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Pentakis(trifluoromethyl)phenyl, a Sterically Crowded and Electron-withdrawing Group: Synthesis and Acidity of Pentakis(trifluoromethyl)benzene, -toluene, -phenol, and -aniline

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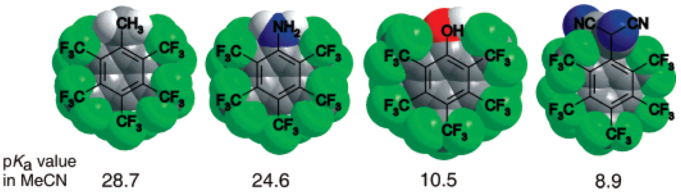

A general route to functionalized pentakis(trifluoromethyl)phenyl ($C_6(CF_3)_5$) derivatives, promising building blocks for designing novel stable carbenes, radical species, superacids, weakly coordinating anions and other practically and theoretically useful species, is presented. This pertrifluoromethylation route proceeds via conveniently pregenerated (trifluoromethyl)copper (CF_3Cu) species in DMF, stabilized by addition of 1,3-dimethyl-2-imidazolidinone (DMI). These species react with hexaiodobenzene at ambient temperature to give the potassium pentakis(trifluoromethyl)phenoxide along with hexakis(trifluoromethyl)benzene and pentakis(trifluoromethyl)benzene in a combined yield of 80%. A possible reaction pathway explaining the formation of pentakis(trifluoromethyl)phenoxide is proposed. Pentakis(trifluoromethyl)phenol gives rise to easily functionalized pentakis(trifluoromethyl)chlorobenzene and pentakis(trifluoromethyl)aniline. Pertrifluoromethylation of pentaiodochlorobenzene and pentaiodotoluene allows straightforward access to pentakis(trifluoromethyl)chlorobenzene and pentakis(trifluoromethyl)toluene, respectively. XRD structures of several $C_6(CF_3)_5$ derivatives were determined and compared with the calculated structures. Due to the steric crowding the aromatic rings in all $C_6(CF_3)_5$ derivatives are significantly distorted. The gas-phase acidities (ΔG_{acid}) and pK_a values in different solvents (acetonitrile (AN), DMSO, water) for the title compounds and a number of related compounds have been measured. The origin of the acidifying effect of the $C_6(CF_3)_5$ group has been explored using the isodesmic reactions approach.

1. Introduction

Fluorination of organic compounds is gaining more and more importance in drug design, materials development, etc.[1,2] A particularly interesting group of fluorinated compounds are the polytrifluoromethylated compounds. Compared to polyfluorination, polytrifluoromethylation of aromatic compounds significantly increases molecular size and steric strain. Anionic species are stabilized by more efficient delocalization of the negative charge.[2] α-Fluorination leads to stabilization of alkyl radicals via delocalization of the odd electron by means of lone electron pairs of the fluorine atom and its competing inductive

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destabilization. The β-fluorine substitution results only in inductive destabilization of a radical. Therefore, in contrast to fluorination, the trifluoromethylation thermodynamically destabilizes the alkyl free radicals.[3] Nevertheless, some of the perfluorinated free radicals are among of the most stable free radicals known.[3] The radical-protective effect (kinetic stabilization) of perfluorinated groups derives from their inertness and steric shielding of the free radical center.[3] Similarly, trifluoromethyl (CF_3) groups are good kinetic protectors for carbenes, including triplet and singlet arylcarbenes,[4a] aminoarylcarbenes[4a] and push−pull arylphosphanylcarbenes.[4b] In addition to steric shielding the C−F bond is almost the only bond that is unreactive toward the carbene center.[4]

Bulky 2,6-bis(trifluoromethyl)phenyl and 2,4,6-tris(trifluoromethyl)phenyl substituents have proved very useful in stabilizing reactive species and have allowed the isolation and characterization of several other groups of carbenoids: bis(aryl)-germylenes,[5]-stannylenes,[6] and -plumbylenes.[7] In addition to the steric shielding factor the electron-donating ability of the fluorine lone pairs of the *ortho*-CF_3 substituents to the electron-deficient center is also responsible for stabilization in this group of carbenoids.

Due to the buttressing effect of the two *meta*-CF_3 substituents (presence of *meta*-CF_3 groups prevents the *ortho*-CF_3 groups from bending), pentakis(trifluoromethyl)phenyl ($C_6(CF_3)_5$) group has to be superior over 2,6-bis(trifluoromethyl)phenyl and 2,4,6-tris(trifluoromethyl)phenyl substituents as kinetic stabilizer. The same effect of $C_6(CF_3)_5$ group should also lead to increased electron donating ability of the fluorine lone pairs of the *ortho*-CF_3 substituents to the electron-deficient center. On the other hand the general electron-withdrawing effect of the $C_6(CF_3)_5$ group has to be superior to that of 2,6-bis(trifluoromethyl)phenyl and 2,4,6-tris(trifluoromethyl)phenyl substituents. It can lead to novel push−pull carbenes where the electron-withdrawing properties are involved in the push−pull stabilization. Therefore the functionalized $C_6(CF_3)_5$ derivatives can be regarded as promising building blocks for stable triplet and singlet push−pull carbenes, weakly coordinating anions,[8] novel types of stable free radicals and superacids, new materials for medicine, agrochemistry,[1] etc.[9] For that reason, developing of a general convenient access to functionalized $C_6(CF_3)_5$ derivatives is desirable.

A number of polytrifluoromethylated aromatic compounds are well-known, among them also pertrifluoromethylated compounds: pentakis-[10] and hexakis(trifluoromethyl)benzene,[11a,b] pentakis(trifluoromethyl)aniline,[12,13] etc.

No general methods to synthesize pentakis(trifluoromethyl)-arenes have been published. Different approaches are used, many of them involving harsh conditions. Thus, the hexakis(trifluoromethyl)benzene ($C_6(CF_3)_6$) was synthesized by thermal (375 °C) or Rh-catalyzed trimerization of 2-hexafluorobutyne.[11] The synthesis of pentakis(trifluoromethyl)benzene was made by high-pressure fluorination of 1-trifluoromethyl-2,3,5,6-tetracarboxybenzene with sulfur tetrafluoride in liquid hydrogen fluoride at 330 °C.[10] The simplest route to date for the synthesis of functionalized $C_6(CF_3)_5X$ compounds ($X = COOMe$, COOH, NH_2) was developed by Yagupolskii et al.[12] The key-point of this approach is a mild and efficient (92% yield) transformation of $C_6(CF_3)_6$ into the orthoester $C_6(CF_3)_5C(OMe)_3$, which gives rise to pentakis(trifluoromethyl)benzoic acid and -aniline. Pentakis(trifluoromethyl)fluorobenzene 30% yield), 1,3-difluoro-2,4,5,6-tetrakis(trifluoromethyl)benzene and traces of 1,3,5-trifluoro-2,4,6-tris(trifluoromethyl)benzene were synthesized by thermolysis (550 °C, 280 Torr) of the mixture of $C_6(CF_3)_6$ and trifluoroacetonitrile (CF_3CN).[13] In this reaction, the presence of CF_3CN is essential to get higher yields of the compounds. Treatment of $C_6(CF_3)_5F$ with ammonia gives $C_6(CF_3)_5NH_2$.

At the same time general approaches for introduction of perfluoroalkyl groups into different compounds and trifluoromethylation in particular do exist and have received considerable attention in several reviews.[14,15] Among the most widely known perfluoroalkylation reagents are the Ruppert−Prakash reagents (R_fSiMe_3),[14] which have found broad use for perfluoroalkylation of arenes and heteroarenes via the in situ "R_fCu" methodology. Generally, among the variety of trifluoromethylation approaches of aromatic compounds trifluoromethylation via (trifluoromethyl)copper (CF_3Cu) species is one of the most important and universal laboratory strategies.[15,16] A number of methods for trifluoromethylation of activated aromatics, vinyl and benzyl halides postulating an in situ generation of CF_3Cu specie have been developed.[16]

By use of the in situ protocol for CF_3Cu[17,18] the straightforward trifluoromethylation of hexaiodobenzene (C_6I_6) under multicomponent (trifluoromethyl)trimethylsilane (CF_3SiMe_3)/KF/CuBr reaction conditions in DMF/*N*-methyl-2-pyrrolidinone (NMP) mixture gave a complex mixture of difficult to identify and separate polyperfluoroalkyl substituted aromatic products containing different numbers of CF_3 and C_2F_5 groups.[19] This

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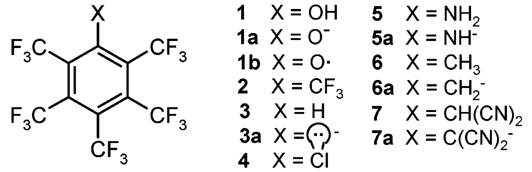
SCHEME 1. Structures of Title Compounds



led us to examine the possibility of using pregenerated CF_3Cu species instead of the in situ protocol.

To the best of our knowledge, only two examples for pregeneration of solution-stable and extremely reactive (even at −50 °C)[15] CF_3Cu species for CF_3-transfer supported by NMR evidence have been published to date.[17,20]

The first is the Burton's procedure, who generated CF_3Cu by means of metathesis of trifluoromethyl cadmium (fast exchange at −70 °C) or zinc (slow reaction even at 20 °C) derivatives with copper halides in 90−95% yield.[17] The second CF_3Cu pregeneration method is based on the reaction of tris(dialkylamino)phosphines with $BrCF_3$ and the reaction of the resulting tris(dialkylamino)(trifluoromethyl)phosphonium bromide (e.g., $[(Et_2N)_3PCF_3]Br$) with KF/CuI system.[20]

In this work we introduce a third pregeneration method based on CF_3SiMe_3 as the source of CF_3 in order to avoid using toxic cadmium compounds and tris(dialkylamino)phosphines. We demonstrate that this $CF_3SiMe_3/F^-/Cu^+$ methodology can be conveniently applied for generation of CF_3Cu species stable also at ambient temperature. We present a novel synthetic strategy to obtain the $C_6(CF_3)_5X$ compounds presented in Scheme 1 based on the reactions of pregenerated active CF_3Cu with polyiodoarenes under mild reaction conditions (Scheme 2). Trifluoromethylation of C_6I_6 provides the access to hexakis(trifluoromethyl)benzene (**2**), pentakis(trifluoromethyl)benzene (**3**) and potassium pentakis(trifluoromethyl)phenoxide (**1a·K$^+$**). Vacuum sublimation from the mixture of **1a·K$^+$** and concentrated sulfuric acid affords hitherto unknown highly acidic and hindered pentakis(trifluoromethyl)phenol (**1**). The compound **1** gives rise to easily functionalized pentakis(trifluoromethyl)cholorobenzene (**4**), and this, in its turn, pentakis(trifluoromethyl)aniline (**5**) and pentakis(trifluoromethyl)phenylmalononitrile (**7**). Pertrifluoromethylation of pentaiodochlorobenzene and pentaiodotoluene allows straightforward access to pentakis(trifluoromethyl)chlorobenzene (**4**) and pentakis(trifluoromethyl)toluene (**6**), respectively. The compounds **1**, **4**, **6** and **7** have not been described before.

We also examine possible routes for functionalization of the title compounds.

Introduction of five CF_3 groups into moderately to weakly acidic compounds, such as phenol, aniline and toluene is expected to significantly increase their acidity. Nevertheless, no data on the acidity of pentakis(trifluoromethyl)aryl compounds have been published to date. In this paper we present the acidity data for compounds **1, 3, 5, 6** and **7** in different solvents and in the gas phase. The origin of the acidifying effect of the $C_6(CF_3)_5$ group is explored using the isodesmic reactions approach.

