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Additivity of Substituent Effects in the Fluoroarene Series : Equilibrium Acidity in the Gas Phase and Deprotonation Rates in Ethereal Solution

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Abstract : Benzene and all mono-, di-, tri-, tetra- and pentafluoro substituted derivatives thereof were equilibrated with the corresponding aryl anions in the gas phase. Perfect additivity of the substituent effects on the acidity was observed. The basicities were diminished by 12, 6 and 4 kcal/mol depending on whether the supplementary fluorine atom occupied the *ortho*, *meta* or *para* position with respect to the deprotonation site. On the other hand, substituent effects on the rates of hydrogen/metal interconversion processes level off with increasing numbers of halogens. For example, while the free energy of activation of *sec*-butyllithium promoted lithiation of fluorobenzene is at least 4 kcal/mol smaller than that of benzene, the difference was found to shrink to less than 2.5 kcal/mol when pentafluorobenzene and 1,2,3,4-tetrafluorobenzene were compared. © 1997 Elsevier Science Ltd.

Acidity belongs to the most fundamental molecular properties. It is a measure for the energy difference between a cationic and a neutral species (*e.g.*, between an ammonium salt and the corresponding amine) or between a neutral and an anionic species (*e.g.*, between a phenol and its phenolate). Substituent effects on acid dissociation constants monitor secondary electronic perturbations which, in general, affect both the charged and the uncharged entity, though one of them preferentially. A successful parametrization of such substituent effects allows one to predict the acid-base behavior of new compounds. This is of practical importance since often protonation or deprotonation are required to initiate a reaction. On the other hand, the study of acid-base equilibria always provides valuable information as to the relationship that exists between structural factors and thermodynamic stability.

Whenever a substituent parametrization is attempted, the issue of additivity has to be addressed. As a literature search reveals, the repetitive introduction of the same substituent into a molecule does generally not lead to a monotonous accumulation, but rather to an attenuation of differences. For example, when moving from acetic acid through mono- and di- to trifluoroacetic acid, the first halogen causes a decrease of the pK_a value by 2.2, the second by 1.7 and the third by only 1.1 units [1]. Also the pK_a intervals between acetic acid and mono-, di- and trichloroacetic acid (pK_a 4.76, 2.86, 1.26 and 0.63, respectively) are unequally spaced [1].

We wanted to explore whether or not substituent effects in the fluoroarene series are additive. What makes fluorine fascinating from a mechanistic point of view is its dualistic nature : strong inductive electron withdrawal, a tribute to its unrivaled electronegativity [2], combined with a remarkably powerful mesomeric electron donation [3 - 5]. The deprotonation of fluoroarenes is an efficacious means to generate reactive organometallic intermediates which can be used to incorporate halogen-bearing building blocks into substances of potential use as pharmaceuticals or agrochemicals. We decided to probe the acidifying effect exerted by one or several fluorine atoms in two different ways.

First, we have equilibrated acid-base couples in the gas phase and determined the ion concentrations by cyclotron mass spectrometry as described previously [6]. The gas phase acidities (free energies of deprotonation ΔG°_g) thus obtained are listed below (Table 1). As illustrated in the figure, when comparing two acids one has to distinguish whether the extra fluorine atom occupies an *ortho*, *meta* or *para* position with respect to the deprotonation site before evaluating its contribution to the overall acidity. Making the assumption that an *o*-F, *m*-F and *p*-F substituent enhances the thermodynamic stability (*i.e.*, lowers the basicity) of a "naked" aryl anion by approximately 12, 6 and 4 kcal/mol, respectively [7], one can reproduce the experimental ΔG°_g values with amazing accuracy (standard deviations averaging less than 1 kcal/mol; see Table 1). Thus, the additivity of substituent effects can be considered as established in the given series.

