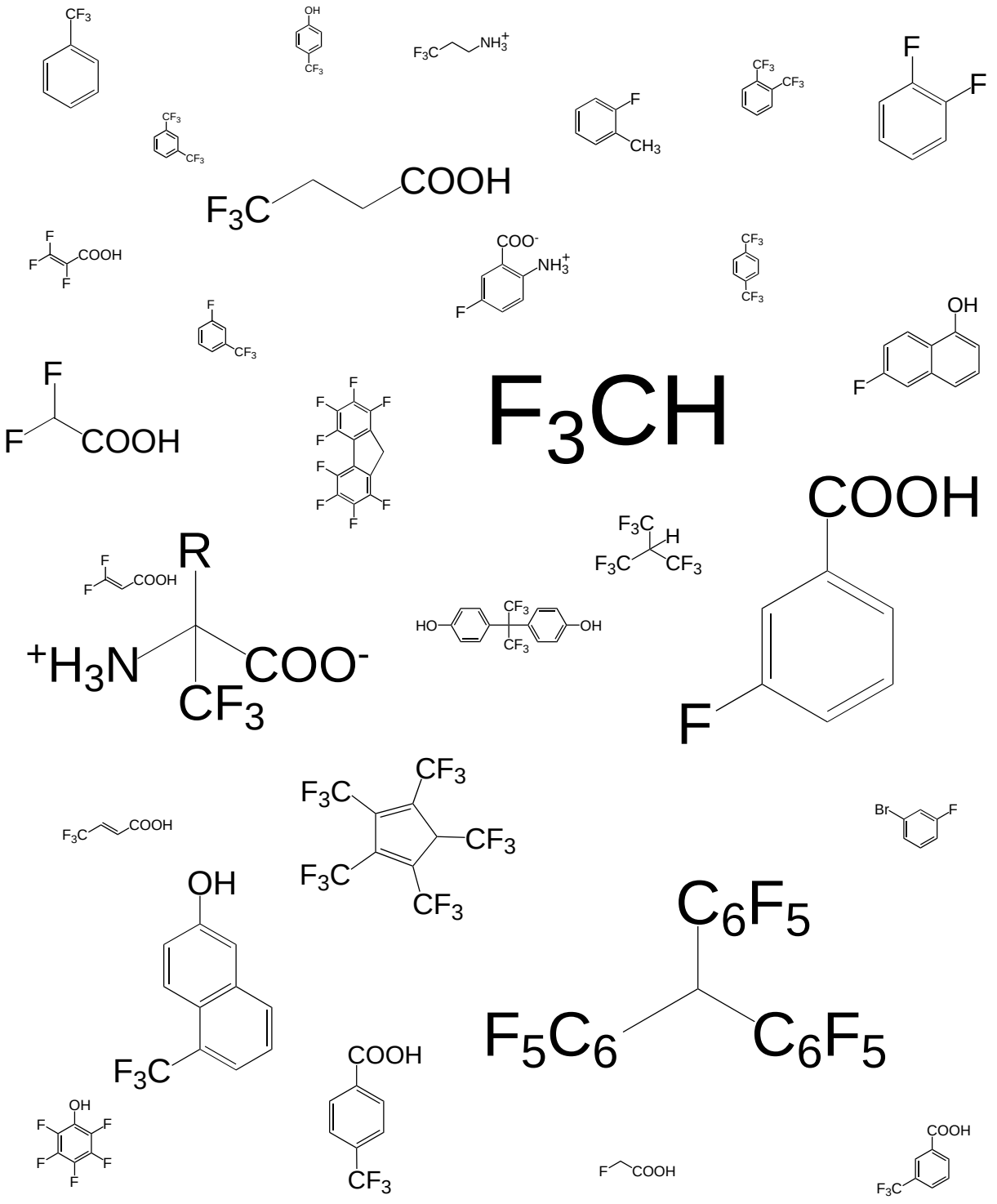

Not only a diverse range of possible substitution patterns, but also numerous, sometimes contradictory, effects the extent of which are seldom measurable, make it difficult to predict the acidity of fluoro compounds. A systematic comparison of the acidities in all relevant media provides a better insight into the influence of fluoro substituents.

Parametrization of Substituents: Effects of Fluorine and Other Heteroatoms on OH, NH, and CH Acidities

Manfred Schlosser*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Fluorine leaves nobody indifferent; it inflames emotions, be that affections or aversions. As a substituent it is rarely boring, always good for a surprise, but often completely unpredictable. It behaves nonconformingly even when fundamental properties such as ionic dissociation are under consideration. Although fluorine scores highest in the Pauling scale of electronegativity, its Hammett constants (σ_m +0.34, σ_p +0.06) are all but spectacular. Alanine and α-fluoroalanine have virtually the same pK_a values, whereas trifluoroalanine proves to be a fairly strong acid. Apparently, the smallest halogen emits different kinds of electronic effects which, depending on the given situation, may counterbalance or amplify each other. To gain better insight, a new approach is undertaken. A comparison between thermodynamic acidity (proton dissociation in aqueous medium and in the gas phase) and kinetic proton mobility (rates of base-catalyzed hydrogen isotope exchange and stoichiometric hydrogen/metal interconversion processes) allows key issues to be addressed, in particular to identify medium effects on acidity and to probe the additivity of substituent effects. In this way fluorine, the heterosubstituent par excellence, which can have a stronger impact on the reactivity in its vicinity than any other element, may serve as a crucial test of any model concerning the origin and transmission of electronic effects. There are, however, also practical implications. Organometallic compounds carrying one, two, or several fluorine atoms are versatile intermediates in organic synthesis; they allow access to a variety of pharmaceutically, agrochemically, or technically attractive products. For this reason, organofluorine chemistry surely must welcome any information that helps to generate more members of this family of reactive species or aids the development of new methodical concepts, such as optional site selectivity.

Keywords: acidity · fluorine · gas-phase chemistry · metalations · substituent effects

1. Introduction

If we had to explain to a pupil the great variety of chemical reactions known, we would probably choose a paradigmatic approach. We would try to reduce the infinite manifold of possibilities and project them on a few archetypal reaction patterns. Subsequently, we would have to breathe life into these reaction chimeras by illustrating them with real examples.

Three types of chemical processes are particularly suited to schematically cover a maximum of reaction events and thus would have to become the cornerstones of our attempt to systematize: redox processes, electrophile–nucleophile interactions, and proton transfers occurring between acid/base couples. The latter category is arguably the most fundamental one; a concept as indispensable for inorganic as for organic chemistry.

This review endeavors to explore some phenomena associated with acidity by using fluorine as a probe. This element combines a pronounced electronic individuality with steric modesty, mimicking hydrogen, as far as Van der Waals radii and bond lengths are concerned, closely enough to delude enzymes and receptors.[1–3] Thus, the lessons it teaches us are informative with respect to physicochemical theory, modern organic synthesis, and the engineering of biological activity.

2. Dissociation Equilibria in Aqueous Medium

Common organic solvents lack sufficient dielectric capacity to sustain ion dissociation. Therefore, no thermodynamically valid acid/base equilibria can be measured in such media. For practical purposes, it is nevertheless important to develop a

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feeling for proton mobilities in ethereal solution. A promising approach to this end is to compare the rates of irreversible deprotonation in organic media with acid dissociation constants, as determined in aqueous solution (pK_a) and in the gas phase (pK_g). If such a correlation can be established it could be applied to predict the site-specific rates with which yet unknown though synthetically useful intermediates may be generated by hydrogen/metal interconversion processes.

Sections 2 and 3 in this review deal solely with thermodynamic parameters, whereas Section 4 presents mainly though not exclusively kinetic data. Acid/base equilibrations by hydrogen/metal countercurrent transfer in organic, polar, or unpolar media (dimethyl sulfoxide, cyclohexylamine, or tetrahydrofuran) are treated in the Sections 4.1–4.5 in connection with hydrogen isotope exchange and metalation rates as well as in Section 2.5 in the context of aqueous dissociation constants of hydrocarbon acids.

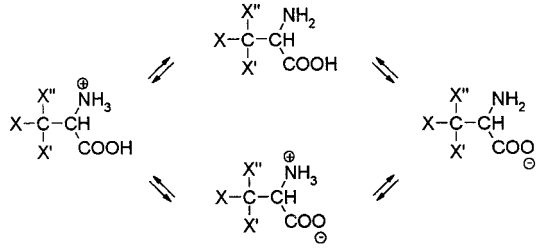
2.1. Amino Acids

Fluorinated α-amino acids are man-made analogues of vital natural building blocks. Like their halogen-free congeners, they have two acidic sites: a carboxy and an ammonio functional group. As a consequence, two dissociation coefficients pK_a can be measured.[4] Their interpretation, however, is not straightforward since there is an ammonium cation and a carboxylate anion, each of them entertaining equilibria with *two* electrochemically neutral species, an uncharged and a zwitterionic one. It is indeed not apparent, for example, why only the second and third halogen atom should cause strong acidification[5] when fluorine is progressively introduced into the β-position of alanine ($\Delta pK_a^{COOH} = 2.3$, $\Delta pK_a^{\oplus NH_3} = 9.9$),[4] while the first substituent has a surprisingly small, practically negligible effect[5] (see Table 1). The replacement of the methyl group in alanine by trifluoromethyl enhances the OH acidity (at the carboxy site) by 1.1 and the NH acidity (at the ammonio site) by 4.5 units.[5, 6] The differences are similar when one compares α-aminoisobutyric acid (ΔpK_a^{COOH}2.4, $\Delta pK_a^{\oplus NH_3} = 0.2$)[4] with its β,β,β-trifluorinated analogue (Table 2).[7]

Unsurprisingly, the acidifying effect levels off with increasing distance between the trifluoromethyl and the acidic groups in the α-aminopropionic, -butyric, -valeric, and -capronic acid derivatives. Nevertheless it is still perceptible even in the latter case (Table 3).[5]

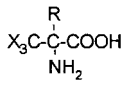
Such effects can be more or less attenuated in the aromatic series. The introduction of fluorine into the 4-position makes anthranilic acid ($\Delta pK_a^{COOH} = 2.2$, $\Delta pK_a^{\oplus NH_3} = 4.9$)[4] considerably more acidic, while the same substituent in the 5-position causes only minor changes (Table 4).[8] Unfortunately, the two other isomers have not yet been investigated.