2. Results

Synthesis. CF_3SiMe_3 reacts with the spray-dried KF/CuBr system in DMF/1,3-dimethyl-2-imidazolidinone (DMI) at 0 °C to give solution-stable CF_3Cu species: $CF_3Cu{\cdot}KBr$ (**8a**), $[(CF_3)_2Cu]^-K^+$(**8b**) and $[(CF_3)_4Cu]^-K^+$(**8c**) (Scheme 3), which were identified by their relevance (^{19}F NMR) to well identified CF_3Cu species from $CF_3ZnBr/CuBr$ metathesis procedure (Scheme 3). It has been found by Burton et al. that the denotation of trifluoromethyl copper derivatives as "CF_3Cu" is an oversimplification. Thus, instead of the anticipated one singlet, a DMF solution of multiple trifluoromethyl copper species exhibits three singlets in the ^{19}F NMR spectrum: −28.8 ppm (A); −32.3 ppm (B) and −35.5 ppm (C).[17,18] Their further investigation revealed that the signal at −35.5 ppm (C) belongs to an inert Cu(III) derivative, $[(CF_3)_4Cu]^-CdI^+$. The structure of tetrakis(trifluoromethyl)cuprate(III) anion **8c** was determined by X-ray crystallography.[18] The species located at −28.8 ppm (A) was found to be $CF_3Cu{\cdot}L$ (L = metal halide) and the signal at −32.3 ppm (B) is from the bis(trifluoromethyl)cuprate $[(CF_3)_2Cu]^-CdI^+$. This anion can be easily oxidized to $[(CF_3)_4Cu]^-$ in contrast to the slowly oxidized $CF_3Cu{\cdot}L$ species.

In the DMF/DMI solution of CF_3Cu obtained in this work using the pregeneration method the same sets of three different species as in ref 18 were found by ^{19}F NMR spectroscopy. Taking into account the similarity in chemical shift values between the trifluoromethyl copper from the $(CF_3)_2Cd/CF_3CdCl/CuBr$ metathesis reaction and the $CF_3SiMe_3/KF/CuBr$ procedure, the observed signals can be assigned as follows: −28.8 ppm: $CF_3Cu{\cdot}KBr$ (**8a**); −32.4 ppm: $[(CF_3)_2Cu]^-K^+$ (**8b**); −35.7 ppm: $[(CF_3)_4Cu]^-K^+$ (**8c**) (spectrum S4 in Supporting Information). **8c** is the product of oxidation of **8b** and **8a**. An oxidation experiment was carried out by directing dry air into the solution containing the pregenerated CF_3Cu. In the initial solution a strong peak corresponding to **8a** (−28.8 ppm) and a weak peak corresponding to **8b** (−32.5 ppm) were observed. After 2 days both **8a** and **8b** disappeared and a peak at −35.8 ppm was seen thus confirming that the same species as in refs 17 and 18 are observed (spectrum S5 and spectrum S6 in Supporting Information).

Tetrakis(trifluoromethyl)cuprate(III) salts are important precursors for preparation of organic cation-radical salt superconductors and semiconductors.[21] During the recent years CF_3SiMe_3 as a "source" of CF_3 anion has become a very popular and useful reagent. Taking into account the availability of this reagent from the green (containing no chlorine or bromine atoms) precursor trifluoromethane CF_3H,[22] the proposed route to $[(CF_3)_4Cu]^-K^+$ (**8a**) represents, apparently, to date the most rational synthetic method for synthesizing this compound.

Reaction of CF_3Cu with C_6I_6 at ambient temperature in DMF/NMP surprisingly gave potassium pentakis(trifluoromethyl)phenoxide **1a·K$^+$**, **2** and the protodeiodination product **3**, common for Ullmann type reactions, in a combined yield of 85%. According to the ^{19}F NMR spectra, C_6I_6 is quantitatively transformed into products **1a·K$^+$**, **2** and **3** with the ratio 1 (**1a·K$^+$**):2 (**2**):1 (**3**). Vacuum sublimation of **1a·K$^+$** from concentrated H_2SO_4 provided **1**. Using DMI instead of NMP, as a stabilizer of CF_3Cu species (suppresses the formation of difluorocarbene), led to a partial chain extension to form C_2F_5-Cu (approximately 3%) and also resulted in a nearly quantitative conversion of C_6I_6 into products **1**, **2** and **3** with the combined

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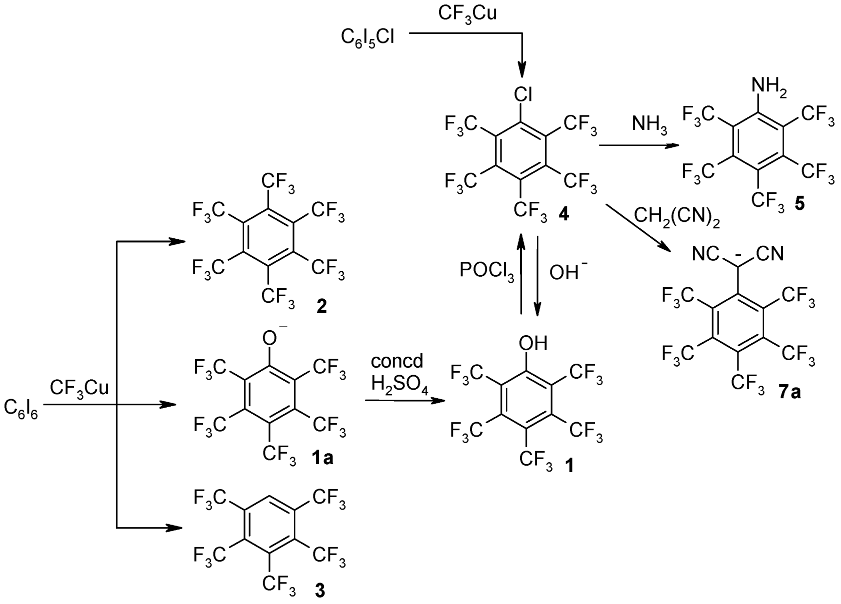
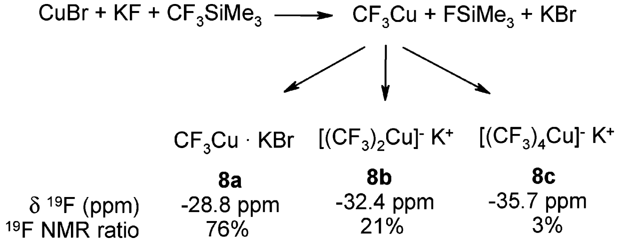
SCHEME 2. General Synthetic Route to Pentakis(trifluoromethyl)aryl Compounds



SCHEME 3. CF_3Cu Species Generated from the CF_3SiMe_3/KF/CuBr System



yield of 79−85%. The ratios between **1a·K**$^+$, **2** and **3** are different as compared to the NMP stabilizer the formation of **2** and **3** is suppressed: 1 (**1a·K**$^+$):1.2 (**2**):0.7 (**3**) (spectrum S7 in Supporting Information). An increase of the content of **1a·K**$^+$ is related to the enhanced oxygen-nucleophilicity of DMI compared to DMF.

XRD and Computational Structures of the Title compounds. Compounds **1a1·Me$_4$N**$^+$, **1a·Me$_4$N**$^+$, and **7a·Et$_4$N**$^+$ have been characterized by single-crystal XRD studies. The structures were solved by direct methods and refined using SHELX program packages.[23,24] Geometries of other compounds in the Table S20 (see Supporting Information) have been obtained computationally.

Functionalization of the Title Compounds. Use of the title compounds as building blocks assumes their functionalization. All products from the trifluoromethylation of hexaiodobenzene, $C_6(CF_3)_5X$ (X = OH, H, CF_3), can be involved in different functionalization reactions. $C_6(CF_3)_6$ can be transformed into pentakis(trifluoromethyl)benzoic acid and -aniline by a published method.[12]

In this work, **1** was easily chlorinated with $POCl_3$/Py (Scheme 2) to obtain **4**. This derivative is a potential reaction partner for diverse nucleophilic substitution reactions and for Pd-catalyzed cross-couplings. Preliminary experiments with some C- and N-nucleophiles confirmed this consideration.

The compound **4** showed no reaction with the CH_3CN/Et_3N system, but with more acidic malononitrile pentakis(trifluoromethyl)phenylmalononitrile (**7**) was obtained. Reaction of **4** with ammonia provided pentakis(trifluoromethyl)aniline (**5**). In this case an earlier described[10] competing substitution reaction of fluorine atoms of the CF_3 groups was also observed, resulting in the concurrent formation of cyano-derivatives.

The obvious way to functionalize **3** would be by its deprotonation and/or metalation. Attempts to deprotonate or lithiate **3** have not been described in the literature (vide infra). Preliminary experiments to deprotonate **3** with the hindered phosphazene superbase EtP_2(dma) were reasonably successful only at low concentrations (approx 5×10^{-5} M in acetonitrile (AN)) and were monitored using UV−vis spectroscopy. The spectra are presented in Supporting Information (see Figure S1) and indicate reversibility of protonation-deprotonation. Reversible protonation-deprotonation was also indicated by the titration curves from potentiometric measurements[26] in DMSO medium at somewhat higher concentrations (approx 3×10^{-3} M) using Bu_4NOH (in mixture of benzene and 2-propanol) and *t*-BuP_4-(dma) (in mixture of heptane and benzene) as titrants. Likewise, reversible deprotonation of **3** was monitored during the determination of ΔG_{acid} values in the gas phase. From the experiments that were carried out at even higher concentrations (approx 5×10^{-2} M) with phosphazene bases *t*-BuP_1(tmg), HP_1-(tmg)[25] and monitored with ^{31}P and ^{19}F NMR, it was not possible

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TABLE 1. Results of Experimental and Computational (DFT B3LYP 6-311+G) Acidity Determinations in Different Media**[a]

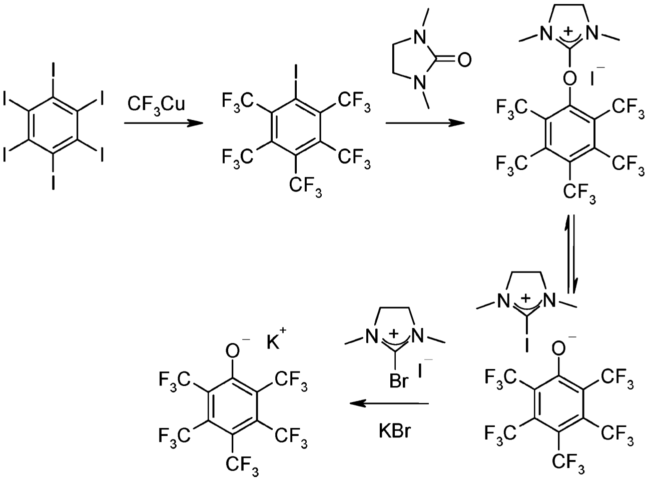
compound	ΔG_{acid} (exp)	ΔG_{acid} (calcd)	pK_a (AN)	pK_a (DMSO)	pK_a (water)
Phenols					
$C_6(CF_3)_5OH$ (**1**)	298.7	290.2	10.46	3.1	1.32
4-CF_3-phenol	330.1[b]	325.2	25.54	14.6	8.68[c]
3-CF_3-phenol	332.4[b]	328.2	26.50	15.1	8.95[c]
2-CF_3-phenol	332.2	327.1	24.88	14.4	8.42
3,5-$(CF_3)_2$-phenol	322.9[b]	318.3	23.78	13.2	8.26
phenol	342.3[b]	339.2	29.14[d]	18.0[e]	9.95[c]
Anilines					
$C_6(CF_3)_5NH_2$ (**5**)	310.8[b]	312.2	24.59	12.5	
4-CF_3-aniline	346.0[b]	345.1		27.0[f]	
3-CF_3-aniline	349.6[b]	348.8		28.2[f]	
2-CF_3-aniline		347.1			
3,5-$(CF_3)_2$-aniline	340.6[b]	338.7		25.7[f]	
aniline	359.1	359.4		30.6[e]	
Toluenes					
$C_6(CF_3)_5CH_3$ (**6**)	318.9	317.6	28.7[h]	13.9	
4-CF_3-toluene	359.8	357.7			
3-CF_3-toluene	362.0	363.0			
2-CF_3-toluene		359.9			
3,5-$(CF_3)_2$-toluene	354.3	352.0			
toluene	373.7	374.9		43[e]	
Benzenes					
$C_6(CF_3)_5H$ (**3**)	331.1[g] 328.4[i]	332.4		20[h]	
4-CF_3-benzene		380.1			
3-CF_3-benzene		380.8			
2-CF_3-benzene	379.0[j]	378.2			
1,3-$(CF_3)_2$-benzene	365.0[j]	363.6			
benzene	390.9[b]	393.3			
Phenylmalononitriles					
$C_6(CF_3)_5CH(CN)_2$ (**7**)		280.9	8.86		
2,3,4,6-$(CF_3)_4$-$C_6HCH(CN)_2$[k]		286.8	10.45		

[a] This work, if not specified otherwise. [b] Reference 27. [c] Reference 28. [d] Value 27.2 has been published in ref 29, however, we consider our value 29.14 more reliable for reasons outlined in ref 30. [e] Reference 31. [f] Reference 32. [g] Approximate value from one single measurement (±1 kcal·mol^{-1}). [h] Approximate value (±1 pK_a units). [i] Value obtained from the correlation of pK_a value of THF/Et_2O/DME vs ΔG_{acid}. [j] Reference 33. [k] Synthesis of this compound is described in Supporting Information.

