanced π donation of the OH group in case of 2-FC and 6-FC is due to energetically lower LUMO orbitals (vide supra) and greater charge transfer; the σ withdrawal is reduced but the larger orbital energy lowering gives the largest net stabilization energy in 6-FC (5.46 kcal/mol). Pertinent experimental data [26, 27] in fluorine substituted phenols qualitatively support this ordering in the gas phase. However, in solvent [27–29] or any biological environment [30] polar molecules are interacting directly with the OH or O^- functional group. This interaction is sensitive to negative charge withdrawal from this group and the charge dispersal in the catechol anion causes a big difference in solvation of the anion and in acidity of the substituted catechoxide ring.

This large dispersal is nicely illustrated by the electron density of the HOMO orbital in this series (Fig. 2a–d). The HOMO orbital electron densities represent the interaction of the HOMO of substituted catechols with the π donating group F. Since the HOMO density in the three molecules C, 2-FC and 5-FC are virtually equal the density in 6-FC being much larger in the C3-C4 bond region we may speculate that the π donor interacts most efficiently at this site confirming a well known phenomenon of through π system interaction. The large electron density in the HOMO means greater mixing of the HOMO and the lone pair orbitals resulting in less effective π-donation into the LUMO. This gives the acid strengthening of the OH-substituent at C4. This effect is combined in the case of 2-FC with the effect of lowering the π orbitals. The catechol hydroxyl oxygen at C4 becomes a poorer electron donor. In the case of 5-FC a less effective donation in the LUMO is a result of the competition of π donating abiliy of the

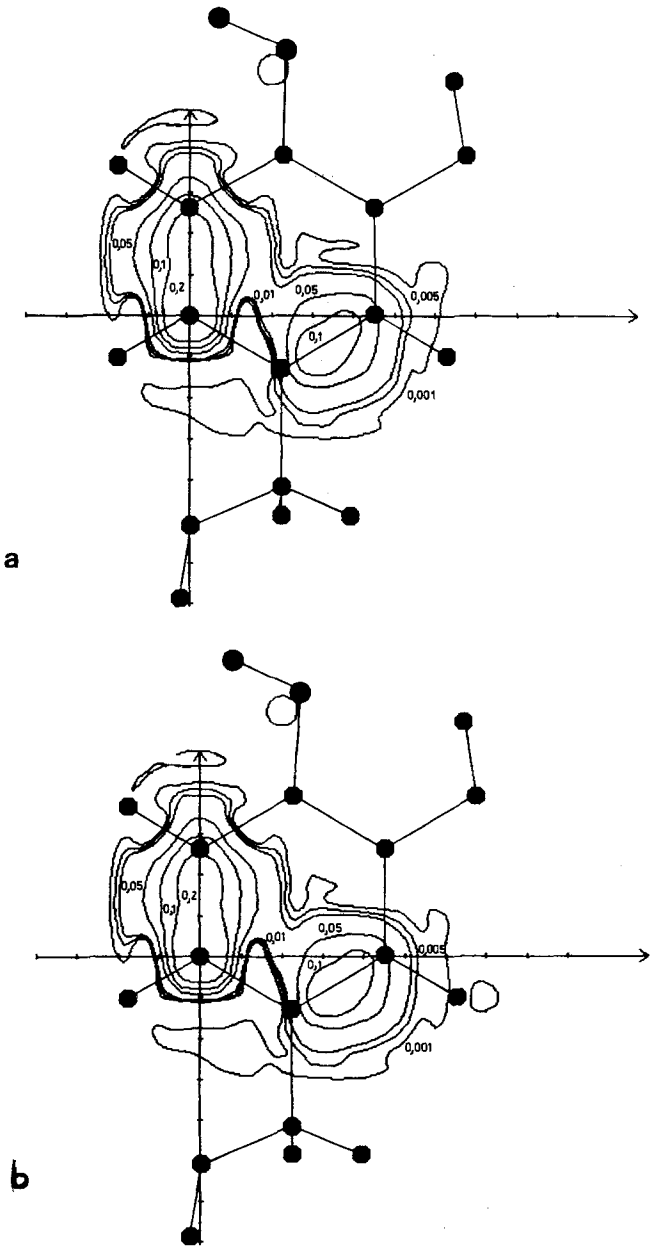
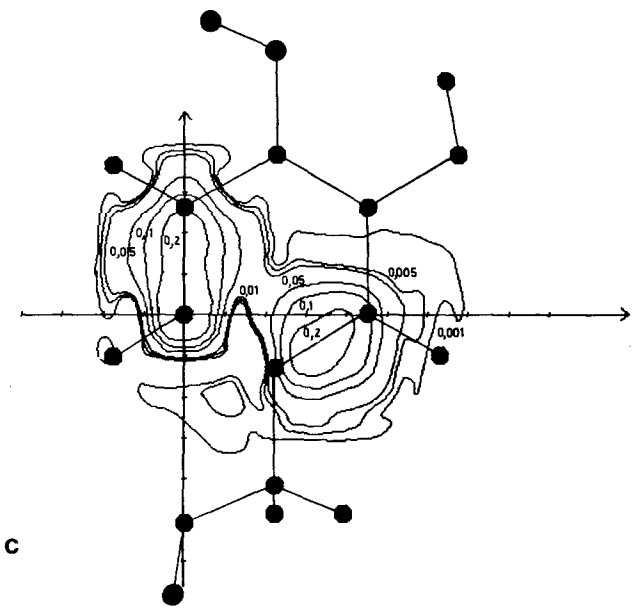