Table 1. Shift in the pK_a values (ΔpK_a) of β-fluoro-, β,β-difluoro-, and β,β,β-trifluoralanine[5] relative to the parent compound ($\Delta pK_a^{COOH} = 2.3$, $\Delta pK_a^{\oplus NH_3} = 9.9$[4]).



X	X′	X″	ΔpK_a^{COOH}	$\Delta pK_a^{\oplus NH_3}$
H	H	H	0.0	0.0
F	H	H	+0.1	−0.1
F	F	H	−0.8	−1.5
F	F	F	−1.1	−4.5

Table 2. ΔpK_a of β,β,β-trifluoroalanine, α-amino-β,β,β-trifluoroisobutyric acid,[5, 6] and α-aminoisobutyric acid[7] relative to alanine.[4]



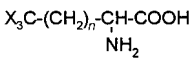
X	R	ΔpK_a^{COOH}	$\Delta pK_a^{\oplus NH_3}$
H	H	0.0	0.0
F	H	−1.1[5] (−0.0[6])	−4.5[5] (−4.3[6])
H	CH_3	+0.1[4]	+0.3[4]
F	CH_3	−0.3[7]	−4.0[7]

2.2. Carboxylic Acids

Fluorine substituents exert remarkably strong effects on the dissociation constants of simple carboxylic acids. Thus, the

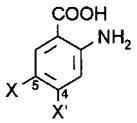
Manfred Schlosser was born in 1934 in Ludwigshafen (Germany). He studied chemistry and, to some extent, medicine, at the Universität Heidelberg, graduating in 1957. He carried out his thesis work under the supervision of Professor Georg Wittig and received his doctorate in 1960. After a research year in Brussels and his "Habilitation" in Heidelberg (1966) he accepted the position of a group leader ("Oberarzt") at the German Cancer Research Center in Heidelberg. In 1971 he was appointed as the successor of Professor Jiří Sicher at the University of Lausanne. He has lectured as a visiting professor in Italy (Perugia, Firenze), Germany (Berlin), Hungary (Budapest), USA (San Jose), and Japan (Kyoto). His research work is characterized by an intimate interplay between novel mechanistic insight and synthetic applications. He coordinates a European network of research in the organofluorine area and is author or editor of three books on organometallic chemistry, a second edition of the most recent one is presently in preparation (Organometallics in Synthesis: A Manual, Wiley, Chichester, **1998**).

Table 3. ΔpK_a of α-aminobutyric, -valeric, and -capronic acid and of their ω,ω,ω-trifluoro derivatives[5] relative to alanine.[4]



X	*n*	ΔpK_a^{COOH}	$\Delta pK_a^{\oplus NH_3}$
H	0	0.0	0.0
F	0	−1.1[5]	−4.5[5]
H	1	0.0[4]	−0.1[4]
F	1	−0.6[5]	−1.6[5]
H	2	0.0[4]	−0.1[4]
F	2	−0.2[5]	−0.9[5]
H	3	0.0[4]	−0.1[4]
F	3	−0.2[5]	−0.2[5]

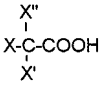
Table 4. ΔpK_a of 4- and 5-fluoroanthranilic acid[8] relative to the halogen-free parent compound.[4]



X	X′	ΔpK_a^{COOH}	$\Delta pK_a^{\oplus NH_3}$
H	H	0.0	0.0
F	H	−0.2[8]	−0.1[8]
H	F	−0.8[8]	−0.3[8]

pK_a values steadily decrease by one to two units when one moves from acetic acid ($pK_a = 4.8$)[9] to mono-, di-, and trifluoroacetic acid[10-13] (see Table 5). When the trifluoromethyl moiety is placed in progressively more remote

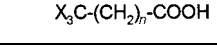
Table 5. ΔpK_a of mono-, di-, and trifluoroacetic acid relative to the parent compound.[9–13]



X	X′	X″	ΔpK_a
H	H	H	0.0
F	H	H	−2.2[10]
F	F	H	−3.5[11, 12]
F	F	F	−4.6[13]

positions, the acidity difference to the halogen-free reference compound rapidly decreases without vanishing completely[13, 14] (Table 6). The remaining, if small, acidifying effect of three fluorine atoms linked to the δ-carbon atom of valeric

Table 6. ΔpK_a of a series of fatty acids and their ω,ω,ω-trifluoro derivatives[13, 14] relative to acetic acid ($pK_a = 4.8$).[9]

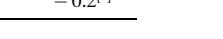


X	*n*	ΔpK_a
H	0	0.0
F	0	−4.6[13]
H	1	+0.1[9]
F	1	−1.9[13]
H	2	0.0[9]
F	2	−0.6[14]
H	3	0.0[9]
F	3	−0.3[13]

acid is startling. It can hardly be rationalized on the basis of an σ-inductive electron withdrawal, since the latter would have to propagate itself across seven consecutive bonds.

Multiple bonds are superior to saturated skeletons in the transmission of polar effects over a long range. (*E*)-γ,γ,γ-trifluoro-2-butenoic acid is considerably more acidic than crotonic acid ($\Delta pK_a = 1.3$), while the difference between γ,γ,γ-trifluorobutyric and butyric acid ($\Delta pKa = 0.6$)[9] is much smaller (Table 7).[13–15] On the other hand, when halogen is

Table 7. ΔpK_a of crotonic, 4,4,4-trifluorobutanoic, and (*E*)-4,4,4-trifluoro-2-butenoic acid[13–15] relative to butanoic acid ($pK_a = 4.8$).



X	Y	ΔpK_a
H	$-CH_2-CH_2-$	0.0
F	$-CH_2-CH_2-$	−0.6[14]
H	(*E*)−CH=CH−	−0.1[9]
F	(*E*)−CH=CH−	−1.4[13–15]

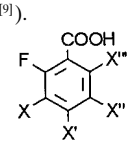
directly attached to the olefinic double bond, the unsaturated acids may be of equal or even inferior strength than saturated analogues (Table 8).[16] Chloro-substituted acids are in general more acidic than their fluorinated counterparts. A comparison of trifluoro- and trichloroacrylic acid[16] confirms this rule-of-thumb (Table 8).

Table 8. ΔpK_a of 3,3-difluoro-, 2-fluoro-, 2,3,3-trifluoro-, and 2,3,3-trichloro-2-propenoic acid relative to the halogen-free parent compound ($pK_a = 4.3$[9]).

X	X′	ΔpK_a
H	H	0.0
F	H	−1.1
H	F	−1.7
F	F	−2.5
Cl	Cl	−3.1

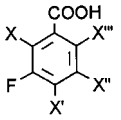
Electronic transmission also operates effectively in aromatic systems. A fluorine atom or a trifluoromethyl group attached to the *meta* position (Table 10) and, in particular, *ortho* position (Table 9) of benzoic acid enhances the acidity of the latter (ΔpK_a 5.5)[9] quite significantly as does a *para*-trifluoromethyl substituent (Table 12)[17–21]. On the other hand, the effect of a *para*-fluoro substituent (Table 11) is a

Table 9. ΔpK_a of 2-fluoro- and four difluorobenzoic acids relative to the parent compound ($pK_a = 4.3$[9]).



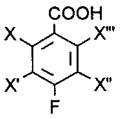
X	X′	X″	X‴	ΔpK_a
H	H	H	H	−0.7[17,18]
F	H	H	H	−1.1[18]
H	F	H	H	−0.8
H	H	F	H	−1.1[18]
H	H	H	F	−2.0[18]

Table 10. ΔpK_a of 3-fluoro- and four difluorobenzoic acids relative to the parent compound ($pK_a = 4.3$[9]).



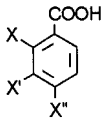
X	X′	X″	X‴	ΔpK_a
H	H	H	H	− 0.3[17]
F	H	H	H	− 1.1[18]
H	F	H	H	− 0.4[18]
H	H	F	H	− 0.7[18]
H	H	H	F	− 1.1[18]

Table 11. ΔpK_a of 4-fluoro- and two difluorobenzoic acids[17] relative to the parent compound ($pK_a = 4.3$[9]).



X	X′	X″	X‴	ΔpK_a
H	H	H	H	0.0[17] (− 0.1[18])
F	H	H	H	− 0.4[18]
H	F	H	H	− 0.8[18]

Table 12. ΔpK_a of 2-, 3-, and 4-(trifluoromethyl)benzoic acid[19–21] relative to the parent compound ($pK_a = 4.3$[9]).



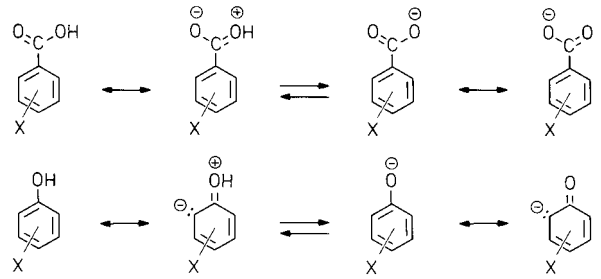
X	X′	X″	ΔpK_a
CF_3	H	H	− 0.0[19]
H	CF_3	H	− 0.4[19, 20] (− 0.6[21])
H	H	CF_3	− 0.4[19, 20] (− 0.6[21])

subtle balance between inductive electron-withdrawing and mesomeric electron-donating resonance effects; the two opposed contributions tend to cancel each other.[17, 18]

2.3. Alcohols and Phenols

When hydrogens bound to the carbon atom in methanol are replaced by trifluoromethyl groups, the acidity of the alcohol is enhanced each time by approximately four powers of ten. The pK_a values of 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-propan-2-ol, and 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol are 12.4, 9.3, and 5.2, respectively.[22]

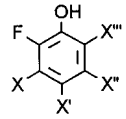
On the basis of a simple comparison of limiting structures (see Scheme 1), one would assume phenols to reflect substituent effects much more sensitively than benzoic acids do. One reason is that the distance between an aromatic substituent and the negatively charged oxygen in a phenolate is shorter by one bond length than the same distance in a benzoate and, as a corollary, electrostatic through-space



Scheme 1. Limiting structures of benzoic acids, phenols, and their anions.

interactions should be much stronger. Moreover, the aryl moiety occupies a nodal position at the carboxylate ("1,3-dioxaallyl") anion, whereas direct electronic resonance between the oxo center and an *ortho* or *para* substituent can occur. In reality, the difference is less marked than may have been expected. The acidifying effect of *ortho*- and *meta*-fluoro substituents is approximately 50 % stronger in the phenol than in the benzoic acid series (compare the data in Tables 13 and

Table 13. ΔpK_a of 2-fluorophenol and derivatives[23–25] relative to the parent compound ($pK_a = 10.0$[9]).