TABLE 2. Results of Acidity Calculations (DFT B3LYP 6-311+G) of Related Compounds**

	ΔG_{acid}	PA(A^-)
1,2-$(CF_3)_2$-benzene	368.0	376.2
1,4-$(CF_3)_2$-benzene	366.6	374.2
1,2,3-$(CF_3)_3$-benzene	357.3	365.2
1,2,5-$(CF_3)_3$-benzene	354.4	362.4
1,3,5-$(CF_3)_3$-benzene	351.9	360.0
1,2,4,5-$(CF_3)_4$-benzene	344.4	352.8
2,4,6-$(NO_2)_3$-benzene	337.5	342.4
2,3,4,5,6-$(NO_2)_5$-benzene	310.4	318.1
2,3,4,5,6-$(CN)_5$-benzene	323.2	331.9
2,4,6-$(CF_3)_3$-phenol	302.5	310.4
$(CF_3)_5C_6O$ (radical)	290.2	297.8
2,4,6-$(NO_2)_3$-phenol	293.5	301.4
2,3,4,5,6-$(NO_2)_5$-phenol	275.8	284.5
2,3,4,5,6-$(CN)_5$-phenol	276.5	282.1
2,4,6-$(NO_2)_3$-aniline	314.3	321.8
2,3,4,5,6-$(NO_2)_5$-aniline	291.0	300.4
2,3,4,5,6-$(CN)_5$-aniline	297.8	305.6
2,4,6-$(NO_2)_3$-toluene (TNT)	307.5	315.1
2,3,4,5,6-$(NO_2)_5$-toluene	297.7	304.2
2,3,4,5,6-$(CN)_5$-toluene	300.4	308.5

SCHEME 4. Possible Reaction Pathway to 1a·K$^+$



to get direct indications about deprotonation of **3** and its analogues with less CF_3 groups.[33]

Acidity. The results of experimental and computational acidity determination of **1**, **5**, **6**, **7** and a number of related compounds in different media are given in Table 1.

pK_a measurement of **3** was unsuccessful in all condensed media except in DMSO. Detailed results (*E*, *H*, *G*) of the calculations and Cartesian coordinates of these compounds are given in Supporting Information.

It is interesting to compare the acidity of compounds containing $C_6(CF_3)_5$ group with acidities of compounds containing pentacyano-, pentanitro- and trinitrophenyl groups. From Table 1 and Table 2 (see also 3.6 in Supporting Information) it is seen that three nitro groups and five CF_3 groups have nearly the same influence to an acidity but much less compared to five cyano or nitro groups.

3. Discussion

3.1. Synthesis. Pertrifluoromethylation of Hexaiodobenzene.

The formation of **1a·K$^+$** on pertrifluoromethylation of C_6I_6 could be rationalized as follows. Considering the nucleophilicity of DMI and the fact that step-by-step trifluoromethylation of C_6I_6 includes formation of the highly activated to nucleophilic substitution pentakis(trifluoromethyl)iodobenzene $C_6(CF_3)_5I$, we propose that the formation of **1a·K$^+$**, presumably includes a Vielsmeier-type intermediate (Scheme 4), generated from DMI and $C_6(CF_3)_5I$. Due to the bulkiness of the pentakis(trifluoromethyl)phenoxy group the intermediate probably exists preferentially in the phenoxide form. Subsequently it undergoes ion-exchange with potassium bromide to afford **1a·K$^+$** and bromoimidazolidinium iodide. This is one possible reaction pathway. $C_6(CF_3)_5I$ can also react with some other oxygen containing substances (copper oxide, traces of water) in solution.

Deprotonation of 3. The acidities and deprotonation/metalation reactions of CF_3-substituted benzenes have been studied and it has been found that the reactivity and reaction route

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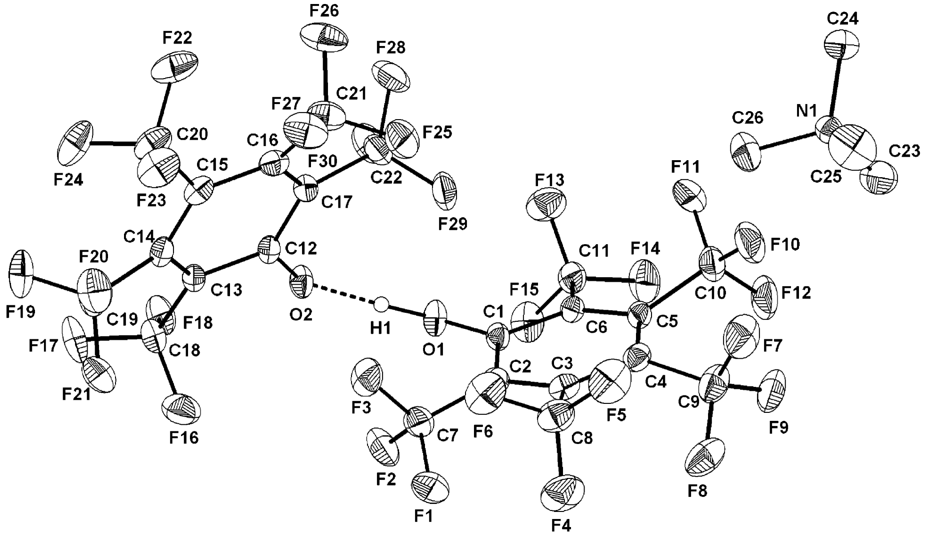

FIGURE 1. Molecular structure of **1a1·Me$_4$N$^+$** with 20% thermal ellipsoids (hydrogen atoms of Me$_4$N$^+$ cation are omitted for clarity). Selected bond distances (Å) and angles (deg): O1−C1 1.305(4), O2−C12 1.289(3), C1−O1−H1 123.24(30), O1−C1−C2 124.04(27), O1−C1−C6 117.24(24), O2−C12−C17 122.97(27), O2−C12−C13 118.88(24).

depends on both the number of CF$_3$ groups and on their positions.[33,34] While bis(trifluoromethyl)benzenes can be lithiated quantitatively and in the case of tris(trifluoromethyl)benzenes, the success and position of lithiation is dependent on conditions and on the reagent used, none of the three isomers of tetrakis(trifluoromethyl)benzene can be lithiated.[34] There are at least three different factors that are in action here:[34] (a) The acidity of the substrate and thus the hydrogen mobility increases with increasing number of CF$_3$ substituents. (b) Increasing the number of CF$_3$ groups increases the steric crowding. The accessibility of a particular hydrogen is dependent not only on the presence of the CF$_3$ groups in positions 2 and 6 relative to it but also on the presence of CF$_3$ groups in the positions 3 and 5 that prevent the adjacent CF$_3$ groups from bending (buttressing effect) and making way for the reagent. (c) Increase of the acceptor properties of the multiply CF$_3$-substituted benzene that can direct the reaction to an addition reaction (an *ipso*-attack of the most electron-deficient aromatic carbon) rather than to a proton abstraction reaction. This is supported by formation of stable CF$_3$-anion addition product, fluorinated cyclohexadienide-anion, in reaction of 1,2,4,5-tetrakis(trifluoromethyl)benzene with CF$_3$SiMe$_3$/TASF system.[35]

3.2. XRD and Calculated Structures of Pentakis(trifluoromethyl)phenyl Derivatives. The full geometry parameters of the title compounds are given in Table S20 in Supporting Information.

Experimental Structures of 1a1 and 1a. Compounds **1a1·Me$_4$N$^+$** (Figure 1) and **1a·Me$_4$N$^+$** have been characterized by single-crystal X-ray diffraction crystallography. It has been shown that the asymmetric unit of **1a1·Me$_4$N$^+$** contains cation Me$_4$N$^+$ and anion [C$_6$(CF$_3$)$_5$OH···OC$_6$(CF$_3$)$_5$]$^-$ with a very strong[36,37] O−H···O intermolecular hydrogen bond: O1−H1 1.03(5), H1···O2 1.43(5), O1···O2 2.439(3) Å, O1−H1···O2 167(5)°. The asymmetric unit of **1a·Me$_4$N$^+$** contains two ion pairs (Figure S2 in Supporting Information). The lengths of the C−F bonds of **1a1** are 1.314(4)−1.354(5) (av 1.330 Å) and **1a** 1.328(5)−1.362(5) (av 1.339 Å), C$_{Ar}$−C$_{Ar}$ in **1a1** 1.388(4)−1.424(4) (av 1.403 Å) and in **1a** 1.387(5)−1.452(5) (av 1.415 Å), and C$_{Ar}$−CF$_3$ in **1a1** 1.510(5)−1.541(6) (av 1.526 Å) and in **1a** 1.500(6)−1.547(5) (av 1.521 Å) and are unexceptional.[38] Due to the steric crowding connected with the bulkiness of CF$_3$ substituents, the phenyl rings are not exactly planar (the deviations from the least-squares planes are, in the case of **1a1**, 0.012−0.038 Å (C1−C6) and 0.020−0.036 Å (C12−C17) and in case of **1a** 0.024−0.039 Å but noticeably distorted toward the "chair" conformation. Formation of **1a** from **1** brings about significant shortening of the C$_{Ar}$−O bond, O1−C1 1.305(3) vs O2−C12 1.289(3) due to the electron-withdrawing effect of the C$_6$(CF$_3$)$_5$ group. This shortening is even more enhanced in **1a** to compare with **1** due to steric overcrowding of O$^-$ with the bulky CF$_3$ substituents of the phenyl ring. Therefore, **1a** is more distorted than **1**. The nonplanarity of the rings can be evaluated by the dihedral angles C1−C2−C3−C4 and C1−C6−C5−C4. The average values for these angles are 7.8° and 7.9° for the phenol and phenoxide rings of **1a1**, respectively, and 8.8° for **1a**. Carbon atoms of the CF$_3$ groups are displaced alternately up and down by 0.02−0.59 Å (av 0.28) relatively to the least-square plane C2−C3−C5−C6 (or C13−C14−C16−C17) of the phenyl rings (see Table S20 in Supporting Information for displacement angles). In general, the geometry parameters of the C$_6$(CF$_3$)$_5$ moieties of **1a1** and **1a** are quite similar to those in C$_6$(CF$_3$)$_6$.[39]

As can be expected, the geometry parameters that are dependent on the effective charge of the structure change in the following row: neutral component of **1a1** → anionic component of **1a1** → **1a**, the former two are more similar to each other than to **1a.** The most prominent example is the considerable shortening of the C1−O1 and C12−O2 bonds (1.289(3) and 1.305(4) Å, respectively, in **1a1**, and 1.247(5) Å