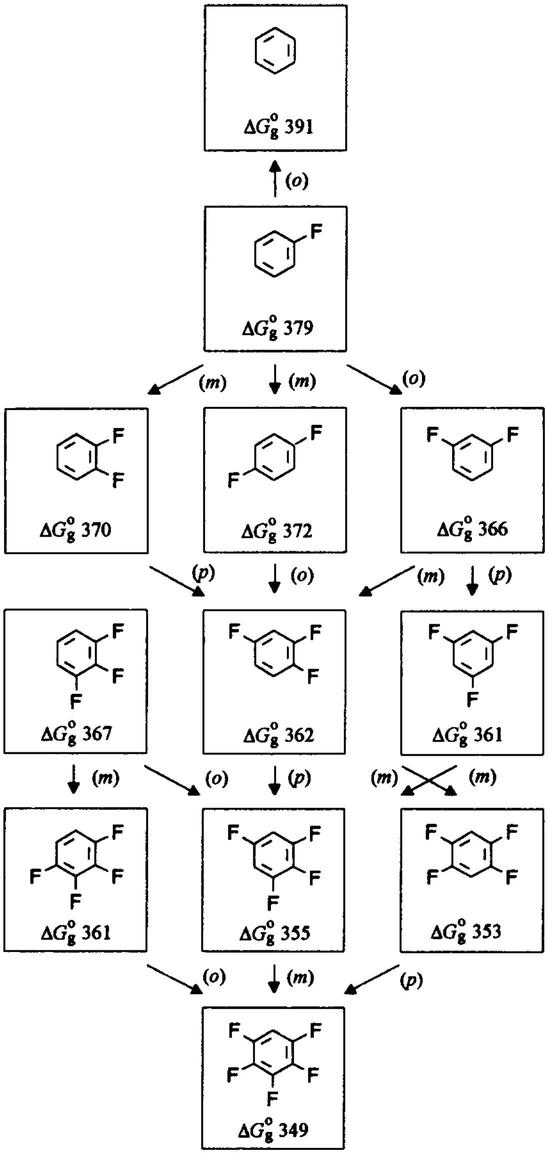

Table 1. Deprotonation equilibria of benzene and fluorinated congeners in the gas phase : enthalpies ΔH°_{g}, free energies ΔG°_{g} and relative free energies $\Delta\Delta G^{\circ}_{g}$ [a, b].

CH-acid	$\Delta\Delta H^{\circ}_{g}$	ΔG°_{g}	$\Delta\Delta G^{\circ}_{g}$
benzene	400.7	390.9	+ 12.3
fluorobenzene	386.9	378.6	≡ 0.0
1,2-difluorobenzene	377.9	369.5	− 9.1
1,4-difluorobenzene	380.2	372.1	− 6.5
1,3-difluorobenzene	373.9	366.3	− 12.3
1,2,3-trifluorobenzene	375.5	367.3	− 11.3
1,2,4-trifluorobenzene	370.2	362.6	− 16.0
1,3,5-trifluorobenzene	369.7	361.4	− 17.2
1,2,3,4-tetrafluorobenzene	369.7	361.6	− 17.0
1,2,3,5-tetrafluorobenzene	363.3	355.4	− 23.2
1,2,4,5-tetrafluorobenzene	361.4	353.3	− 25.3
1,2,3,4,5-pentafluorobenzene	356.6	349.0	− 29.6

a) All energies in kcal/mol.

b) The deprotonation enthalpies ΔH°_{g} were calculated from the ΔG°_{g} values in the usual way [8] by taking into account the entropy changes due to proton dissociation and rotational symmetry changes.

Base catalyzed hydrogen isotope exchange reactions reflect the spread of gas phase acidities not in full extent. A fluorine substituent accommodated in the *ortho*, *meta* or *para* position lowers the barrier to dedeuteration by about 7.5, 4.0 and 2.5 kcal/mol, respectively, when the exchange is accomplished with potassium amide in liquid ammonia [9a] and about 7.5, 3.0 and 1.5 kcal/mol with lithium cyclohexylamide in cyclohexylamine [9b-d]. The attenuation of gas phase basicity differences in solution may be partially ascribed to a bulk solvent effect (dipole-dipole interactions), but should mainly reflect structural changes, since the negatively charged intermediates should no longer exist as free fluoroaryl anions but rather be coordinated through hydrogen bonds to amine molecules.