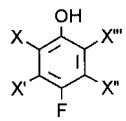


X	X′	X″	X‴	ΔpK_a
H	H	H	H	− 1.2[23, 24]
F	H	H	H	− 2.3[24]
H	F	H	H	− 1.6[24]
H	H	H	F	− 2.9[24]
F	F	F	F	− 4.5[24, 25]

14 with that in Tables 9 and 10, respectively). The effect of a fluorine substituent in the *para* position[23] is virtually negligible in both cases (Table 15 vs. Table 11). Apparently inductive electron withdrawal and mesomeric electron donation compensate each other in the *para*-fluorophenolate anion.

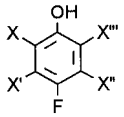
Again trifluoromethyl groups enhance the OH acidity more strongly than does a single fluorine atom (Table 16).[27] Furthermore, the CF_3 effect is a far reaching one; the *para*-(trifluoromethyl)phenol is only slightly less acidic than the *ortho* isomer.[27, 28] Trifluoromethyl groups attached to the

Table 14. ΔpK_a of 3-fluorophenol and derivatives[23–25] relative to phenol ($pK_a = 10.0$[9]).



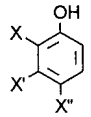
X	X′	X″	X‴	ΔpK_a
H	H	H	H	− 0.7[23]
F	H	H	H	− 2.3[24]
F	F	F	F	− 4.5[24, 25]

Table 15. ΔpK_a of 4-fluorophenol and derivatives[23, 24, 26] relative to phenol ($pK_a = 10.0$ [9]).



X	X′	X″	X‴	ΔpK_a
H	H	H	H	– 0.1[23, 26]
F	H	H	H	– 1.6[24]
F	F	F	F	– 4.5[24, 26]

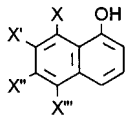
Table 16. ΔpK_a of the three (trifluoromethyl)phenols[27, 28] relative to phenol ($pK_a = 10.0$[9]).



X	X′	X″	ΔpK_a
H	H	H	0.0
CF_3	H	H	– 1.7[27]
H	CF_3	H	– 1.0[27, 28]
H	H	CF_3	– 1.3[27, 28]

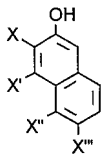
non-phenolic benzene ring of 1-naphthol (Table 17) and 2-naphthol (Table 18) still lower the pK_a values by at least half a unit, thus stressing the long-range potential of this substituent.[27] 8-Trifluoromethyl-1-naphthol is the only somewhat mysterious exception (Table 17).[27]

Table 17. ΔpK_a of (trifluoromethyl)-1-naphthols[27] relative to 1-naphthol ($pK_a = 9.4$ [9]).



X	X′	X″	X‴	ΔpK_a
H	H	H	H	0.0
CF_3	H	H	H	+ 0.7[27]
H	CF_3	H	H	– 0.6[27]
H	H	CF_3	H	– 0.5[27]
H	H	H	CF_3	– 0.6[27]

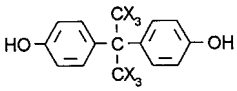
Table 18. ΔpK_a of (trifluormethyl)-2-naphthols[27] relative to 2-naphthol ($pK_a = 9.6$[9]).



X	X′	X″	X‴	ΔpK_a
H	H	H	H	0.0
CF_3	H	H	H	– 1.2[27]
H	CF_3	H	H	– 0.9[27]
H	H	CF_3	H	– 0.5[27]
H	H	H	CF_3	– 0.6[27]

4,4′-(1,1,1,3,3,3-hexafluoropropan-2,2-diyl)diphenol is a widely used component for thermal fluoroelastomer curing. For reasons of solubility, dissociation constants had to be determined in dimethyl sulfoxide.[29] As it turned out, a *para*-$\beta,\beta,\beta\beta'\beta'\beta'$-hexafluoroalkyl substituent exerts only a minor acidifying effect (Table 19).[29]

Table 19. ΔpK_a of 4,4′-(propane-2,2-diyl)diphenol[29] and its hexafluoro derivative[29] relative to phenol ($pK_{DMSO} = 13.7$[30]).



X	ΔpK_{DMSO}
H	– 0.4[29]
F	– 1.3[29]

2.4. Aliphatic and Aromatic Amines

A series of straight-chain (ω,ω,ω-trifluoroalkyl)ammonium salts is compared with the corresponding halogen-free parent compounds in Table 20.[32]. As one would have predicted, the acidifying effect decreases with distance. This effect is similar

Table 20. ΔpK_a of (ω,ω,ω-trifluoralkyl)ammonium salts relative to the halogen-free ethyl, propyl, and butyl parent compounds (for all three: $pK_a = 10.7$[4]).[32, 33]

$X_3C\text{-}(CH_2)_n\text{-}NH_3\oplus$

X	*n*	ΔpK_a
H	1	0.0[4]
F	1	– 4.8[31, 32]
H	2	0.0[4]
F	2	– 1.8[31]
H	3	0.0[4]
F	3	– 1.1[31]

in magnitude to that found with ω,ω,ω-trifluorinated fatty acids having the same number of carbon atoms (see Table 6).

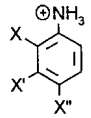
As assumed with phenolates (see Section 2.3), direct resonance interactions between the basic nitrogen center and *ortho* or *para* substituents should occur also within anilines. The quantitative agreement between the acidities of anilinium ions[4] (Table 21) and the phenols (Tables 13 – 16) is satisfactory (anilinium ions: $\Delta pK_a = -1.2$ (*o*-F), -1.0 (*m*-F), 0.0 (*p*-F); phenols: $\Delta pK_a = -1.2$ (*o*-F), -0.7 (*m*-F), 0.1 (*p*-F)). The long-range effect of a *para*-positioned trifluoromethyl group (Table 21) is again remarkable.[35–37]

2.5 Arylmethanes and Cyclopentadienes

In general, pure hydrocarbons are not acidic enough to dissociate in aqueous media. Therefore, acidity measurements dealing with such kinds of substrates are mostly performed in dimethyl sulfoxide or cyclohexylamine.

The data collected with substrates of the diaryl- and triarylmethane series are too few to permit a quantification

Table 21. ΔpK_a of fluoro- and (trifluoromethyl)anilinium ions relative to the parent ion ($pK_a = 4.6$[4]).[35–37]

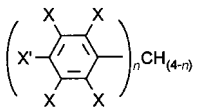


X	X′	X″	ΔpK_a
H	H	H	0.0
F	H	H	– 1.4[4, 33–35]
H	F	H	– 1.0[4, 33, 34]
H	H	F	0.0[4, 33, 35]
CF_3	H	H	– 1.8[36][a]
H	CF_3	H	– 1.1[4, 37]
H	H	CF_3	– 2.1[4, 37]

[a] Measured: $pK_a = 2.85$ at 20 °C;[36] estimated: $pK_a = 2.80$ at 25 °C, the reference temperature of all dissociation constants listed in this article.

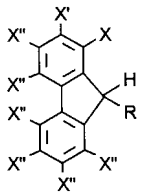
of the effect of individual fluorine atoms upon pK values. However, replacement of a phenyl by a pentafluorophenyl ring favors the dissociation to the extent of approximately five pK units (Tables 22 and 23).[38, 39]

Table 22. ΔpK_{DMSO} and $\Delta pK_{C_6H_{11}NH_2}$ of fluorinated di- and triarylmethanes relative to diphenylmethane ($pK_{DMSO} = 32.2$; $pK_{C_6H_{11}NH_2} = 33.1$).[38, 39]



X	X′	n	ΔpK_{DMSO}	$\Delta pK_{C_6H_{11}NH_2}$
H	H	2	0.0[38]	0.0[39]
F	F	2	– 10.2[38]	– 11.8[39]
H	H	3	– 1.6[38]	– 1.6[39]
F	H	3	– 18.8[38]	–
F	F	3	–	– 17.3[39]

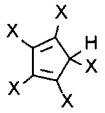
Table 23. ΔpK_{DMSO} of fluorinated fluorenes relative to fluorene ($pK_{DMSO} = 22.6$).[38]



X	X′	X″	R	ΔpK_{DMSO}
H	H	H	H	0.0
F	H	H	H	– 1.6[38]
H	F	H	H	– 0.5[38]
F	F	F	H	– 11.8[38]
H	H	H	C_6H_5	– 4.7[38]
H	H	H	C_6F_5	– 7.9[38]

Most cyclopentadienes are chemically unstable and undergo rapid cyclodimerization. Such problems hamper reliable acidity measurements. According to the available approximative data, cyclopentadiene[40] and pentafluorocyclopentadiene[41] have quite similar pK_a values, whereas pentakis(trifluoromethyl)cyclopentadiene[42] is a very strong acid (Table 24).

Table 24. ΔpK_{DMSO} of pentafluorocyclopentadiene[41] and pentakis(trifluoromethyl)cyclopentadiene[42] relative to cyclopentadiene[40] (pK_a = 16.0; 15.6 per hydrogen atom).



X	ΔpK_a
H	0[40]
F	ca. – 2[41]
CF_3	$\leq$ – 18[42]

3 Dissociation Equilibria in the Gas Phase

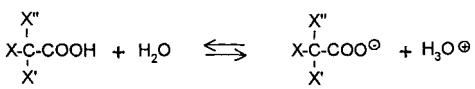
So far, one could have gained the impression that fluorine operates mainly through anion stabilization by inductive electron withdrawal and that exceptions from this rule, if observed, can easily be accounted for. This picture is too simplistic, however. First of all, substituents affect the ground state energy levels of both, acid and base, regardless of whether they are directly conjugated to a double bond or attached to the nodal point of an allyl (or dioxaallyl) moiety.[43, 44] The substituent may stabilize or destabilize both the neutral and the charged species, but it may also exert opposite effects on each of them. Whenever such an uncertainty exists it may invalidate an attempt at rationalization.