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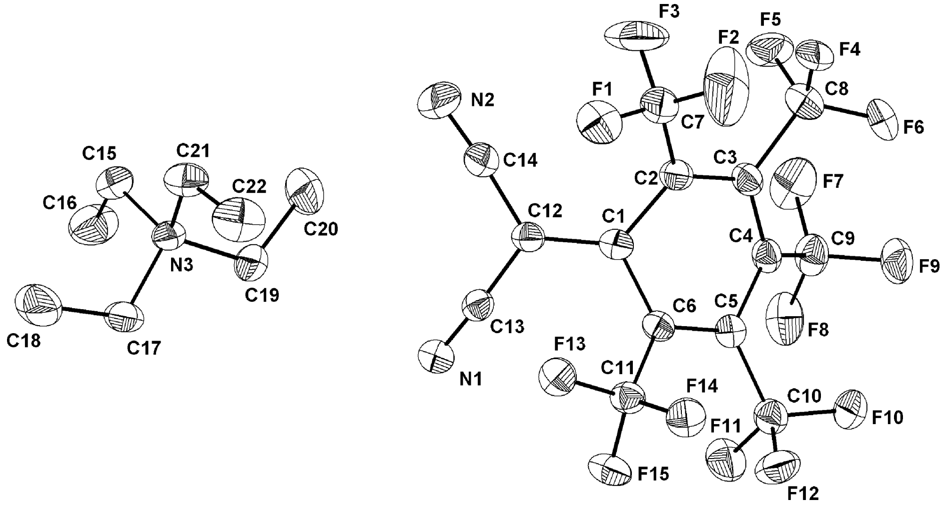

FIGURE 2. Molecular structure of **7a·Et$_4$N$^+$** with 50% thermal ellipsoids (hydrogen atoms of Et$_4$N$^+$ cation are omitted for clarity, other view of the same molecule to demonstrate distortions is in Supporting Information, Figure S4). Selected bond distances (Å), angles (deg) and dihedral angles (deg): C1−C12 1.390(2), C1−C2 1.447(2), C1−C6 1.452(2), C2−C1−C6 112.15(12), C3−C4−C5 116.87(13), C13−C12−C14 112.25(12), C14−C12−C1−C2 −4.27(24), C1−C2−C3−C4 −11.92(21), C1−C6−C5−C4 9.09(20).

in **1a**) in comparison with the corresponding values in phenol derivatives (1.35−1.37 Å),[38] reflecting the total strong electron-withdrawing influence of the five CF$_3$ groups and the partial double-bond character of the C−O bonds. The same is true for the average *ipso*-*ortho* C$_{Ar}$−C$_{Ar}$ bondlengths of the aromatic nuclei. The distances in the sequence of **1a1** and **1a** are 1.414, 1.419, 1.452 Å, respectively. These distances are elongated compared to the averages of the remaining C$_{Ar}$−C$_{Ar}$ distances in the aromatic rings (1.397, 1.399, 1.400 Å) indicating reduced bond order, which is coherent with the increased bond order of the C$_{Ar}$−O bonds. This is accompanied by the decreasing of the C2−C1−C6 and C13−C12−C17 bond angles in **1a1** to 118.1(3) and 118.7(3)° in comparison with remained C$_{Ar}$−C$_{Ar}$ bond angles of 119.4−120.8(3)° (av 120.1°). In **1a** the same pattern appears: the C2−C1−C6 angle is 116.2(3)° (the remaining C$_{Ar}$−C$_{Ar}$ bond angles are 120.7−121.5°).

Experimental Structure of 7a. The anion **7a** (Figure 2) has significantly more deformed aromatic ring than **1a1** or **1a**. In particular, the malononitrile fragment C(CN)$_2^-$ together with the *ipso*-carbon C1 are strongly forced out of the C2−C3−C5−C6 plane by the two *ortho*-CF$_3$ groups: the angle between this and the C1−C2−C6 plane is 35.3°. At the same time, the angle between the C1−C2−C6 plane and the bond C1−C12 is only 3.8° and the whole C1−C2−C6−C12−C13−C14−N1−N2 moiety (see Figure 2) is nearly planar. This is the reason for the abovementioned strong deformation; there is strong resonance within this moiety. Bonds C1−C2 and C1−C6 are considerably longer compared to the other bonds in aromatic ring, being 1.45 Å, whereas the other bonds in the ring are in range of 1.39−1.42 Å. The angle of C2−C1−C6 is also lower than is typical to aromatic ring: 112.1(1)°. The locations of the CF$_3$ groups are slightly different from **1a1** and **1a**: instead of being displaced alternately up and down from the ring the four *ortho*- and *meta*-CF$_3$ groups are on the opposite side of the aromatic ring with respect to the C(CN)$_2^-$ fragment while the *para*-CF$_3$ group is on the same side. Differently from **1a1** and **1a**, the aromatic ring in this case is not chairlike but boatlike. The bond lengths and angles in the CF$_3$ groups are not much different from **1a1** and **1a**.

Computational Structures of 1, 1a, 1b and 7a. The geometries of **1**, **1a** and **7a** obtained computationally at DFT B3LYP 6-311+G** can be compared to the XRD structures of the neutral fragment of **1a1** (if some caution is exercised), **1a** and **7a**. The computed structures of **1** and **1a** are rather similar to their experimental counterparts. Both have slightly chairlike structure and alternating CF$_3$ displacement patterns as the XRD structures. The most prominent difference between computational and experimental geometry of **1a** is in the planarity parameters: computation predicts stronger distortion of the ring, while experiment indicates lesser distortion of the ring and at the same time stronger out-of-plane deformation of the CF$_3$ groups (see Table S20 in Supporting Information). The computational structure of the radical **1b** is very similar to that of the anion **1a**. The dimer C$_6$(CF$_3$)$_5$-O-O-C$_6$(CF$_3$)$_5$ is by 30.1 kcal·mol^{-1} less favorable than two separated free radicals **1b**.

The XRD structure does not permit to assess whether there is an intramolecular hydrogen bond in **1**. Analysis of the computational structure reveals that the H-F2 distance is 1.794 Å and the respective C7−F2 distance is 1.377 Å, while the rest of the C−F distances are in the range of 1.33 to 1.35 Å. This indicates a weak hydrogen bond between the OH group and a fluorine atom of the *ortho*-CF$_3$ group.

The differences between the XRD and computational geometries of **7a** are more pronounced. The ring of the computational structure of **7a**, differently from the boat geometry observed by XRD, displays an "asymmetric chair" geometry: C1 (the same numeration is used as in Figure 1) is out of the C2−C3−C5−C6 plane by 0.371 Å (0.468 Å according to XRD), while C4 is out of the plane to the opposite side by only 0.043 Å (0.232 Å to the same side according to XRD). Concurrently, differently from the XRD geometry, the computational structure of **7a** has alternating displacement of the CF$_3$ groups from the C2−C3−C5−C6 plane. The computed geometry of the moiety composed of the C1−C2−C6 fragment and the C(CN)$_2^-$ group is rather similar to the experimental one.

Computational Structures of 3, 5, 5a, 6, 6a and 7 are similar to those of **1** and **1a**. All aromatic rings are chairlike.

The rings in the anions are more distorted than in neutrals. The CF_3 groups are somewhat distorted. One of the C−F bonds is longer at the expense of the other two. The CF_3 groups are alternately twisted out of the aromatic plane up to 27°. The nearest F−F distances between the adjacent CF_3 groups are in 2.5 Å range. In general the geometries of the anions are similar to each other and the geometries of the neutrals are similar to each other. The full geometry data are available in Supporting Information (Table S20). The structure of neutral **7** is similar to the other neutral compounds. The aromatic ring is only slightly distorted, the CF_3 groups are slightly out of plane. When comparing the $C(CN)_2^-$ and $CH(CN)_2$ groups in **7a** and **7** it is evident that two CN groups in **7** are not on the same plane with aromatic ring but oriented almost perpendicularly to the ring to incur the least possible steric destabilization.

It is also of interest to compare the C1−X distances in the neutrals and anions. In all cases deprotonation leads to decrease of the C1−X distance. The decrease is by 0.104, 0.066, 0.165 and 0.161 Å in **1**, **5**, **6** and **7**, respectively, and reflects the increase in resonance delocalization of the charge from X on deprotonation. The largest change is in **6** and **7** where resonance in the anions is very strong and is absent in the neutrals. The smallest change in **5** indicates a resonance also in the neutral.

Structure of 3a. Contrary to the anions **1a**, **5a** and **6a**, the computational geometry of the anion **3a** is not chairlike, but strongly twisted. The twist is so strong that it is impossible to define any plane similar to one defined for the other compounds. The twist can be characterized by dihedral angles C1−C2−C3−C4 and C1−C6−C5−C4 that are 29.5°. This strong distortion renders it impossible to rigorously assess the out-of-plane distortion of the CF_3 groups. Some insight can be gained from the dihedral angles C7−C2−C3−C8 41.41°, C8−C3−C4−C9 −21.01°, C4−C9−C5−C10 −18.96°, C10−C5−C6−C11 39.80° and C7−C2−C6−C11 −63.18°. These numbers demonstrate the severity of the distortion of the whole molecule. The latter angle reveals the tendency of the *ortho*-CF_3 groups to assume perpendicular orientation and indicates somewhat allenic character of the C1 carbon. Based on the computations at the same level, none of the following pentakis-substituted phenyl anions displays nonplanarity to any noticeable extent: $C_6H_5^-$, $C_6(CN)_5$, $C_6(OCF_3)_5^-$.

3.3. Acidities of Pentakis(trifluoromethyl)phenyl Derivatives. Acidities of 1, 5, 6 and 3 in the Gas Phase. As is seen from Table 1 the acidities of the $C_6(CF_3)_5$ substituted compounds decrease in the following order in all media where comparison is possible: **1** > **5** > **6** > **3**. The acidity differences between the three consecutive pairs of compounds **1**, **5**; **5**, **6**; and **6**, **3** are significantly smaller (12.9, 8.1 and 13.7 kcal·mol^{-1} in the gas phase, respectively) than in the case of the unsubstituted parent compounds (16.8, 14.6 and 19.5 kcal·mol^{-1} in the gas phase, respectively), reflecting the decrease of importance of the first atom of the protonation center compared to the substituted aromatic nucleus. The only condensed phase, where similar comparison can be carried out, is DMSO. In DMSO the same differences between pairs **1**, **5** and **5**, **6** (data for **3** are not available) in the case of substituted compounds are 10.48 and 2 pK_a units and in the case of unsubstituted compounds 12.6 and 12.4 pK_a units. Particularly noteworthy is the remarkable strength of **6** in this solvent compared to **5**; the latter is only by 2 pK_a units stronger.

Normally the effect of stepwise introduction of multiple electron-acceptor substituents into the phenol aromatic ring of phenol does not display additive behavior; the gross effect of the introduction of the substituents is usually smaller than the sum of single substituent effects. This is attributable to the saturation of the substituent effects and has been extensively discussed, e.g., in ref 40. For small substituents, notably fluorine, it can also be observed that the gross acidifying effect of multiple substituents in polysubstituted compounds is larger than the additive sum of single substituent effects (see Supporting Information for detailed information on additivity calculations). There are five bulky substituents in the molecules of **1**, **3**, **5** and **6**. Thus, there is every reason to expect a less-than-additive behavior. In the gas-phase this is really the case for **1**, **3**, **5** and **6**: according to both experimental and computational results the gross acidifying effect of the five CF_3 substituents forms around 80% of the sum of the acidifying effects of the single substituents in **1**, **5** and **6**. In **3** there is 88% additivity. It is of interest to analyze the acidifying effect of the five CF_3 substituents in order to get some insight into the acidity of these rather peculiar molecules. We use the method of isodesmic reactions.[41] The acidity of a $C_6(CF_3)_5$ substituted derivative $C_6(CF_3)_5X$, denoted as $\Delta G_{acid}(C_6(CF_3)_5X)$, can be calculated from the acidity of the unsubstituted compound $\Delta G_{acid}(C_6H_5X)$ and the acidifying/deacidifying effects of different interactions as follows:

$$\Delta G_{acid}(C_6(CF_3)_5X) = \Delta G_{acid}(C_6H_5X) + \Delta\Delta G_{GAIE} + \Delta\Delta G_S + \Delta\Delta G_{RCC} + \Delta\Delta G_{RCX} \quad (1)$$

The $\Delta\Delta G$ values in eq 1 are defined as follows:

$$\Delta\Delta G = \Delta G(\text{anion}) - \Delta G(\text{acid}) \quad (2)$$

The ΔG values are defined as follows:

- ΔG_{GAIE} (defined via eq 4) is the estimate of the gross interaction energy between the reaction center and the CF_3 substituents in the idealized pentasubstituted molecule where there are no steric or other interactions between the CF_3 groups and the interactions between the CF_3 groups and the reaction center are just as strong as in the respective monosubstituted molecules. The steric interaction in twice the extent present in 2-CF_3-C_6H_4X is also included in ΔG_{GAIE}.
- ΔG_S is the energy contribution due to saturation of the substituent effects.
- ΔG_{RCC} is the energy contribution due to steric repulsion between the CF_3 groups.
- ΔG_{RCX} is the energy contribution due to additional steric repulsion between the two CF_3 groups in position 2 and the group X (or its deprotonated form). The additional contribution has two reasons: (1) in the pentakis-substituted derivative there are simultaneously two CF_3 groups in positions 2 and 6, and (2) there are CF_3 groups also in positions 3 and 5 that reduce the flexibility of the 2- and 6-CF_3 groups.