Fig. 2. Electron density of the HOMO orbital in substituted fluorocatechols: **a** 1-methylenehydroxy-catechol (C), **b** 1-methylenehydroxy-2-fluorocatechol (2-FC), **c** 1-methylenehydroxy-5-fluorocatechol (5-FC), **d** 1-methylenehydroxy-6-fluorocatechol (6-FC)


0,1
0,05
0,2
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0,005
0,05
0,1
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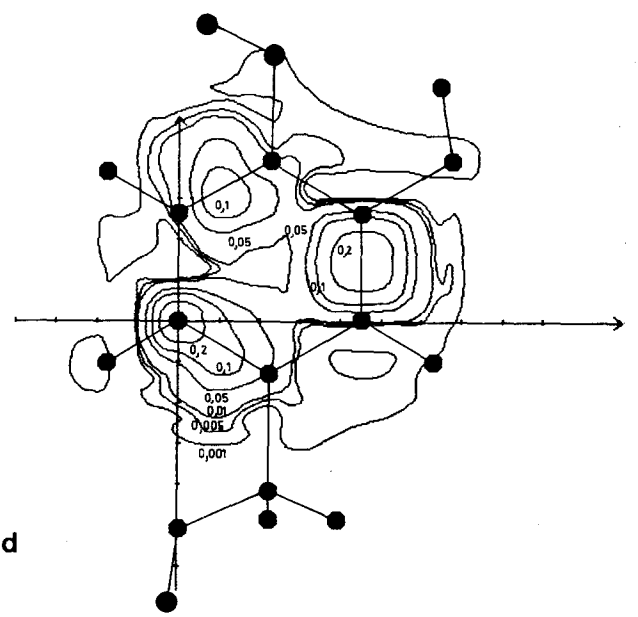
c


0,1
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0,1
0,05
0,01
0,005
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d

Fig. 2 (*cont.*)

4-OH group and orto substituted F. The interaction of a hypothetical electrophile with the aromatic rings of this series involves principally the HOMO orbital and the vacant orbital of the electrophile. A consequence of this interaction is that charge transfer from the former to the latter orbital occurs. In the case of 2-FC there is a removal of binding electron density between F and C4 and the development of binding electron density between F and electrophile. Since the two effects are energetically opposite no effect is expected in 3,4 substituted hydroxyles. On the other hand, in the case of 6-FC there is a removal of antibonding electron density between F and C1 and the development of bonding density in the region C3-C4. Hence the enhancement of interaction with the electrophile in this region. It is not possible to make a definitive conclusion about the mode of action of the title compounds on the basis of data presented above, but we may comment that

(i) different dipole moment of 6-FC may cause a different "steering" of this molecule by electrostatic forces of the receptor site and different solvation properties than for the other three molecules.
(ii) in contrast to the three β-adrenergic agonists C, 2-FC, and 5-FC whose HOMO electron densities in the region of C3-C4 atoms (Fig. 2a-c) do not change there is an alternation of this quantity in 6-FC. This may be correlated with enhanced electrophile affinity in the 3,4-hydroxyle substituents region of the latter molecule.

These results may be of value in the directed synthesis of adrenergic compounds and/or model receptor-drug interaction studies.

4. Conclusions

Due to the importance of fluorine substituted catechol rings for the understanding of adrenergic pharmacology, a theoretical study was undertaken. The differences in electronic properties of these rings are the following:

1. Dipole moments of C, 2-FC, and 5-FC are considerably larger than for 6-FC indicating that dipolar forces act differently in this series.
2. The fluorine substituent interacts with the OH and O^- groups by both σ withdrawal and π donating effects bringing about a positive stabilization energy. This finding is qualitatively supported by experimental data on substituted phenols in the gas phase. These changes in interaction are mainly governed by substituent interactions in the catecholate anion.
3. Electron densities of the HOMO orbitals in C, 2-FC and 5-FC are virtually the same while in 6-FC the density is much larger in the C3-C4 bond region. Therefore greater mixing of the HOMO orbital with the lone pair orbitals is induced.

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