Another principle objection to an uncritical view that focuses exclusively on electronegativity is that such a one-parameter model entirely neglects the specific role of the solvent. It is evident, however, that the solvent must be of paramount importance whenever charged species are involved.

3.1. Carboxylic Acids

The acidity enhancing effect of fluorine or other heterosubstituents is most frequently ascribed to anion stabilization by a straightforward inductive effect. Actually, the thermodynamic parameters (Table 25) of the fatty acid dissociation are incompatible with such an assumption. They rather argue in

Table 25. The acidity of acetic acid and halogenated congeners in aqueous medium as well as free energies (ΔG_a^0), enthalpies and (ΔH_a^0) entropies (ΔS_a^0) of dissociation.[45]



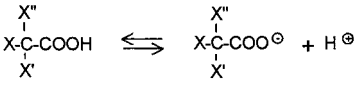
X	X′	X″	pK_a	$\Delta G_a^{0[a]}$	$\Delta H_a^{0[a]}$	$\Delta S_a^{0[a]}$
H	H	H	4.8	6.4	– 0.1	– 22
I	H	H	3.2	4.3	– 1.4	– 19
Br	H	H	2.9	4.0	– 1.2	– 17
Cl	H	H	2.9	3.9	– 1.1	– 17
F	H	H	2.6	3.5	– 1.4	– 17
F	F	H	1.3	1.7	0.0	– 6
F	F	F	0.2	0.3	0.0	– 1

[a] [kcal mol^{-1}]

favor of a dipole-mediated assistance to solvent organization. Thus, halogen substituents have little effect on the enthalpy of dissociation ΔH_a^0, which is small anyway (-1.5 to 0.0 kcal mol^{-1}), but can substantially lower the dominant entropy term $\Delta S_a^0 T$ (from 6.5 to 0.3 kcal mol^{-1} when going from acetic to trifluoroacetic acid). Thus, polarization of the surrounding medium rather than of the acid/base pair itself seem to be at the origin of halogen effects on the acidity of carboxylic acids.[45]

Gas phase studies provide an unambiguous test of the hypothesis of substituent-mediated solvent organization. In the absence of any solvent, the entropies of ionization vary little within the family of acetic acids and all fall in the range of 22 – 25 cal mol^{-1}K^{-1},[46] a number which is consistent with the disorder-favoring splitting of one molecule into two particles, partially compensated by the loss of one degree of rotational freedom upon deprotonation. The enthalpy term is largely preponderant this time, reflecting the absence of cation and anion solvation (Table 26).

Table 26. Free energies (ΔG_g^0) and enthalpies (ΔH_g^0) of deprotonation of acetic acid derivatives in the gas phase.[46]



X	X′	X″	$\Delta G_g^{0[a]}$	$\Delta H_g^{0[a]}$
H	H	H	341.5	348.5
I	H	H	327.7	334.7
Br	H	H	328.2	335.2
Cl	H	H	329.0	336.0
F	H	H	331.6	338.6
F	F	H	323.8	330.8
F	F	F	317.4	324.4

[a] [kcal mol^{-1}].

3.2. Amines

The introduction of one fluorine atom into α-, β-, or γ-positions of primary or tertiary amines (Tables 27 and 28, respectively) diminishes the basicity drastically. The substituent effect appears to be roughly additive and, of course, decreases as a function of distance. Thus the proton affinities of these amines decrease by about 10, 4, 1.5, and 0.5 kcal mol^{-1} per fluorine atom in the α-, β-, γ-, or δ-position.[47]

Gas phase studies offer the advantage that one can cover an extraordinarily wide spectrum of acidities, ranging from strong mineral acids to extremely weak hydrocarbons ("CH acids"). By constructing isoionic or isoelectronic relationships, the acidities of, for example, phenols can be correlated with those of anilines and similarly those of toluenes with anilinium ions (see Figure 1). When one plots the free energies of the gaseous deprotonation of anilinium ions against that of toluenes, the result is quite impressive (Figure 2).[47] Most points fall closely on a straight line. The moderate deviation of the *meta*- and *para*-nitro substituents can be well understood. The only "strayshot" is caused by the *meta*-cyano group, for as yet unknown reasons.

Table 27. Shift in the proton affinities ($\Delta\Delta G_g^0$) in the gas phase of fluorinated amines relative to ethylamine.[47]

H_2NCH_2R

R	$\Delta\Delta G_g^0$ [kcal mol^{-1}]
CH_3	0.0
CH_2F	– 3.2
CHF_2	– 8.1
CF_3	– 13.7
CH_2CF_3	– 5.0
$CH_2CH_2CF_3$	– 1.7

Table 28. Shift in the proton affinities ($\Delta\Delta G_g^0$) in the gas phase of dimethyl(trifluoromethyl)amine and dimethyl(β,β,β-trifluoroethyl)amine relative to trimethylamine ($\Delta G_g^0 = 222.1$ kcal mol^{-1}).[47]

$(H_3C)_2N$-R

R	$\Delta\Delta G_g^0$ [kcal mol^{-1}]
CH_3	0.0
CF_3	– 30.2
CH_2CF_3	– 9.6

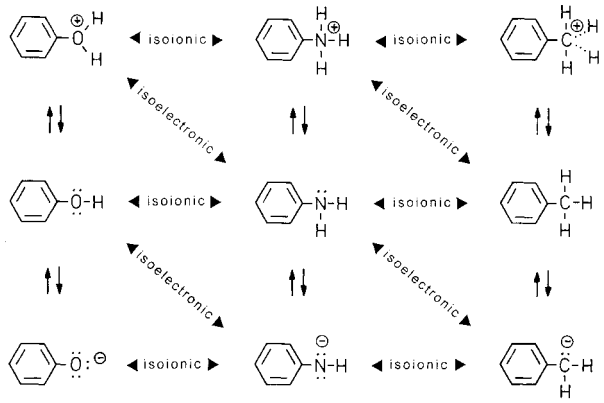


Figure 1. Isoionic and isoelectronic relationships between phenol, aniline, and toluene and their ions.

Noteworthy is the effect of *p*-fluoro substituents. Both *p*-fluoroanilinium and *p*-fluorotoluene are distinctly more acidic than the corresponding parent compounds. This may be again considered as a manifestation of the "volume effect" (see Section 3.5), the improved anion stabilization due to the polarization of a larger assembly of atoms. Interactions with counterions and solvent molecules widely replace this specifically intramolecular mechanism of anion stabilization through charge dispersion when the charged species is surrounded by an organic medium. New factors become crucial such as lone-pair/lone-pair repulsions between excess electron density and adjacent heteroatoms.[48, 49] Previously, evidence was presented according to which a fluorine atom, when directly attached to a carbanionic center, exerts a destabilizing effect.[50] More recently, two striking examples of benzyl anion destabilization by a *para*-positioned fluorine atom have been identified.[51, 52] Lithium 2,2,6,6-tetramethylpiperidide (LITMP) in the presence of potassium *tert*-butoxide and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine was found to abstract a proton from the benzylic position of

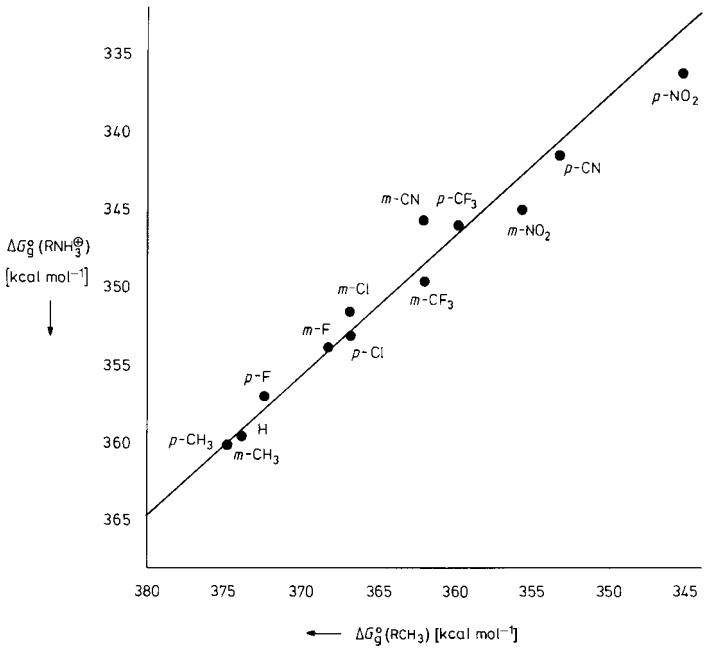


Figure 2. Free energies of deprotonation in the gas phase: correlation between anilinium ions (ΔG_g^0 ($RNH_3^{\oplus}$) and toluenes (ΔG_g^0 (RCH_3)).[47]

p-fluorotoluene 10 times more slowly than from toluene, while the reactivity of the *meta* and *ortho* isomer was 10 times higher than that of the reference compound.[51] The proton mobility of *all* chloro- and bromotoluenes proved to be 3 to 30 times that of toluene under the same conditions.[51] The introduction of a fluorine atom into the *para* position of the benzyl group of the triphenylphosphonio-α-phenylmethanide, a benzylic phosphorus ylid, lowers the barrier to rotation around the $C^{\alpha}-C^{i}$ axis from 8.5 to 7.7 kcal mol^{-1}, while *o*- or *m*-fluoro substituents or chloro substituents at any position raise the torsional energy.[52] The latter is a measure for the benzylic resonance delocalization.

3.3. Mono-, Di-, and Polyfluorohydrocarbons

The proton affinities of trifluoromethyl[53] and pentafluoroethyl[54] anions are in the gas phase some 40 kcal mol^{-1} smaller than that of the methyl anion. According to ab initio MO calculations, the perfluoro-*tert*-butyl anion is again about 40 kcal mol^{-1} more stable than the trifluoromethyl anion.[55]

A compilation of the gas phase acidities of fluorobenzene, pentafluorobenzene, and all di-, tri-, and tetrafluorobenzene isomers was published recently.[56] What makes these experimental data particularly meaningful is their completeness and consistency (Table 29). The measured free enthalpies of deprotonation can be reproduced with high fidelity (standard deviation < 1 kcal mol^{-1}) when "acidity increments" of 12, 6, and 4 kcal mol^{-1} are assigned to each extra fluorine atom located at an *ortho*, *meta*, and *para* position, respectively. Thus, the additivity of substituent effects as well as their distance dependence has been convincingly demonstrated.