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[40] Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignatev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047−3057.

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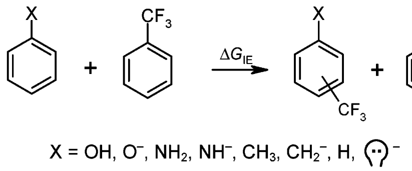
The ΔG_{GAIE} contributions can be estimated from the following series of reactions:

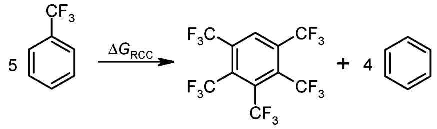


(3)

The energy effects of this reaction with the 1,2-, 1,3- and 1,4-product can be summarized as follows, directly providing the ΔG_{GAIE}:

$$\Delta G_{\mathrm{GAIE}} = \Delta G_{\mathrm{IE}}(1{,}4) + 2\,\Delta G_{\mathrm{IE}}(1{,}3) + 2\,\Delta G_{\mathrm{IE}}(1{,}2) \quad (4)$$

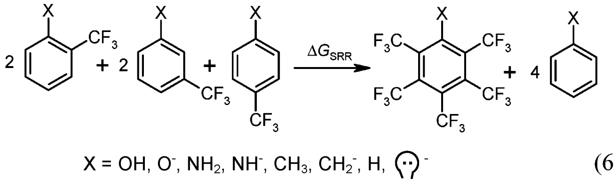
The ΔG_{RCC} is found via the following equation:



(5)

Since the group X is not involved in this reaction this contribution is the same in all species leading to $\Delta\Delta G_{\mathrm{RCC}} = 0$ kcal·mol^{-1}.

No single isodesmic reaction equations can be written for obtaining the remaining two ΔG contributions: the contributions $\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}}$ can in the framework of this isodesmic reaction approach be estimated only jointly. The following series of reactions was used:



(6)

The negative free energy change of these reactions can be expressed as follows:

$$\Delta G_{\mathrm{SRR}} = \Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCC}} + \Delta G_{\mathrm{RCX}} \quad (7)$$

From eqs 5 and 7 follows that

$$\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}} = \Delta G_{\mathrm{SRR}} - \Delta G_{\mathrm{RCC}} \quad (8)$$

The results of the analysis according these equations are presented in Table 3.

The ΔG_{GAIE} contributions in the anions of **1**, **3**, **5** and **6** are vastly larger than in the neutrals and change monotonously when moving from **1a** to **5a** to **6a** to **3a** indicating increase in stabilization of the anion in the row. It is interesting that the ΔG_{GAIE} in **3a** is by 4.6 kcal·mol^{-1} more negative than in **6a**, in spite of the seemingly unfavorable geometry (from the point of view of resonance and hyperconjugation[42] stabilization) of the free electron pair of the anion **3a**. When looking at the contributions of the individual substituents then it is evident that this is first of all caused by the large stabilizing interaction with the two CF_3 groups in positions 2 and 6: −15.1 kcal·mol^{-1} (per one CF_3 group). This value is clearly the most negative in the row followed by −11.8 kcal·mol^{-1} of **6a**. Most likely, the reason is twofold: (1) the lack of steric repulsion between the deprotonated acidity center and the 2-CF_3 groups and (2) the shorter distance (2 bonds, vs 3 bonds in **1a**, **5a** and **6a**) between the acidity center and the 2-CF_3 substituents.

TABLE 3. Results of Analysis According to Eq 1 (all Values in Kcal·mol^{-1})[a]

	1	5	6	3
Contributions from isodesmic reactions eqs 4-8				
ΔG_{GAIE}(neutral)	3.8	−0.9	6.9	0
ΔG_{GAIE}(anion)	−56.5	−60.9	−63.9	−68.5
$\Delta\Delta G_{\mathrm{GAIE}}$	−60.3	−60.0	−70.8	−68.5
ΔG_{RCC}(neutral, anion)	56.0	56.0	56.0	56.0
ΔG_{S}(neutral) + ΔG_{RCX}(neutral)	5.0	6.9	6.4	0
ΔG_{S}(anion) + ΔG_{RCX}(Anion)	16.3	19.7	20.0	7.6
$\Delta\Delta G_{\mathrm{S}} + \Delta\Delta G_{\mathrm{RCX}}$	11.3	12.8	13.5	7.6
Contributions estimated from additional approximations				
ΔG_{S}(neutral)	0	0	0	0
ΔG_{S}(anion)	11.3	12.8	13.6	7.6
ΔG_{RCX}(neutral)	5.0	6.9	6.4	0
ΔG_{RCX}(anion)	5.0	6.9	6.4	0
Gross acidifying effects				
computational	−49.0	−47.2	−57.3	−60.9
experimental	−48.5	−48.3	−54.8	−62.5

[a] Enthalpies would be preferred in the analysis by isodesmic reactions (see Supporting Information). However, in this case all the reactions have the same number of molecules on both sides of the equation and no intramolecular cyclization is involved. Therefore the use of Gibbs free energies is justified.

Contrary to this the gross additive interaction energies of five CF_3 substituents in the neutrals display complex behavior. The effect is destabilizing in the case of **1** and **6**. This is primarily due to the destabilizing effect of the 2-substitution in **1** (1.6 kcal·mol^{-1}) and **6** (3.2 kcal·mol^{-1}) and is not compensated by the weak stabilizing effect of 4-substitution (−0.6 and −0.2 kcal·mol^{-1}, respectively). 3-substitution shows slight destabilizing effect in both **1** and **6** (0.6 and 0.4 kcal·mol^{-1}, respectively). In **5**, the effect of 2-substitution is weakly destabilizing (0.8 kcal·mol^{-1}) but it is compensated by the stabilizing effects of 3- (−0.4 kcal·mol^{-1}) and 4-substitution (−1.6 kcal·mol^{-1}). As a result, the ΔG_{GAIE} contributions do not change monotonously from **1** to **3**. Instead, the effects of **1** and **5** are very similar and significantly lower than in the case of **6**. From the analysis we may conclude that the acidifying effect in **5** is lower mainly because the interaction energy between the CF_3 substituents and the acidity center -NH_2 is significantly more negative than in the case of -OH or -CH_3. The observed acidifying effects, both experimental and computational, follow the trend. Obviously, as the ΔG_{GAIE} is defined by eq 3, $\Delta G_{\mathrm{GAIE}}(\mathbf{3}) = 0$ kcal·mol^{-1}.

In order to separate the joint contributions $\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}}$ into components we use the following additional approximations.

1. As seen from the ΔG_{GAIE} values of the neutrals **1**, **3**, **5** and **6**, the interaction energies in them are small. We can therefore assume that the effect of saturation of the interaction energy is still a lot smaller and thus forms a negligible part of the joint contribution $\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}}$ in the neutrals, that is ΔG_{S}(neutral) = 0 kcal·mol^{-1}.

2. Geometries of the neutrals and anions of **1**, **5** and **6** are similar. Proton abstraction does not markedly change the geometry of **1**, **5** and **6** or release the steric strain. This claim is confirmed by the geometry analysis (see above). Thus we

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[42] Schleyer, P. v. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141−1150.

TABLE 4. Scaling Correlation Equations of the Relationship between Calculated at DFT B3LYP 6-311+G Level Gas-Phase Acidities ΔG_{acid}(calc) and Respective Experimental Quantities ΔG_{acid}(exp), $\Delta G_{acid}(calc) = a + b\Delta G_{acid}(exp)$**

series	a	s(a)	b	s(b)	r	S	n	comments
A	−22.65	4.8	1.054	0.015	0.994	1.89	33	substituted OH acids, all
B	−38.3	8.5	1.103	0.027	0.993	1.36	15	substituted phenols, **1** included
b_1	−34.2	9.4	1.091	0.029	0.992	1.36	14	substituted phenols, **1** excluded
D	−25.8	4.1	1.063	0.012	0.996	1.57	29	substituted phenols, aliphatic alcohols and carboxylic acids, **1** included
E	16.9	14.2	0.954	0.039	0.989	1.0	10	substituted benzenes, **3** included
e_1	−1.6	16.5	1.004	0.045	0.986	1.88	9	substituted benzenes, **3** excluded
F	−9.5	7.4	1.025	0.022	0.977	1.7	8	substituted toluenes, **6** included
f_1	−10.1	8.2	1.027	0.024	0.997	1.8	7	substituted toluenes, **6** excluded

[a] See Supporting Information Tables S3−S5 for compounds included.

may assume that as a first approximation the steric destabilization effects in the neutrals and the anions are equal: ΔG_{RCX}(neutral) = ΔG_{RCX}(anion). The only exception is the anion **3a**.

From the above analysis and from the geometries of the species it is possible to draw the following principal conclusions:

1. The abrupt changes in the acidifying effects of five CF_3 groups in phenol, aniline and toluene are caused by the complex behavior of the neutrals, not the anions.

2. The effect of release of steric strain on deprotonation is of minor importance: the steric distortion of the molecules **1**, **5** and **6** does not change significantly with deprotonation. Instead, the ca. 80% additivity of the effect of substituents on acidity is primarily caused by saturation of the substituent effects. However, the saturation may well have the steric distortion of the anion as a major cause.

3. The low acidity of **3** is not caused by inefficiency of the substituents in stabilizing the anion as might be expected from the classic substituent effect considerations but by the very low acidity of the parent compound, C_6H_6. The acidifying effect of the five CF_3 substituents in **3** is in fact the highest in the row **1**−**5**−**6**−**3**. This is remarkable because the anion **3a** is the least planar of the anions in the row **1a**−**5a**−**6a**−**3a**.

At the same time, the measured and in this work calculated ΔG_{acid} value of compound **3** is in a very good agreement with the results of gas-phase acidity measurements[27,33] of eight mono- to 1,2,4,5-tetrakis(trifluoromethyl) substituted benzenes for which also the additivity of the substituent effects (**3** included) is observed.