In contrast to isotope exchange, hydrogen/metal interconversion ("metalation") reactions are down-hill processes in energy terms. Therefore, their transition states have little resemblance with carbanionic intermediates and consequently less pronounced substituent effects are to be predicted. Competition experiments [10] performed with lithium 2,2,6,6-tetramethylpiperidide (LITMP; partially reversible deprotonation) and *sec*-butyllithium (LIS; entirely irreversible deprotonation) in tetrahydrofuran have indeed confirmed this expectation (Table 2). The maximum acceleration upon introduction of one additional fluorine atom was observed between the pair benzene and fluorobenzene. The rate ratio k_{rel} of 20000 (reaction with *sec*-butyllithium) corresponds, after statistical correction, to a rate factor $k^{\mathrm{f}}_{\mathrm{rel}}$ of 60000 and a lowering of the activation barrier of more than 4 kcal/mol. To close this huge gap, anisole ($k^{\mathrm{f}}_{\mathrm{rel}}$ 3000) and benzotrifluoride ($k^{\mathrm{f}}_{\mathrm{rel}}$ 600) were used as relay compounds. With increasing numbers of substituents, the reactions become more and more exothermic. As a corollary, the transition states progressively shift to the side of the starting components and their carbanionic character continues to be eroded.

Table 2. Benzene and fluorinated congeners as substrates in hydrogen/metal interconversion reactions promoted by lithium 2,2,6,6-tetramethylpiperidide (LITMP) or *sec*-butyllithium (LIS) in tetrahydrofuran at -75 °C : approximate relative rates k_{rel}, factorized rates $k^{\mathrm{f}}_{\mathrm{rel}}$ (statistically corrected for the number of equivalent hydrogen atoms at exchange positions) and factorized differences in activation energies $\Delta\Delta G^{\ddagger}$ [kcal/mol].

substrate	reagent : LITMP			reagent : LIS		
	k_{rel}	$k^{\mathrm{f}}_{\mathrm{rel}}$	$\Delta\Delta G^{\ddagger}$	k_{rel}	$k^{\mathrm{f}}_{\mathrm{rel}}$	$\Delta\Delta G^{\ddagger}$
benzene	$\geq 7\cdot10^{-4}$	$\geq 1\cdot10^{-4}$	≥ 3.6	$1\cdot10^{-4}$	$2\cdot10^{-5}$	$+4.2$
fluorobenzene	$\equiv 2\cdot10^{0}$	$\equiv 1\cdot10^{0}$	$\equiv 0.0$	$\equiv 2\cdot10^{0}$	$\equiv 1\cdot10^{0}$	$\equiv 0.0$
1,2-difluorobenzene	$8\cdot10^{1}$	$4\cdot10^{1}$	-1.4	$4\cdot10^{1}$	$2\cdot10^{1}$	-1.1
1,4-difluorobenzene	$8\cdot10^{1}$	$2\cdot10^{1}$	-1.2	$4\cdot10^{1}$	$1\cdot10^{1}$	-0.9
1,3-difluorobenzene	$4\cdot10^{5}$	$4\cdot10^{5}$	-5.1	$8\cdot10^{2}$	$8\cdot10^{2}$	-2.6
1,2,3-trifluorobenzene	$8\cdot10^{4}$	$4\cdot10^{4}$	-4.2	$2\cdot10^{2}$	$1\cdot10^{2}$	-1.8
1,2,4-trifluorobenzene	$2\cdot10^{6}$	$2\cdot10^{6}$	-5.7	$4\cdot10^{3}$	$4\cdot10^{3}$	-3.3
1,3,5-trifluorobenzene	$2\cdot10^{6}$	$7\cdot10^{5}$	-5.3	$4\cdot10^{3}$	$1\cdot10^{3}$	-2.7
1,2,3,4-tetrafluorobenzene	$2\cdot10^{6}$	$1\cdot10^{6}$	-5.4	$3\cdot10^{3}$	$2\cdot10^{3}$	-3.0
1,2,3,5-tetrafluorobenzene	$1\cdot10^{8}$	$5\cdot10^{7}$	-6.9	$7\cdot10^{4}$	$4\cdot10^{4}$	-4.2
1,2,4,5-tetrafluorobenzene	$2\cdot10^{8}$	$1\cdot10^{8}$	-7.2	$4\cdot10^{5}$	$2\cdot10^{5}$	-4.8
1,2,3,4,5-pentafluorobenzene	$1\cdot10^{9}$	$1\cdot10^{9}$	-8.1	$6\cdot10^{5}$	$6\cdot10^{5}$	-5.2

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