Table 29. Absolute and relative[a] free deprotonation enthalpies (ΔG_g^0 and $\Delta\Delta G_g^0$, respectively) as well as relative[a] logarithmic dissociation constants (ΔpK_g) of benzene[57, 58] and fluorinated benzenes[56] in the gas phase.

Substitution	$\Delta G_g^{0[b]}$	$\Delta\Delta G_g^{0[b]}$	ΔpK_g
–	391	+12	+8.8
F	379	0	0
1,2-F_2	370	−9	−6.6
1,3-F_2	366	−13	−9.6
1,4-F_2	372	−7	−5.1
1,2,3-F_3	367	−12	−8.8
1,2,4-F_3	362	−17	−12
1,3,5-F_3	361	−18	−13
1,2,3,4-F_4	361	−18	−13
1,2,3,5-F_4	355	−24	−18
1,2,4,5-F_4	353	−26	−19
F_5	349	−30	−22

[a] Relative to fluorobenzene. [b] [kcal mol^{-1}].

3.4. Mono-, Bis-, and Tris(trifluoromethyl)benzenes

Highly trifluoromethylated arenes are not only difficult to prepare but are also of relatively low volatility. Therefore, gas phase studies[59] have not embraced all members of the poly(trifluoromethyl)benzene family. Nevertheless, the results are conclusive (Table 30). Accumulated substituent effects are again additive. (Trifluoromethyl)benzene has approximately the same gas phase acidity as fluorobenzene. However, in contrast to what has been found in the fluoroarene series (see Section 3.3), the acidifying effect of a trifluoromethyl unit shows only a weak distance dependence. While it favors the deprotonation at the *ortho* position by approximately 13 kcal mol^{-1}, it still causes an acidity exaltation of some 10 kcal mol^{-1} at both *meta* and *para* positions (Table 30). This divergence in substituent behavior clearly indicates that inductive electron withdrawl cannot be the only operative mechanism of anion stabilizaion. Presumably the polarization[60] of the aromatic sextet by π donation[61] (by fluorine) and hyperconjugation[62] (by trifluoromethyl) plays an equally important role.

Table 30. Absolute and relative[a] free deprotonation enthalpies (ΔG_g^0 and $\Delta\Delta G_g^0$, respectively) as well as relative[a] logarithmic dissociation constants (ΔpK_g) of benzene and trifluoromethyl-substituted benzenes in the gas phase.[59]

Substitution	$\Delta G_g^{0[b]}$	$\Delta\Delta G_g^{0[b]}$	ΔpK_g
–	391	+13	+9.6
CF_3	378	0	0
1,2-$(CF_3)_2$	369	−10	−7.0
1,3-$(CF_3)_2$	365	−14	−9.6
1,4-$(CF_3)_2$	367	−12	−8.4
1,2,3-$(CF_3)_3$	357	−221	−16
1,2,4-$(CF_3)_3$	355	−23	−17
1,3,5-$(CF_3)_3$	354	−24	−18
1,2,4,5-$(CF_3)_4$	341	−36	−27

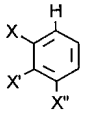
[a] Relative to (trifluoromethyl)benzene. [b] [kcal mol^{-1}].

3.5. Chlorobenzene

The *o*-chlorophenyl anion has been generated in the gas phase by direct deprotonation, the *m*- and *p*-chlorophenyl

anions by fluoride-promoted desilylation of the corresponding (chlorophenyl)trimethylsilanes.[63] The astonishingly similar basicities (Table 31) are most remarkable provided they stand the test of independent verification.

Table 31. Free deprotonation enthalpies $\Delta\Delta G^0_g$ of chlorobenzene[63] relative to benzene ($\Delta G^0_g = 391$ kcal mol^{-1}[57, 58]).



X	X′	X″	$\Delta\Delta G^0_g$ [kcal mol^{-1}]
H	H	H	0.0
Cl	H	H	−11
H	Cl	H	−9
H	H	Cl	−9

Attention is also drawn to the quasi-identity of fluorobenzene and chlorobenzene gas phase acidities ($\Delta G^0_g = 379$ and 380 kcal mol^{-1}, respectively). On the basis of deprotonation studies in solution one might have expected a considerably greater difference. At this stage a word of warning may be appropriate. To work in the gas phase avoids complications arising from interactions with solvent molecules and counterions. At the same time, a special artefact is introduced. Left without any possibility of external stabilization, the electron excess of the anion spreads out over the entire species in such a way that it creeps over its molecular surface and covers it like a film. The bulkier the particle, the more effective the charge dissipation (the "volume effect" already briefly mentioned in Section 3.1). This kind of polarization is, for example, the reason why in the gas phase *tert*-butyl alcohol is more acidic than methanol, and the latter more acidic than water,[64] and may also explain why in the gas phase iodoacetic acid is considerably more acidic than fluoroacetic acid.[46]

4. Deprotonation Rates and Equilibria in Organic Solvents

The aqueous standard state and the gas phase represent two extremes. Somewhere in between condensed media of moderate or low polarity are situated (Figure 3). Organic

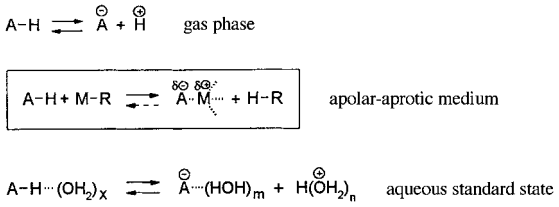


Figure 3. Three fundamental options to select a reaction medium: water, organic solvent, or gas phase.

and, in particular, organometallic reactions are typically carried out in such solvents. It is quite instructive to scrutinize the three systems for similarities and discrepancies.

4.1. Alkanes

Although far less acidic than chloroform (p$K_a = 24$[65]), trifluoromethane (fluoroform, p$K \approx 30$[66]) dissociates much more readily than the parent compound methane (p$K \geq 47$[67]). Replacement of one fluorine atom by a trifluoromethyl stabilizes the anion by 3.0 ± 0.8 kcal mol^{-1} (Table 32). The relative acidities have been probed by base-catalyzed isotope exchange in methanol[68] and have been subsequently linked to the ion pair acidity scale established with cesium cyclohexylamide in cyclohexylamine[66] (Table 32).

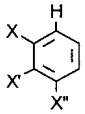
Table 32. ΔpK_{H_3COH} of polyfluoroalkanes relative to methane ($\Delta pK_{C_6H_{11}NH_2} \approx 47.5$[68]).

X	X′	X″	$\Delta pK_{C_6H_{11}NH_2}$
H	H	H	0.0
F	F	F	−17.0
$F_{13}C_6$	F	F	−17.8
F_3C	F	F	−19.3
F_3C	F_3C	F	−22.3
F_3C	F_3C	F_3C	−26.5

4.2. Mono-, Di-, and Trifluoroarenes

When fluorobenzene is treated with alkyllithium reagents in ethereal solvents, a hydrogen/lithium exchange occurs exclusively at the *ortho* position.[69, 70] However, as can be shown indirectly, also the *meta* and *para* positions are acidified. The effect of fluorine can be monitored at any ring site, when the deprotonation is brought about under the conditions of a base-catalyzed deuterium exchange, a process that energetically involves an "up-hill reaction" as the crucial step. The relative rates of deprotonation measured in liquid ammonia[71, 72] (Table 33) and those found in methanol[73] correlate with differences in activation energies. These reflect

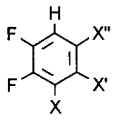
Table 33. Deprotonation of fluorobenzene under the conditions of a potassium amide catalyzed deuterium/hydrogen exchange in liquid ammonia: Rates $k^{H/D}_{rel}$ relative to benzene ($k^{H/D}_{rel} = 1.0$).[71]



X	X′	X‴	$k^{D\rightarrow H}_{rel}$
H	H	H	1×10^0
F	H	H	$\geq 4 \times 10^6$
H	F	H	4×10^3
H	H	F	2×10^2

the differences in gas phase acidities to the extent of approximately 60%. The attenuation of basicities in the condensed phase can be attributed to carbanion stabilization by hydrogen-bonding with the solvent. In general, the reprotonation ("backward" or "off") rates of such isotope exchange processes are supposed to be diffusion-controlled and hence identical for all members of a substrate family. Under these circumstances the deprotonation ("forward" or "on") rates parallel equilibria positions. Direct or indicator-mediated equilibration of metalated intermediates has been achieved by employing lithium cyclohexylamide in cyclohexylamine and cesium cyclohexylamide in tetrahydrofuran or cyclohexylamine (Table 34).[73] Under these conditions the differences in the gas phase basicities are retained to the extent of roughly 45%, 55%, and 60%, respectively.[73]

Table 34. The cesium pair acidities $\Delta pK_{C_6H_{11}NH_2}$ of polyfluorobenzenes relative to benzene ($pK_{C_6H_{11}NH_2} = 43.0$).[73]



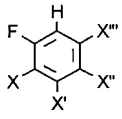
X	X′	X″	$\Delta pK_{C_6H_{11}NH_2}$
H	H	H	−8.0
F	F	H	−11.5
F	F	F	−17.2

In contrast, the hydrogen/metal exchange ("metalation") by treatment of a fluoroarene with a strong organolithium base (e.g. *sec*-butyllithium in tetrahydrofuran) is a "downhill process". It has not yet been possible to directly compare the lithiation rate of fluorobenzene with that of benzene itself. Indirect evidence, however, places the rate ratio in the range of 10^4 to 10^5.[56] If this is true, the multiple substituent effects are no longer additive as can be deduced from the relative proton mobilities of the di- and trifluorobenzenes (Table 35).[56]

4.3. Mono-, Bis-, and Tris(trifluoromethyl)benzenes

The base-catalyzed isotope exchange in deuterium-labeled (trifluoromethyl)benzenes (benzotrifluorides) confirms the long-range action of the trifluoromethyl group. The proton mobility at the *meta* and *para* positions falls behind that at the *ortho* position by less than two powers of ten (Table 36).[71, 72]

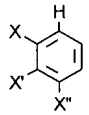
Table 35. Lithiation of di- and trifluorobenzenes with *sec*-butyllithium in THF: relative rates (k_{rel}) and rate factors (k^f_{rel}).[56]



X	X′	X″	X‴	k_{rel}	k^f_{rel}[a]
H	H	H	H	2.0	1.0
F	H	H	H	40	20
H	H	H	F	800	800
H	H	F	H	40	10
F	H	H	F	2000	2000
H	F	H	F	3600	1200

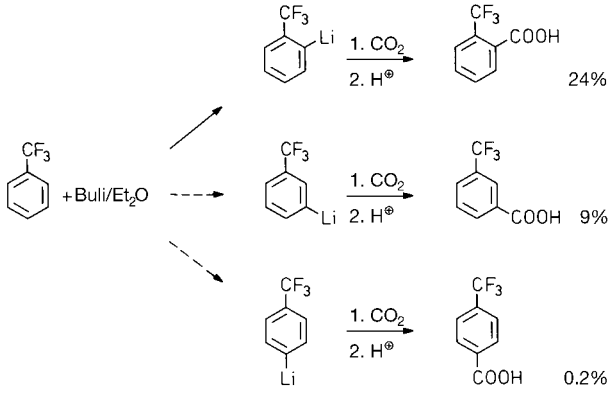
[a] Corresponds to k_{rel} divided by the number of equivalently acidic sites.