Experimental ΔG_{acid} vs Computational ΔG_{acid}. The used computational level has been tested and found in general suitable for prediction of acidity of different acids (see refs 43−45 and references therein) using empirical correlation (equation in Table 4) between experimental and calculated gas-phase acidity values. The correlation was based on the analysis of acidity data of 48 relatively small molecules.[43] The correlation has a non-zero intercept and non-unity slope, which counter-balances the tendency of this basis set to overestimate the calculated acidity (i.e., the stabilization of the anion) of some classes of compounds (sulfonic and carboxylic acids, HNO_3, HNO_2, HCl, alcohols, cyanoalkanes, etc.) in the stronger acidity region and underestimate the acidity of the weakest acids (≤340−300 kcal•mol^{-1}). The unsubstituted benzene, toluene and aniline did not deviate from the ideal behavior. At the same time, neither phenol nor its derivatives were included in the analysis. Also, none of the title compounds of this paper were included in the analysis. The respective calculations done in this work show that in this case the DFT B3LYP 6-311+G** approach overestimates the predicted acidity of phenols. Indeed the analysis using the representative dataset for 14 phenols (Table 4 and Tables S3−S5 in Supporting Information) covering the experimental ΔG_{acid} range from 342 to 291 kcal•mol^{-1} leads to the scaling equation b_1 (all equations in this section are presented in Table 4). Within the error limits, the measured in this work ΔG_{acid} value of **1** fits this equation (scaled value 297.6 kcal•mol^{-1}, measured value 298.7 kcal•mol^{-1}). If **1** is included in the correlation then only slightly different equation B is obtained and the scaled value will be 297.6 kcal•mol^{-1}, which supports the reliability of the measured ΔG_{acid} value for **1**. Similar scaling equations hold for 7 alcohols and H_2O (C, details in Supporting Information) and for a combined series of 29 data points of phenols alcohols, sulfonic acids and carboxylic acids (D). The scaled value for **1** from eq D is 297.1 kcal•mol^{-1}, which only slightly deviates from that of eq A.

On the contrary for the series of gas-phase acidities of substituted toluenes and benzenes the experimental and calculated (on the basis of the DFT B3LYP 6-311+G** approach) ΔG_{acid} values are indistinguishable within the limits of experimental uncertainties whereas the slope and intercept of the scaling relationship are close to unity and zero, respectively, within their uncertainty limits (eqs E and F). The predicted scaled ΔG_{acid} value for **3** from eq E is 332.8 kcal•mol^{-1}. If **3** is included in the correlation then eq E changes into e_1. From the latter eq the value for **3** is 330.9 kcal•mol^{-1}, which is also close to the measured value (331.1 kcal•mol^{-1}). The scaled value for **6** from eq F is 319.0 kcal•mol^{-1} and from eq f_1 319.2 kcal•mol^{-1} (experimental value is 318.9 kcal•mol^{-1}).

Acidity of 1 and 7 in Condensed Phase. Contrary to the gas phase, the acidity of **1** in all condensed media (no comparison is possible for **5**, **6** and **3** due to lack of data) considered is either close (AN 107%, DMSO 91%) to that predicted from fractional additivity or even surpasses it (H_2O 133%). Surely, all the above-discussed effects are also in operation in condensed phase and the (apparent) additivity has to be caused by solvation. The higher than expected solution acidity can be due to either additional stabilization of the anion or the absence of some factor stabilizing the neutral (in both cases with respect to the respective monosubstituted compounds). It is difficult to see how **1a** can be efficiently stabilized by solvation: the charge is delocalized across the large anion and the phenoxide group is hidden between the bulky CF_3 groups. Contrary to that the neutral **1** has extremely polarized

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O−H bond and is in principle a powerful hydrogen bond (HB) donor. This HB donating ability, however, is almost lost due to two *ortho*-CF_3 groups. This leaves the neutral poorly solvated compared to the singly substituted phenols. We thus suggest that the higher-than-expected solution acidity of **1** is not due to an extra stabilization effect of **1a** but is caused by the lack of possibility of stabilizing the neutral by HB. This hypothesis is partially supported by the observation that the non-additivity is especially pronounced in H_2O, which is the strongest HB acceptor of the three solvents.

The acidity of **7** is lower than would be expected based on the acidity data of different substituted phenylmalononitriles (lack of data does not allow calculation of additivity). The lower than expected acidity is easily rationalized considering that the aromatic ring is only slightly distorted in the neutral and is very strongly distorted in the anion. The reasons leading to lowered acidity are destabilization of the anion via reduced aromaticity of the ring and less-than-optimal resonance delocalization of the negative charge.

In conclusions it is possible to say that five trifluoromethyl groups in a phenyl ring lead to a considerable increase of acidity compared to unsubstituted derivatives. Calculations show that their influence is practically the same as that of three nitro groups but definitely weaker than that of five cyano or nitro groups.

4. Experimental Section

4.1. Synthesis. All manipulations concerning trifluoromethylation were performed using standard Schlenk techniques in an atmosphere of dry nitrogen. All glassware was previously dried at 130−150 °C and cooled under nitrogen. All solvents were dried by standard procedures and distilled. Spray-dried KF was dried at 250 °C for 12 h, CuBr was dried at 60 °C for 5 h. ^1H, ^{13}C and ^{19}F NMR spectra were recorded using different spectrometers (operating at the frequencies (in MHz) of 200.1, 50.3, 188.3 or 360.1, 90.5 or 400.1, 100.6). IR spectra were recorded using an FT-IR spectrometer with an ATR accessory (resolution: 4 cm^{-1}, number of scans: 128). ^{19}F NMR spectra were referenced against C_6F_6 (−162.59 ppm)[46] or $C_6H_5CF_3$ (−63.56 ppm). Melting points were determined with capillary melting point apparatus and are uncorrected.

Preparation of the Periodinated Starting Compounds. Pentaiodotoluene was obtained via permercurated toluene triiodide ions following the published method.[47] Hexaiodobenzene, pentaiodochlorobenzene, and 2,3,5-I_3-4-CF_3-C_6HCl were synthesized using the iodination procedure with iodine, and periodic acid in concentrated sulfuric acid.[48] Detailed synthesis of periodinated starting compounds is described in Supporting Information

General Procedure for Pregeneration of CF_3Cu and Pertrifluoromethylation of C_6I_6, Synthesis of 1, 2 and 3. For replacing all iodine atoms in 5 mmol of C_6I_6, 45 mmol (6.46 g; 1.5 equiv for replacing one iodine atom) of CuBr was mixed with of dry DMF (30 mL). Then at −5 to 0 °C, CF_3SiMe_3 (37.5 mmol, 5.33 g; 1.25 equiv) was added and afterward KF (37.5 mmol, 2.18 g; 1.25 equiv) was added gradually by controlling that the temperature of the reaction mixture did not exceed over 0 °C. After that dry DMI (6 mL) was added to stabilize of formed CF_3Cu. The mixture was stirred at 0 °C for approximately 1.5 h and the ^{19}F NMR spectrum (spectrum S4 in Supporting Information) was recorded to confirm the presence of activated CF_3Cu. If there was too much unreacted CF_3SiMe_3 left, then the mixture was stirred for longer time (up to 3 h). At 0 °C C_6I_6 (5 mmol, 4.2 g) and extra DMI (30 mL) were added, the solution was stirred for 24 h while the temperature was allowed to slowly rise to the room temperature. Again, a ^{19}F NMR spectrum was recorded to check disappearance of active CF_3Cu (−28.8 ppm and −32.4 ppm). Before workup, known amount of ^{19}F NMR reference compound was added to the reaction mixture and the ^{19}F NMR yield of **1a·K**$^+$, **2** and **3** vs internal CF_3Ph was calculated to be 85−90%.

It is important to note that the formation of **1a·K**$^+$, **2** and **3** depends on the quality of CuBr (it should be ideally colorless or as pale green as possible) and the content of water in solutions. When CuBr was dark green then the ratio of **1a·K**$^+$, **2** and **3** was 1 (**1a·K**$^+$):3 (**2**):2.5 (**3**). The content of **1a·K**$^+$ was found to be from 16 to 35% from the sum of all compounds depending on the reaction conditions.

Then, solvents (DMF/DMI) and volatile **2** and **3** were removed in vacuo and were trapped for further workup (see below). The dry pale greenish residue that remained in the bulb was extracted 4 times with diethyl ether (checked with ^{19}F NMR) to get **1a·K**$^+$. The solution of **1a·K**$^+$ in ether extract was dried over $MgSO_4$ and filtered through a thin (5-10 mm) layer of silica to remove traces of copper salts. Evaporation of ether followed by sublimation of the residue in static vacuum (15 mbar, 70−90 °C) from concd H_2SO_4 (2 mL) afforded **1**.

The mixture of DMF/DMI with **2** and **3** was steam-distilled. The compounds obtained from the cold receiver were extracted with diethyl ether. The ether layer was separated, dried over $MgSO_4$ and concentrated at −20 °C (to prevent the volatilization of **2** and **3**) to approximately one-third of the initial volume. From the obtained cold solution, **2** was filtered off as a white solid. The solution was concentrated completely at −20 °C and the dry residue was sublimed twice and pure compound collected. For further purification, **2** was recrystallized from diethyl ether and **3** was recrystallized from pentane. Summarized yield of all three compounds **1**, **2** and **3** is up to 79%.

Pentakis(trifluoromethyl)phenol (1). Synthesis from C_6I_6 is described above. Colorless sweet-scented crystals. Yield from C_6I_6 approximately 20%. The yield somewhat depends on the quality of CuBr and the moisture content of solvents. Mp 88−90 °C. ^1H NMR (200.1 MHz, $CDCl_3$) δ: 7.85 (s, OH, 1H); ^{19}F NMR (188.3 MHz, CD_3CN) δ: −49.36 (sept, $^5J_{F-F} = 17.2$ Hz, *p*-CF_3, 3F), −51.53 (qq, $^5J_{F-F} = 17.2$, $^5J_{F-F} = 17.2$ Hz, *m*-CF_3, 6F), −55.80 (q, $^5J_{F-F} = 17.2$ Hz, *o*-CF_3, 6F); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 157.5 (s, *i*-C_{Ar}), 136.8 (qm, $^2J_{C-F} = 37.8$, *m*- or *p*-C_{Ar}),136.8 (qm, $^2J_{C-F} = 33.1$ Hz, *m* or *p*-C_{Ar}),123.6 (qm, $^2J_{C-F} = 50$ Hz, *o*-C_{Ar}), 122.4 (q, $^1J_{C-F} = 276.7$ Hz, *m*-CF_3), 121.7 (q, $^1J_{C-F} = 278.2$ Hz, *o*-CF_3), 121.4 (q, $^1J_{C-F} = 276.7$ Hz, *p*-CF_3); EIMS (% relative intensity, ion) *m/z*: 434 (60%, M^+), 415 (60%, $M^+ - F$), 395 (40%, $M^+ - 2F$), 386 (100%, $M^+ - CF_2$); HRMS-EI *m/z*: M^+ calcd for $C_{11}HF_{15}O$, 433.97820; found, 433.97820.

Hexakis(trifluoromethyl)benzene (2). Synthesis from C_6I_6 is described above. White solid. Yield from C_6I_6 approximately 45%. The yield somewhat depends on the quality of CuBr and the moisture content of solvents. Mp 220 °C in sealed capillary (lit.[11] 209 °C); ^{19}F NMR (188.3 MHz, $CDCl_3$) δ: −52.60 (s, CF_3, 18F); EIMS (% relative intensity, ion) *m/z*: 486 (25%, M^+); 467 (96%, $M^+ - F$), 417 (100%, $M^+ - CF_3$), 398 (5%, $M^+ - CF_3 - F$), 379 (6%, $M^+ - CF_3 - 2F$), 367 (24%, $M^+ - CF_3 - CF_2$), 348 (14%, $M^+ - 2CF_3$), 329 (9%, $M^+ - 2CF_3 - F$), 298 (5%, $M^+ - 2CF_3 - CF_2$), 279 (9%, $M^+ - 3CF_3$).

Pentakis(trifluoromethyl)benzene (3). Synthesis from C_6I_6 is described above. White solid. Yield from C_6I_6 approximately 14%. The yield somewhat depends on the quality of CuBr and the moisture content of solvents. Mp 146−148 °C; ^1H NMR (400.1 MHz, $CDCl_3$) δ: 8.51 (s, ArH, 1H); ^{19}F NMR (188.3 MHz, $CDCl_3$) δ: −52.35 (sept, $^5J_{F-F} = 16.3$ Hz, *p*-CF_3, 3F), −54.80 (qq, $^5J_{F-F} = 16.3$, $^5J_{F-F} = 16.3$ Hz, *m*-CF_3, 6F), - 59.26 (q, $^5J_{F-F} = 16.3$ Hz,

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o-CF_3, 6F); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 134.5 (qm, $^{2}J_{C-F}$ = 35.6 Hz, *o*- or *m*-C_{Ar}), 134.4 (qm, $^{2}J_{C-F}$ = 37.1 Hz, *o*- or *m*-C_{Ar}), 134.0 (m, *p*-C_{Ar}), 131.1 (sept, $^{3}J_{C-F}$ = 6.4 Hz, *i*-C_{Ar}), 121.3 (q, $^{1}J_{C-F}$ = 276.2 Hz, *o*-CF_3), 121.2 (q, $^{1}J_{C-F}$ = 278.0 Hz, *p*-CF_3), 120.9 (q, $^{1}J_{C-F}$ = 277.6 Hz, *m*-CF_3); EIMS (% relative intensity, ion) *m/z*: 418 (24%, M^+), 399 (75%, $M^+ - F$), 394 (100%, $M^+ - CF_3$), 330 (15%, $M^+ - CF_3 - F$), 299 (8%, $M^+ - CF_3 - CF_2$), 280 (12%, $M^+ - 2CF_3$).

Pentakis(trifluoromethyl)chlorobenzene (4). Method A. For pregeneration of CF_3Cu, CuBr (0.16 mol, 23.5 g), CF_3SiMe_3 (0.14 mol, 20 mL), KF (0.14 mol, 8.0 g), and DMF (100 mL) were mixed as described in general procedure. For stabilization of CF_3Cu NMP (20 mL) was applied. To the pregenerated CF_3Cu species were consequently added pentaiodochlorobenzene (0.021 mol, 15.9 g) (for synthesis see Supporting Information) and NMP (80 mL). The mixture was stirred at 0−20 °C for 24 h. The solvents with volatile **4** were distilled and the distillate was diluted with water (120 mL) and extracted with pentane (3 × 200 mL). The pentane phase was washed with water (3 × 100 mL), and dried over $MgSO_4$. After removal of pentane in vacuo at room temperature, the raw product was recrystallized from pentane or methanol to give **4**. Yield 81% (17.5 mmol, 7.9 g), mp 146−148 °C.

Method B. Compound **1** (0.68 mmol, 0.30 g), $POCl_3$ (1.5 mL), PCl_5 (ca 50 mg) and dry pyridine (0.3 mL) were mixed under nitrogen. After stirring for 2 h at 80 °C, volatiles were removed in vacuo at room temperature and the residue was extracted several times with pentane (25 mL). Pentane was removed in vacuo to get **4** as white solid. Yield 84% (0.57 mmol, 0.26 g), mp 131−133 °C. ^{19}F NMR (188.3 MHz, $CDCl_3$) δ: −51.64 (sept, $^{5}J_{F-F}$ = 17.2 Hz, *p*-CF_3, 3F), −52.93 (qq, $^{5}J_{F-F}$ = 17.2, $^{5}J_{F-F}$ = 17.2 Hz, *m*-CF_3, 6F), −57.34 (q, $^{5}J_{F-F}$ = 17.2 Hz, *o*-CF_3, 6F); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 140.2 (s, *i*-C_{Ar}), 135.7 (qm, $^{2}J_{C-F}$ = 82 Hz, *m*-C_{Ar}), 135.0 (qm, $^{2}J_{C-F}$ = 52 Hz, *o*-C_{Ar}), 131.5 (qm, $^{2}J_{C-F}$ = 82 Hz, *p*-C_{Ar}), 121.4 (q, $^{1}J_{C-F}$ = 306 Hz, *p*-CF_3), 121.1 (q, $^{1}J_{C-F}$ = 272 Hz, *o*-CF_3), 120.7 (q, $^{1}J_{CF}$ = 263 Hz, *m*-CF_3); EIMS *m/z*: 452 (57%, M^+), 433 (54%, $M^+ - F$), 417 (12%, $M^+ - Cl$), 398 (13%, $M^+ - F - Cl$), 383 (100%, $M^+ - CF_3$), 367 (11%, $M^+ - Cl - CF_2$), 349 (20%, $M^+ - Cl - CF_3$), 333 (14%, $M^+ - CF_3 - CF_2$), 314 (9%, $M^+ - 2CF_3$); HRMS-EI *m/z*: M^+ calcd for $C_{11}F_{15}Cl$, 451.94430; found, 451.94430.

Hydrolysis of 4. Compound **4** (0.3 g, 0.66 mmol) was dissolved in dimethoxyethane (DME, 7.5 mL) and water (ca 1.5 mL) was added under stirring. At 0 °C NaOH solution (0.66 mmol, 0.8 mL; containing 0.2 g NaOH in 6 mL 1:1 mixture of DME/water) was added. The solution became yellowish and ^{19}F NMR spectrum showed besides the starting **4** and **1a·Na**$^+$ a lot of minor peaks. The mixture was stirred at room temperature for 2 days, and then the same NaOH solution (0.8 mL) was added. The solvents were removed in vacuo and the dry residue (0.3 g) was extracted twice with petrol ether to remove the unreacted **4**. The washed residue was dissolved in diethyl ether and transferred to the sublimator. Ether was removed in vacuo and the residue was sublimed in static vacuum from concd H_2SO_4 (1 mL) to obtain **1**. Yield: 38% (0.23 mmol, 0.10 g). The data of product corresponds to the data of **1** obtained from trifluoromethylation of C_6I_6 described in general procedure.

Pentakis(trifluoromethyl)aniline (5). A solution of **4** (1.80 mmol, 0.78 g) in 20 mL of dichloromethane was placed in a pressure tube with Teflon stopcock and cooled with liquid nitrogen and filled on a vacuum line with ca. 5 mL of ammonia. The resulting solution was kept at −30 to −40 °C for 24 h and then stirred at room temperature for 40 h. The ^{19}F NMR spectra of the solution indicated presence of **5**, a small amount of **4** and some impurities. The solution was filtered to remove ammonium chloride (NH_4Cl). The solvent was distilled off in vacuum from a cooled flask (−20 °C, to prevent sublimation of **5**) to afford the target product (0.46 mmol, 0.20 g) as a yellow solid. Yield 28%, mp 93−95 °C (lit.[12] 115 °C). ^{1}H NMR (200.1 MHz, $CDCl_3$) δ: 5.61 (br s, NH_2, 2H); ^{19}F NMR (188.3 MHz, $CDCl_3$) δ: −50.98 (sept, $^{5}J_{F-F}$ = 17.2 Hz, *p*-CF_3, 3F), −53.25 (qq, $^{5}J_{F-F}$ = 17.2, $^{5}J_{F-F}$ = 17.2 Hz, *m*-CF_3, 6F), −58.89 (q, $^{5}J_{F-F}$ = 17.2 Hz, *o*-CF_3, 6F); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 148.3 (s, *i*-C_{Ar}), 136.8 (qm, $^{2}J_{C-F}$ = 32 Hz, *m*-C_{Ar}), 122.2 (q, $^{1}J_{C-F}$ = 168 Hz, *m*-CF_3), 121.3 (q, $^{1}J_{C-F}$ = 262.7 Hz, *p*-CF_3), 119.6 (qm, $^{2}J_{C-F}$ = 34 Hz, *p*- or *o*-C_{Ar}), 118.3 (qm, $^{2}J_{C-F}$ = 39 Hz, *p*- or *o*-C_{Ar}), 118.1 (q, $^{1}J_{C-F}$ = 272 Hz, *o*-CF_3); EIMS *m/z* (% relative intensity, ion): 433 (100%, M^+), 414 (95%, $M^+ - F$), 394 (20%, $M^+ - 2F$), 324 (85%, $M^+ - CF3$); HRMS-EI *m/z*: M^+ calcd for $C_{11}H_2NF_{15}$, 432.99417; found, 432.99501.

It is known[49] that reaction of $(CF_3)_3C_6$ with liquid ammonia leads to conversion of CF_3 group into CN groups. Apparently, this transformation accounts for reduced yield of **5**. The compound **5** is easily separated from less volatile cyano-derivatives by sublimation.

Pentakis(trifluoromethyl)toluene (6). For pregeneration of CF_3Cu according to general procedure, CuBr (93.4 mmol,13.4 g), CF_3SiMe_3 (70.3 mmol, 10 mL), KF (70.6 mmol, 4.1 g), DMF (45 mL) and NMP (6 mL) were mixed. Pentaiodotoluene (11.8 mmol, 8.5 g) and NMP (40 mL) were added to the solution of pregenerated CF_3Cu, and the reaction mixture was stirred at 65−70 °C for 14 h. After cooling to 0 °C the colorless crystals of the product were filtered and washed with methanol to remove Cu-salts. Yield 41% (4.9 mmol, 2.1 g), mp 166−167 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ: 2.74 (sept, $^{5}J_{H-F}$ = 3.3 Hz, CH_3, 3H); ^{19}F NMR (188.3 MHz, DMSO-d_6) δ: −52.35 (sept, $^{5}J_{F-F}$ = 17.6 Hz, *p*-CF_3, 3F), −53.51 (qq, $^{5}J_{F-F}$ = 17.6, $^{5}J_{F-F}$ = 17.6 Hz, *m*-CF_3, 6F), −55.46 (qq, $^{5}J_{F-F}$ = 17.6, $^{5}J_{H-F}$ = 3.3 Hz, *o*-CF_3, 6F); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 145.7 (m, *i*-C_{Ar}); 135.5 (qm, $^{2}J_{C-F}$ = 33.1 Hz, *o*- or *m*-C_{Ar}), 134.6 (qm, $^{2}J_{C-F}$ = 36.0 Hz, *o*- or *m*-C_{Ar}), 131.3 (qm, $^{2}J_{C-F}$ = 36.8 Hz, *p*-C_{Ar}), 122.0 (q, $^{1}J_{C-F}$ = 277.9 Hz, *o*- or *m*-CF_3), 121.6 (q, $^{1}J_{C-F}$ = 276.9 Hz, *p*-CF_3), 121.3 (q, $^{1}J_{C-F}$ = 277.7 Hz, *o*- or *m*-CF_3), 20.4 (hept, $^{4}J_{C-F}$ = 5.0 Hz, CH_3); EIMS *m/z* (% relative intensity, ion): 432 (31%, M^+), 413 (100%, $M^+ - F$), 363 (93%, $M^+ - CF_3$); HRMS-EI *m/z*: M^+ calcd for $C_{12}H_3F_{15}$, 431.99893; found, 432.00033.

Tetraethylammonium Dicyano[pentakis(trifluoromethyl)-phenyl]methanide (7a·Et$_4$N$^+$). A magnetically stirred solution of (1.5 mmol, 0.1 g) of malononitrile in of dry THF (1 mL) kept at −78 °C was consequently treated with NaH (2.5 mmol, 0.06 g) in dry THF (5 mL) and **4** (1.1 mmol, 0.5 g, dissolved in 1 mL of dry THF). The mixture turned yellow. After warming up to room temperature the mixture turned dark red. The solution was additionally stirred for additional 4 h. ^{19}F NMR spectra indicated the formation of the sodium salt **7a·Na**$^+$. The solution was filtrated to remove NaCl. From filtrate all the volatiles were removed in vacuo. The residue was dissolved in water and Et_4NCl (1.1 mmol, 0.18 g) was added to the solution. A dark oily substance formed, which turned solid after cooling the solution to 0 °C. Removing of water via filtration followed by recrystallization from EtOH/water mixture (1:7) afforeded the target product **7a·Et$_4$N$^+$**. Yield: 67% (0.65 mmol, 0.40 g), mp 90−93 °C, ^{1}H NMR (400.1 MHz, acetone-d_6) δ: 3.50 (q, $^{3}J_{H-H}$ = 7.3 Hz, CH_2, 8H), 1.40 (qt, $^{3}J_{H-H}$ = 7.3 Hz, $^{3}J_{H-14N}$ = 1.8 Hz, CH_3, 12H); ^{19}F NMR (188.3 MHz, CD_3CN) δ: −47.59 (sept, $^{5}J_{F-F}$ = 16.6 Hz, *p*-CF_3, 3F), −49.30 (q, $^{5}J_{F-F}$ = 16.6 Hz, *o*-CF_3, 6F), −51.89 (qq, $^{5}J_{F-F}$ = 16.6, $^{5}J_{F-F}$ = 16.6 Hz, *m*-CF_3, 6F); ^{13}C NMR (100.6 MHz, acetone-d_6) δ: 152.0 (m, *i*-C_{Ar}), 131.6 (qm, $^{2}J_{C-F}$ = 34.9 Hz, *m*-C_{Ar}), 125.0 (q, $^{1}J_{C-F}$ = 271.1 Hz, *p*-CF_3), 123.5 (q, $^{1}J_{C-F}$ = 275.9 Hz, *m*-CF_3), 122.9 (q, $^{1}J_{C-F}$ = 273.5 Hz, *o*-CF_3), 116.6 (s, CN), 107.3 (qm, $^{2}J_{C-F}$ = 36.7 Hz, *p*-C_{Ar}), 105.4 (qm, $^{2}J_{C-F}$ = 35.9 Hz, *o*-C_{Ar}), 69.6 (s, *C*(CN)$_2$), 53.1 (t, $^{1}J_{C-14N}$ = 3.0 Hz, CH_2), 7.7 (s, CH_3); HRMS-ESI *m/z*: M^- calcd for $C_{14}N_2F_{15}$, 480.98270; found, 480.98264; Et_4N^+ calcd for $C_8H_{20}N$, 130.15902; found, 130.15968.