Table 36. Treatment of 2-, 3-, and 4-deutero(trifluoromethyl)benzene with potassium amide in liquid ammonia at −33 °C: Rates of isotope exchange relative to monodeuterobenzene ($k^{H\rightarrow D}_{rel} = 1.0$).[71]



X	X′	X″	$k^{D\rightarrow H}_{rel}$
CF_3	H	H	6×10^5
H	CF_3	H	1×10^4
H	H	CF_3	1×10^4

The simultaneous activation of all aromatic sites compromises the site-selective metalation of (trifluoromethyl)benzene. When butyllithium in refluxing diethyl ether is employed as the reagent, subsequent trapping of the organometallic intermediates with carbon dioxide affords, besides *o*-(trifluoromethyl)benzoic acid (24%), substantial amounts of the *meta* isomer (9%) and traces of the *para* isomer (0.2%) (Scheme 2).[74] Only the superbasic mixture of butyllithium and potassium *tert*-butoxide in tetrahydrofuran at −75 °C is capable of accomplishing clean *ortho* metalation (67%).[70, 75]



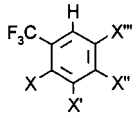
Scheme 2. Metalation of (trifluoromethyl)benzene.

Hydrogen/metal exchange studies are difficult to execute with poly(trifluoromethyl)benzene. In particular, single-electron transfer and nucleophilic addition processes compete with proton abstraction or outperform it.[76] As a consequence, the data listed below (Table 37) are incomplete and subject to large error derivations.[59] Moreover, the necessity to employ bulky amides as bases makes steric hindrance a crucial factor.

4.4. Chlorobenzenes and Bromobenzenes

A direct comparison between various halobenzenes may provide the clue to identify the origin of heteroatom effects on acidity. A key experiment was the simultaneous lithiation of

Table 37. Rates k_{rel} of the deprotonation of bis- and tris(trifluoromethyl)-benzene relative to mono(trifluoromethyl)benzene ($k_{rel} = 1.0$).[a] [59]



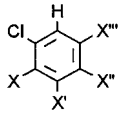
X	X′	X″	X‴	k_{rel}
H	H	H	H	1×10^0
CF_3	H	H	H	1×10^2[b]
H	H	CF_3	H	6×10^2
H	CF_3	H	H	3×10^2[c]
H	CF_3	H	CF_3	6×10^2
H	CF_3	CF_3	H	5×10^4[d]

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in diethyl ether. [b] Deprotonation at the 2- and 3-positions in the ratio 3:1. [c] Deprotonation at the 2, 4-, and 5-positions in the ratio $<1:50:500$. [d] Deprotonation at the 3-, 5-, and 6-positions in the ratio $<1:50:20$.

fluoro- and chlorobenzene under the conditions of competition kinetics. Fluorobenzene proved to be eight times more reactive than chlorobenzene towards *sec*-butyllithium in tetrahydrofuran at $-100\,^{\circ}C$ [77]. The reactivity difference exceeded 20 when lithium 2,2,6,6-tetramethylpiperidide (LITMP) was employed in tetrahydrofuran at $-75\,^{\circ}C$.

Equilibration studies that employ cesium cyclohexylamine as the base in tetrahydrofuran have been performed with a series of polychlorobenzenes (Table 38). Under the assumption of additivity of individual substituent contributions, one

Table 38. Deprotonation of polychlorobenzenes by cesium cyclohexylamide and equilibration of the resulting organometallic intermediates in THF: factorized (statistically corrected) dissociation constants $\Delta pK^{f}_{Cs/THF}$ relative to benzene ($\Delta pK^{f}_{Cs/THF} = 47.0$).[73]

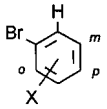


X	X′	X″	X‴	$\Delta pK^{f}_{Cs/THF}$
H	Cl	H	Cl	−10.7
Cl	H	Cl	H	−10.9
Cl	Cl	Cl	H	−11.8
Cl	Cl	H	Cl	−13.2
Cl	H	Cl	Cl	−15.1
Cl	Cl	Cl	Cl	−15.9

can define acidity by increments $\Delta pK_{Cs/THF}$ of -4.2, -2.7, and -2.1 for each chlorine atom in an *ortho*, *meta* or *para* position with respect to the deprotonation site ($\Delta\Delta G_{Cs/THF} = -4.8$, -3.1 and -2.4 kcal mol^{-1}, respectively) [73].

When treated with lithium piperidide in diethyl ether, bromoarenes set free 1,2-dehydroarenes ("arynes") which are instantaneously trapped by the nucleophilic addition of the amide [78]. The over-all reaction occurs in several steps, the first one being a deprotonation at the halogen adjacent position generating a 2-bromoaryllithium species. Since according to all available evidence this process is a reversible one, the relative rates of dehydrobromination (listed in Table 39)[78] may be taken as a measure of 2-haloaryl anion stability.

Table 39. Rates of dehydrobromination of *ortho*-, *para*-, and *meta*-substituted bromoarenes k^{o}_{rel}, k^{p}_{rel}, and k^{m}_{rel}, respectively, relative to bromobenzene ($k_{rel} = 1.0$).[78]



X	k^{o}_{rel}	k^{p}_{rel}	k^{m}_{rel}
Br	140	83	940
F	34	25	1700
CF_3[a]	4.6	3.4	58
OCH_3	1.4	1.2	600
$N(CH_3)_2$	0.58	0.23	7.3
C_6H_5	1.9	2.0	1.8
CH_3	0.50	0.45	0.35
$CH(CH_3)_2$	0.37	0.53	0.19

[a] Chloroarenes instead of bromoarenes were used as the substrates.

4.5. Fluorohalobenzenes

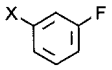
Intramolecular competition experiments have revealed the relative "*ortho* directing" power of various halo substituents. In all examples investigated, fluorine was found to outperform the heavier halogens chlorine[79] and bromine,[80] let alone the trifluoromethyl substituent.[70] Both chlorine and bromine have a stronger acidifying effect than trifluoromethyl[80] but differ little from each other.[81]

Although it is certainly helpful to have identified such a *qualitative* hierarchy of reactivity, *quantitative* relationships would be far more conclusive. For example, 1,3-dichlorobenzene[82] and 1,3,5-trichlorobenzene[83] react with butyllithium or *sec*-butyllithium much more readily than chlorobenzene.[84] However, is this reactivity gap big enough to enable selective transformations if both structural features are present in the same starting material?

Furthermore, in the case of di- and polysubstituted arenes one certainly wishes to distinguish whether the subsidiary halogens occupy *ortho*, *meta*, or *para* positions with respect to the metalation site. To address the latter question, sets of substrates having the proper regioisomeric pattern were selected and submitted to competition experiments. All *m*-fluorohalobenzenes are deprotonated at the doubly activated position flanked by the two substituents. In other words, both the fluoro and the other halo atom occupy an *ortho* position with respect to the center attacked by the base. Lithium alkylamides are mandatory to avoid halogen/metal interconversions with bromo- and iodoarenes. Under these conditions, proton abstraction occurred roughly 2.5 times more rapidly, when the second halogen was also fluorine rather than chlorine or bromine, and almost five times more rapidly when it was fluorine rather than iodine (Table 40).[77] When treated with *sec*-butyllithium, 1-chloro-3-fluorobenzene reacted faster than 1,3-dichlorobenzene and fluorobenzene, but more slowly than 1,3-difluorobenzene.[77]

The effects of subsidiary halogen substituents located in *meta* positions can be evaluated with 1-fluoro-2-halobenzenes and 1-fluoro-4-halobenzenes. Remarkably, this time the heavier halogens enhance the proton mobility more strongly than fluorine does.[77] 1,3-Difluoro-5-halobenzenes are suit-

Table 40. Deprotonation rates of 1-fluoro-3-halobenzenes:[a][77] Rates (k_{rel}), statistically corrected rate factors (k^f_{rel}), and the logarithmus thereof ($\lg k^f_{rel}$) relative to fluorobenzene ($k^f_{rel} = 1.0$).



X	k_{rel}	k^f_{rel}	$\lg k^f_{rel}$
H	2.0	1.0	0.0
F	800	800	2.9
Cl	315	315	2.5
Br	355	355	2.6
I	175	175	2.2

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF at $-75\,^{\circ}C$.

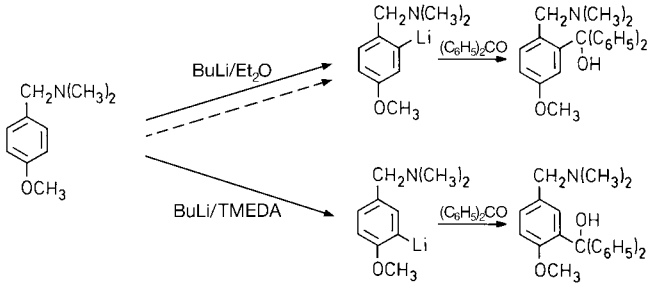
able models to probe the effect of a subsidiary halogen at the *para* position. The results are in line with the expectations: the more distant the substituent is, the smaller is its contribution to the overall acidity of the substrate.[77]

One issue still needs to be clarified. How can one claim to have generated haloaryllithium species irreversibly ("under kinetic control") if a lithium amide acts as a base and hence inevitably an amine is present? Should, under such circumstances, not instantaneous reprotonation occur and, as a corollary, the organometallic intermediates be subject to rapid equilibration (i.e. form "under thermodynamic control")? The latter menace does exist and it needs a trick to prevent it. Whenever relative rates were determined, the intermediates were trapped in situ[85] by treating the haloarene *simultaneously* with LITMP and chlorotrimethylsilane. The variation of the electrophile concentration did not alter the product ratios. This means, the haloaryllithium species were more rapidly intercepted by silylation rather than by reprotonation.

On the other hand, the acid–base pairs will interconvert if one of the involved haloaryllithium species is separately generated before being incubated with the partner haloarene. The time required to approach the equilibrium from both extremes depends on several reaction parameters, in particular the concentration of the free amine. Generally a few hours suffice. The product ratios are more extreme when the lithiation reactions are accomplished under reversible rather than irreversible conditions. This appears to be plausible. Ground states (equilibrating species) should be more sensitive to noncoordinative substituent effects than transition states (rate-determining structures).[78]

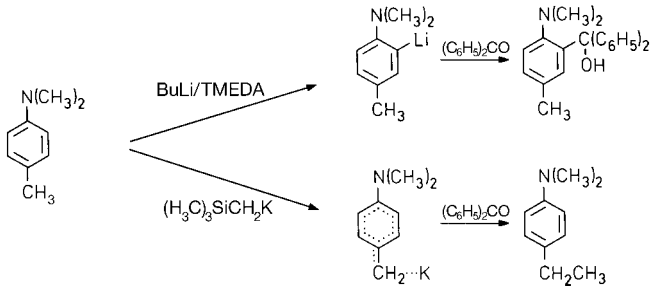
5. Optional Site Selectivities

The term "optional site selectivity" has been coined to characterize a crossing of synthetic pathways. More precisely, it refers to the fortunate situation that the same substrate can be alternatively metalated at either of two or three different positions just by choosing the appropriate reagent and other variable reaction parameters. An early impressive example of this type was reported almost three decades ago. When treated with butyllithium in diethyl ether, (4-methoxybenzyl)dimethylamine undergoes a lithium/hydrogen exchange cleanly at a position adjacent to the nitrogen-bearing side chain (Scheme 3).[85] However, in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) the same reagent attacks preferentially, though not exclusively, the aromatic sites in the immediate vicinity of the methoxy group (regioisomeric ratio $\approx 1{:}8$) [86, 87] (Scheme 3).



Scheme 3. Optional site selectivity in the metalation of (4-methoxybenzyl)dimethylamine.

Similarly, the proper choice of the reagent permits the selective proton abstraction either from the nitrogen-adjacent or the benzylic position of *N,N*-4-trimethylaniline (Scheme 4). Upon consecutive treatment with TMEDA-activated butyllithium in hexane at 25 °C and benzophenone, (2-dimethylamino-5-methylphenyl)diphenylmethanol (80 %)[88] is formed, while generation of an organometallic intermediate with trimethylsilylmethylpotassium in tetrahydrofuran at $-75\,^{\circ}C$ and subsequent trapping with methyl iodide affords 4-ethyl-*N,N*-dimethylaniline (65 %).[89]



Scheme 4. Selective proton abstraction from *N,N*,4-trimethylaniline.

Often the reaction can be controlled only in one sense. Pentylsodium in hexane was reported to convert *o*-methyl anisole (*o*-cresyl methyl ether) cleanly into 2-methoxybenzylsodium (acid obtained after carboxylation: crude product 69 %, pure product 21 %).[90] The reaction with butyllithium in refluxing diethyl ether turns the *p* isomer into 2-methoxy-5-methylphenyllithium (crude product 32 %).[90] TMEDA or potassium *tert*-butoxide activated butyllithium[91–93] give product mixtures due to simultaneous proton abstraction from benzylic and aromatic positions.

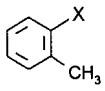
Lack of regioselectivity is also frequently encountered with alkylarenes. For example, butyllithium in the presence of potassium *tert*-butoxide (LIC-KOR) or trimethylsilylmethylpotassium, are required to deprotonate toluene[92] and cumene (isopropylbenzene),[94] respectively, exclusively at the benzylic position. Concomitant attack at benzylic and aromatic sites occurs under all other reaction conditions.[95–98]

This compilation of regioselectively sensitive metalations was aimed at tracing the origins of optionally site controlled reactions. In the meantime, mechanistic rationale for the various dichotomies observed has been elaborated.[99] Since then, new examples have emerged in rapid succession. For reasons of space limitations they cannot be exhaustively covered. The following Sections are limited to cases where substitution with fluorine plays a crucial role.

5.1. Halotoluenes

Competition experiments have been carried out to assess the proton mobility in the various fluoro-, chloro-, and bromotoluene isomers.[51] The data collected (Tables 41 – 43) are very approximate since under the reaction conditions (lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran in the presence of potassium *tert*-butoxide and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine at $-75\,^{\circ}C$ or $-100\,^{\circ}C$) the *o*-chloro- and *o*-bromoaryllithium intermediates instantaneously lose lithium halide to set free 1,2-dehydroarenes ("arynes")

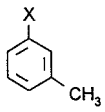
Table 41. Rates of the deprotonation of 2-halotoluenes[a] relative to toluene.[b][51]



X	k_{rel}^{Σ}[c]	k_{rel}^{o}[d]	k_{rel}^{α}[e]
F	13	3	10
Cl	10	5	5
Br	75	50	25

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine in THF at $-75\,^{\circ}C$ (X = F) or $-100\,^{\circ}C$ (X = Cl, Br). [b] Toluene is exclusively deprotonated at the methyl group ($k_{rel}^{\Sigma} = k_{rel}^{\alpha} \equiv 1.0$). [c] Rate of global deprotonation ($k_{rel}^{\Sigma} = k_{rel}^{o} + k_{rel}^{\alpha}$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

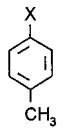
Table 42. Rates of the deprotonation of 3-halotoluenes[a] relative to toluene.[b][51]



X	k_{rel}^{Σ}[c]	k_{rel}^{o}[d]	k_{rel}^{α}[e]
F	13	3	10
Cl	10	5	5
Br	30	25	5

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine in THF at $-75\,^{\circ}C$ (X = F) or $-100\,^{\circ}C$ (X = Cl, Br). [b] Toluene is exclusively deprotonated at the methyl group ($k_{rel}^{\Sigma} = k_{rel}^{\alpha} \equiv 1.0$). [c] Rate of global deprotonation ($k_{rel}^{\Sigma} = k_{rel}^{o} + k_{rel}^{\alpha}$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

Table 43. Rates of the deprotonation of 4-halotoluenes[a] relative to toluene.[b][51]

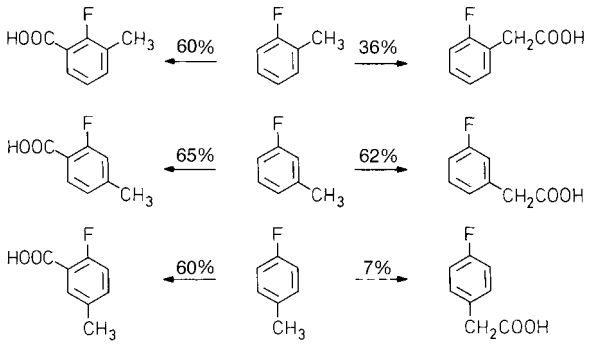


X	k_{rel}^{Σ}[c]	k_{rel}^{o}[d]	k_{rel}^{α}[e]
F	10	10	0.1
Cl	13	10	3
Br	33	30	3

[a] Reaction with lithium 2,2,6,6-tetramethylpiperidide, potassium *tert*-butoxide, and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine in THF at $-75\,^{\circ}C$ (X = F) or $-100\,^{\circ}C$ (X = Cl, Br). [b] Toluene is exclusively deprotonated at the methyl group ($k_{rel}^{\Sigma} = k_{rel}^{\alpha} \equiv 1.0$). [c] Rate of global deprotonation ($k_{rel}^{\Sigma} = k_{rel}^{o} + k_{rel}^{\alpha}$) relative to toluene. [d] Relative rate of deprotonation at halogen-adjacent arene positions. [e] Relative rate at benzylic positions.

as transient species. Nevertheless, trends are apparent. The introduction of a chlorine substituent in any ring position of toluene accelerates proton abstraction by one power of ten; aromatic and benzylic sites are attacked at roughly equal rates ($k_{rel}^{o} \approx k_{rel}^{\alpha}$). The three bromotoluenes behave similarly, although the deprotonation of all aromatic positions and of the α-position in the *ortho* isomers appears to occur still more readily than with the chloro analogue. Most intriguing are the results found with the fluorotoluenes. While the kinetic acidity of the halogen-adjacent aromatic sites has uniformly increased by a factor of 3 – 10, only the *ortho* and *meta* isomers undergo metalation at the α-position more rapidly, in fact 10 times more rapidly, than toluene itself (Tables 41 and 42). In contrast, deprotonation of *p*-fluorotoluene at the α-position occurs 10 times more slowly than with the halogen-free parent compound (Table 43, $k_{rel}^{\alpha} = 0.1$).[51]

The deactivation of the benzylic site in *p*-fluorotoluene seems to be caused by n-π electron – electron repulsion[48, 49] (Section 3.2). This has practical consequences. 4-Fluorophenylacetic acid can be obtained in not more than 7% yield when 4-fluorotoluene is consecutively treated with potassium *tert*-butoxide activated lithium diisopropylamide (LIDA-KOR) in tetrahydrofuran at $-75\,^{\circ}C$ and carbon dioxide, whereas the *ortho* and *meta* isomers form in yields of 37% and 62%, respectively (Scheme 5).[100]

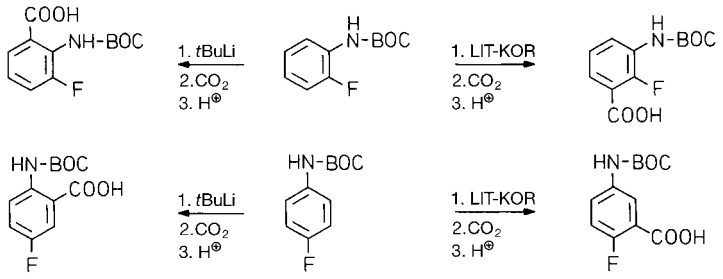


Scheme 5. Different yields in the deprotonation and carboxylation of the benzyl position of *o*-, *m*-, and *p*-fluorotoluene.