Attempts to obtain the free acid **7** by sublimation of **7a·Et$_4$N$^+$** from concd H_2SO_4 were unsuccessful. GC-MS measurement of the

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[49] Yagupolskii, L. M.; Lukmanov, V. G.; Boiko, V. O.; Alekseeva, L. A. *Zh. Org. Khim.* **1977**, *11*, 2388−2391.

obtained crude product contained traces of **1**, **2**, **3**, and **4**. Compound **7** was not detected in the sublimed material.

Tetramethylammonium Pentakis(trifluoromethyl)phenoxide ($1a{\cdot}Me_4N^+$). To a solution of freshly sublimed **1** (0.39 mmol, 0.17 g) in methanol was added solution of tetramethylammonium hydroxide (0.16 mL, 0.25% solution in methanol) at −30 °C. The solution turned yellowish. The solvent was removed in vacuo and the solid was recrystallized from H_2O/EtOH mixture (2:1). X-ray quality crystals were grown by slow evaporation of MeOH. Yield 87% (0.34 mmol, 0.17 g), mp 235−237 °C. ^{1}H NMR (200.1 MHz, DMSO-d_6) δ: 3.10 (m, CH_3, 12H); ^{19}F NMR (188.3 MHz, DMSO-d_6) δ: −47.11 (sept, $^5J_{F-F}$ = 15.8 Hz, *p*-CF_3, 3F), −52.34 (qq, $^5J_{F-F}$ = 15.8, $^5J_{F-F}$ = 15.8 Hz, *m*-CF_3, 6F), −58.23 (q, $^5J_{F-F}$ = 15.8 Hz, *o*-CF_3, 6F); ESI-MS (MS/MS) *m*/*z* (relative intensity %, ion): 433 (25%, M^-), 405 (100%, M^- − CO).

Complex of Tetramethylammonium Pentakis(trifluoromethyl)phenoxide and Pentakis(trifluoromethyl)phenol $1a1{\cdot}Me_4N^+$. To a stirred and cooled till −30 °C solution of freshly sublimed **1** (0.23 mmol, 0.10 g) in MeOH (4 mL) was added a solution of tetramethylammonium hydroxide (0.093 mL, 0.25% in MeOH). The mixture was placed to refrigerator at 8 °C for 3 days. The precipitated crystalline product was collected and suitable for XRD structural determination single crystals were selected. Yield 61% (0.07 mmol, 0.07 g), mp 170−174 °C dec, ^{1}H NMR (200.1 MHz, DMSO-d_6) δ: 5.6−4.6 (bs, OH + H_2O), 3.09 (m, CH_3, 12H); ^{19}F NMR (188.3, DMSO-d_6) δ: −47.11 (sept, $^5J_{F-F}$ = 15.8 Hz, *p*-CF_3, 3F), −52.31 (qq, $^5J_{F-F}$ = 15.8, $^5J_{F-F}$ = 15.8 Hz, *m*-CF_3, 6F), −58.18 (q, $^5J_{F-F}$ = 15.8 Hz, *o*-CF_3, 6F).

4.2. Calculations. ΔG_{acid} of an acid HA is the Gibbs' free energy change on deprotonation of the acid according to the following equilibrium:

$$\mathrm{HA} \xrightleftharpoons{\Delta G_{acid}} \mathrm{A}^- + \mathrm{H}^+ \qquad (9)$$

The ΔG_{acid} values were calculated in the usual way[44] taking into account zero-point energies, finite temperature (298 K) correction and the pressure−volume work term. Density functional theory (DFT) calculations at B3LYP 6-311+G** level were used. The Gaussian 03 system of programs was used.[50] Full geometry optimizations were carried out for all acids and anions. Several different starting geometries were used in doubtful cases. In order to confirm that calculated structures correspond to true minima, frequency calculations were run in all cases and the absence of imaginary frequencies (N_{imag} = 0) was taken as the criterion of the stability of the species.

4.3. Gas-Phase Acidity Measurements. The FT-ICR spectrometric ΔG_{acid} measurements were carried out at Kyushu University using a pulsed FT ion cyclotron resonance mass-spectrometer with 3 T superconducting magnet. Major details of the experiments were the same as those described previously.[40,51] The directly measured quantities were the equilibrium constant (*K*) of the proton-transfer reaction:

$$\mathrm{A_iH} + \mathrm{A_0}^- \xrightleftharpoons{K} \mathrm{A_i}^- + \mathrm{A_0H} \qquad (10)$$

$$\delta\Delta G = -RT \ln K$$

where A_i refers to the investigated (A_iH) acid and A_0 refers to the reference compound (A_0H) with known gas-phase acidity (see Table S2 in Supporting Information). All experiments were performed at a cell temperature of 100 °C. The partial pressures of the compounds were in the 10^{-8}−10^{-7} Torr range and these were used as partial pressures of the neutrals in the *K* calculation. Ratios of the intensities of the ions in the mass spectrum were used as the estimates of the ratios of partial pressures of the ions. The pressure in the system was measured using the Bayard−Alpert gauge. The partial pressures used for calculations were corrected for the differences in the ionization cross-sections of the compounds (see ref 51 for details). The equilibrium constants were calculated according to the standard procedure.

The equilibrium measurements were carried out at different partial pressures of the neutrals. Good agreement was obtained between the $\Delta G_{acid}(A_iH)$ values obtained with different references (difference mostly not more than 0.5 kcal·mol^{-1}). At given partial pressures of the neutrals the equilibrium measurements were carried out as series of pulse sequences with different reaction times. Each sequence consisted of generating ions (by an electron impact pulse from a few to 30 ms), giving them time to react (reaction time) and detecting the ions (see refs 40 and 52 for more details). From the ion intensity ratios at different reaction times (and at constant partial pressures of the neutrals) time plots were constructed. From the time plots it was found that between 1 and 20 s of reaction time was necessary to reach the equilibrium (depending on the reacting acids and their partial pressures). To ensure that the equilibrium has been reached significantly longer reaction times than required to reach the plateau on the time plot were used in all cases.

4.4. Determination of pK_a Values in AN. The spectrophotometric titration method used in this work for determination of pK_a values in AN is mostly the same as described earlier.[30,53] The method is based on UV−vis spectrophotometric titration of a mixture of two acids with a nonabsorbing base to obtain neutral and anionic forms of the solution of mixture. Both acids were also titrated separately to obtain spectra of neutral and ionized forms. From the titration data the relative acidity of the two compounds, the difference of their pK_a values (ΔpK_a), is obtained.

The protonation-deprotonation process was reversible with all acids. AN has very low solvating ability for anions. This is the main reason why homoconjugation[54] of some anions is extensive in AN. In particular, the anions of the phenols with CF_3 substituents (except **1**) all undergo rather extensive homoconjugation in AN solution, which was also taken into account when calculating the pK_a values. In order to avoid further complicating the system by introducing besides homoconjugation also heteroconjugation the reference acids for homoconjugating acids were chosen so that most of them were CH and NH acids that do not undergo homo- or heteroconjugation processes.[30] As there are no homoconjugation constants for the studied phenols available in the literature, the homoconjugation constants used in the ΔpK_a calculations of this work were estimated as log K_{aha} = 5 for all three singly substituted trifluoromethylphenols, 3,5-bis(trifluoromethyl)phenol and phenol.

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[50] *Gaussian 03*, Revision C.02; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Wallingford, CT, 2004.

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[53] Yagupolskii, L. M.; Petrik, V. N.; Kondratenko, N. V.; Sooväli, L.; Kaljurand, I.; Leito, I.; Koppel, I. A. *J. Chem. Soc., Perkin Trans. II* **2002**, *11*, 1950−1955.

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From the spectra of all these compounds it was estimated that these compounds indeed homoconjugated to a similar extent.

Two calculation methods were used: (a) a method based on moles (not using the spectra of the acid undergoing homoconjugation) as described in ref 30, and (b) a method based on spectra, which is described in Supporting Information.

It was observed that for the method based on moles the small variations in homoconjugation constant values do not have significant influence on the calculated ΔpK_a values. For the calculation method based on spectra, the variations in homoconjugation constant values have in some cases strong influence on the calculated ΔpK_a values. To find the best estimate of the homoconjugation constant and ΔpK_a value, several reference acids were used for each phenol and both calculation methods were used for all measurements. The agreement between the pK_a values obtained from different measurements ranged from satisfactory (for 3-CF_3-phenol) to good (for all other phenols except **1**) and excellent (for **1**).

4.5. Determination of pK_a Values in DMSO and in Water. Determination of pK_a values in DMSO was carried out using the same method as described in ref 26. pK_a determination in water was carried out using a combined method of spectrophotometry and potentiometry as described in ref 55 and 26. The spectra of 1 were not stable in time and were extrapolated to zero time.

4.6. Voltammetric Measurements with 1 and 1a. Voltammetric measurements were carried out for compounds **1** and **1a** in anhydrous AN using glassy carbon working electrode and saturated calomel reference electrode. The results indicate that the radical **1b** is relatively stable while the radical-anion is unstable. Details are given in Supporting Information.

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Supporting Information Available: Computational geometries of the species **1**, **1a**, **1b**, **3**, **3a**, **5**, **5a**, **6**, **6a**, **7** and **7a** and related compounds; calculations of additivities of ΔG_{acid} and pK_a values of trifluoromethylated compounds; detailed description of calculation of ΔpK_a values in AN; results of experimental relative measurements of ΔG_{acid} values and pK_a values; detailed results of cyclic voltammetry studies of **1** and **1a**; ^{19}F NMR spectrum of pregenerated CF_3Cu and spectrum after the oxidation reaction; ^{19}F NMR spectrum of reaction mixture of compounds **1a·K**$^+$, **2** and **3**; ^1H, ^{13}C, ^{19}F, $^{13}C-^1H$ HMBC, $^{13}C-^1H$ HSQC NMR spectra of synthesized compounds; IR spectra of **1**, **1a·Me$_4$N**$^+$, and **1a1·Me$_4$N**$^+$; table of the results of the ΔG_{acid} calculations of some pentakis(trifluoromethyl) substituted compounds and related compounds; X-ray diffraction crystallographic measurements and refinement data; table of bond lengths, angles and dihedral angles, etc. of calculated and measured structures; pictures of molecular structures of pentakis(trifluoromethyl)phenyl derivatives; description of synthesis of periodinated compounds and 2,3,4,6-tetrakis-(trifluoromethyl)phenyl derivatives; UV−vis spectra of deprotonation-protonation of **3**; correlations of experimental and calculated ΔG_{acid} values; calculations of ΔG and ΔH values of isodesmic reactions; cif files of **1a1·Me$_4$N**$^+$, **1a·Me$_4$N**$^+$, and **7a·Et$_4$N**$^+$. This material is available free of charge via the Internet at http://pubs.acs.org.

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