5.2. Fluorinated Anilines, Benzylamines, and Anisoles

Optional site selectivity can also be established with aromatic substrates bearing two different heterosubstituents. The mechanism-based rule of thumb is that the more polar reagent (e.g., LIC-KOR) favors the metalation in the immediate vicinity of the more electronegative function, whereas uncomplexed alkyllithium complexes preferentially attack positions adjacent to a strong electron-donating and hence metal-coordinating moiety.[99, 101] The success depends entirely on the appropriate matching of reagents and reaction conditions with the targeted neighboring groups.

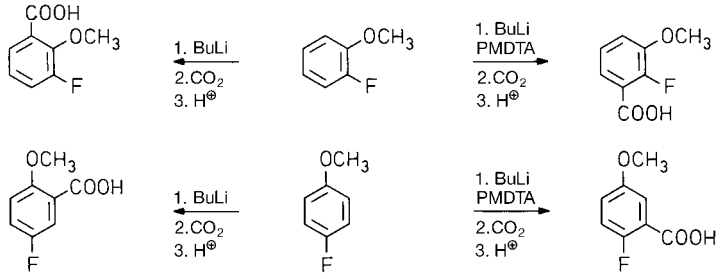
The *N*-*tert*-butoxycarbonyl(BOC)-2-fluoroaniline and -4-fluoroaniline react with two equivalents of *tert*-butyllithium in tetrahydrofuran at $-50\,^{\circ}C$ exclusively at the N-adjacent site (86% and 80%, respectively, of the corresponding anthranilic acids after carboxylation; Scheme 6).[102] On the other hand,



Scheme 6. Optional site selectivity for *N*-*tert*-butoxycarbonyl(BOC) fluoroanilines.

the same substrates are metalated at the position next to the halogen when *tert*-butyllithium is employed in the presence of potassium *tert*-butoxide (42% and 36% of the corresponding 2-fluorobenzoic acids are obtained after consecutive treatment with LIT-KOR in tetrahydrofuran at $-75\,^{\circ}C$ and carbon dioxide; Scheme 6). [102, 103]

2- and 4-Fluoroanisole offer other striking examples of optional site selectivity. The reactions with butyllithium in tetrahydrofuran at $-75\,^{\circ}C$ followed by carboxylation afford the 2-methoxybenzoic acids (50% each), but only 2-fluorobenzoic acids (87% and 85%) when the metalation is carried out in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenediamine (PMDTA) under otherwise unaltered conditions (Scheme 7). All products are regioisomerically uncontaminated.

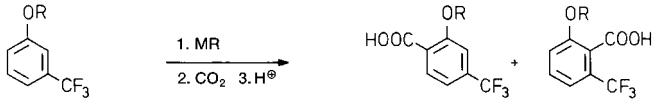


Scheme 7. Site selectivity for 2- and 4-fluoroanisole.

5.3. *meta*-Substituted (Trifluoromethyl)benzenes

The trifluoromethyl entity is relatively large.[105] When another group is located in the *meta* position, the site flanked by the two substituents, even if doubly activated, may be sterically too congested to be reached by a bulky reagent. This opens the door to optional site selectivity. Thus, 3-(trifluoromethyl)phenol (Table 44; R = H) reacts with butyllithium

Table 44. Optional site selectivities for *meta*-(trifluoromethyl)phenol derivatives.

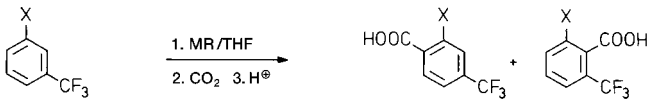


OR	MR	Solvent	Yield [%]	
H	LIC-KOR-TMEDA	hexane	5	91
OCH_2OCH_3	LIC-KOR	THF	0	100
OCH_2OCH_3	LIS-TMEDA	THF	94	0

in the presence of potassium *tert*-butoxide and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in hexane at $0\,^{\circ}C$ at positions 2 and 4 in the ratio of 93:7.[77] After protection of the hydroxy group as a methoxymethyl ether ($R = CH_2OCH_3$), the metalation by a 0.1M solution of potassium *tert*-butoxide activated butyllithium in tetrahydrofuran at $-75\,^{\circ}C$ occurs exclusively at the 2-position but with *sec*-butyllithium (LIS) in the presence of TMEDA exclusively at the 4-position.[77]

Although the space requirements of a single fluorine atom are moderate, the site between the substituents in 1-fluoro-3-trifluoromethylbenzene seems to be already too crowded to accommodate a reagent as bulky as the *sec*-butyllithium/PMDTA complex. Besides small amounts of the "double-*ortho*" derivative, mainly the trapping product of the intermediate generated by metalation of the F-adjacent, CF_3-remote site is obtained (Table 45, X = F).[70] When LIC-KOR is used, only the former 1,2,3-trisubstituted isomer is isolated.[106] With 1-chloro-3-trifluoromethylbenzene the optional site selectivity becomes once again perfect. Metalation with butyllithium and subsequent carboxylation gives the 2,6-disubstituted benzoic acid, whereas the same reaction performed with *sec*-butyllithium affords pure 2-chloro-4-(trifluoromethyl)benzoic acid.[107]

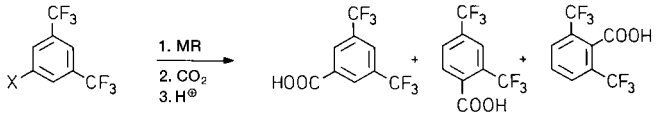
Table 45. Optional site selectivities for *meta*-halo(trifluoromethyl)benzenes.



X	MR		
F	LIS-PMDTA	68	17
F	LIC-KOR	0	46
Cl	LIS	80	0
Cl	LIC	0	67

1,3-Bis(trifluoromethyl)benzene leads to the greatest variety of organometallic intermediates. It is selectively deprotonated at the 2-position by the superbasic LIC-KOR mixture and at the 4-position by LIS-PMDTA, both times in tetrahydrofuran at $-75\,^{\circ}C$ (Table 46).[70] When *tert*-butyllithium (LIT) in tetrahydropyran at $-25\,^{\circ}C$ is employed, the 4- and 5-position are simultaneously attacked and a 1:1 mixture of

Table 46. Optional site selectivities for *meta*-bis(trifluoromethyl)benzenes.



X	MR	Solvent		Yield [%]	
Br	LIC	Et_2O	94	–	–
H	LIT	THP[a]	43	39	–
H	LIS-PMDTA	THF	–	56	–
H	LIC-KOR	THF	–	–	78

[a] THP = tetrahydropyran.

the respective organolithium species is obtained.[70] Pure 3,5-bis(trifluoromethyl)phenyllithium can be generated by halogen/metal interconversion between 1-bromo-3,5-bis(trifluoromethyl)benzene and butyllithium (LIC) in diethyl ether.[108]

6. Conclusions and Outlook

Acidity is not only a physicochemical key property but it also controls many features of reactivity and bioactivity. Apart from a few exceptions, fluorine stabilizes anions and hence facilitates ionic dissociation. Thus, the smallest halogen may be used to fine-tune acidity. Organophosphorus compounds can serve to illustrate this. Alkylphosphonic acids are often tested as enzymatically stable mimics of monoalkyl phosphates. However, their dissociation constants ($pK_a \approx 2.6$, $pK_a' \approx 8.1$) are significantly lower than those of the phosphates ($pK_a \approx 1.9$, $pK_a' \approx 6.7$).[109] The introduction of one or two fluorine atoms into the α-position of phosphonic acids brings the critical second dissociation constants pK_a' (about 6.2 and 5.6) back in the desired range. The acidity readjustment overshoots upon introduction of a third halogen atom, trifluoromethylphosphonic acid having a pK_a' of 3.9.[110]

When moving from OH through NH to CH acids, the acidity progressively decreases. Strong bases have to be employed in inert solvents to achieve deprotonation of alkanes, arenes, and heterocycles. The degree to which fluorine enhances the kinetic and thermodynamic acidity of such substrates depends on many factors. Electrostatic forces alone cannot explain the observed variations in acidity; all available evidence points to a subtle balance of different effects including induction, resonance, polarization, hyperconjugation, and dipole interactions, both of the internal type (causing conformational changes) and external type (affecting the solvent shell). Thus, the detailed knowledge of heteroelement effects on anion stability provides a basis for understanding the origin and transmission of electronic interactions. At the same time, such fundamental studies give valuable clues about how to generate new reactive species that can be exploited for synthetic purposes.

Progress in the rationalization of fluorine effects has not only been made in the area of anionic, but also cationic[111–118] and radical[119] species. In contrast, little is known about exactly how fluorine and other halogens improve the metabolic stability of aliphatic and aromatic hydrocarbons, in particular by retarding cytochrome P-450 promoted oxidations. Resistance to catabolic degradation is, of course, a prime target in pharmaceutical chemistry. The same holds for the lipophilicity of drugs on which also depends their membrane permeability and specific tissue accumulation. Related are phenomena such as the surface tension and wettability of highly fluorinated coatings and the elasticity of many fluoropolymers. Fluorine substituents play a crucial role also in other technologically important fields. For example, they increase the dielectrical anisotropy of liquid crystals and thus enable the design of improved thin film transistor liquid crystal displays.[120] The details of how fluorine alters all such physical properties are still poorly understood if not mysterious. In other words, much remains to be done until one can claim to have succeeded in the "parametrization" of fluorine.

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