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Polytrifluoromethylation versus Polyfluorination of the Isomers of Kekulé Benzene and Phenol: A Theoretical Study

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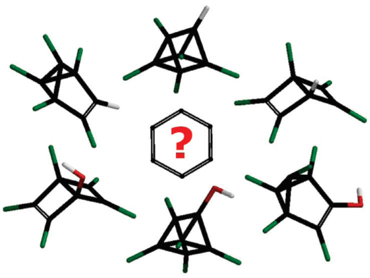

The study of the polyfluorination and polytrifluoromethylation effects on electronic structure and intrinsic acidities has been performed using DFT B3LYP and NBO calculations for the valence isomers of benzene and phenol, i.e., the structures of prismane, benzvalene, Kekulé, and Dewar systems. Also the isodesmic reaction analysis approach to estimate the effects of the substituents on the acidity of the compounds has been used. Although in some systems the additivity of fluorine substituents was more than 100%, the acidifying effects of the fluorine substituents were comparable to that of the CF_3 in only one case. Isodesmic reaction analysis of substituent effects shows that steric effects of poly-CF_3 substitution in the alicyclic cage compounds are significantly smaller. The relative thermodynamic stabilities of the valence isomers of Kekulé benzene were significantly lower than that of the aromatic cycle. The introduction of fluorine substituents often destabilized the compounds even further. Out of the fluorinated hydroxy derivatives of prismane, Dewar benzene, and benzvalene, not all are predicted to be stable enough to be able to undergo a reversible protonation−deprotonation process. In the case of several hydroxy derivatives deprotonation is accompanied by the rupture of a C(α)−C(β) bond and in some cases by the rearrangement to the corresponding phenolate anion. The isomerization of benzene derivatives resulted in more cases where the acidities increased compared with the respective phenol derivatives. The only hydroxy compound with significantly higher acidity than the respective phenol was pentafluorinated 2-OH-Dewar benzene, which was expected to rival the gas-phase acidity of perfluoro-1-adamantanol, currently the most acidic experimentally measured perfluorinated alcohol.

Introduction

Polyfluorinated compounds have been attracting the attention of chemists for a long time. Polyfluorination generally increases the thermal stability and often decreases the reactivity of the molecules. In addition they might exhibit unique solubility, surface-wetting, etc., properties. These factors have led to whole new generations of materials and chemicals, such as fluoropolymers,[1] fluorinated catalysts,[2] self-assembling structures,[3] weakly coordinating anions,[4]

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and ionic liquids.[5] Polyfluorination of a (potentially) acidic molecule can dramatically increase its acidity, and thus the polyfluorination or introduction of fluorinated substituents is an established approach to design acidic and superacidic molecules.[6-8] Although the fluorine atom is considered the most electronegative, the complicated interplay of different properties[9] of fluorine (i.e., resonance/hyperconjugation,[9-13] electronegativity, polarizability, field(inductive), p$-\pi$ repulsion effect[14,15]) significantly depends on the position of the substitution center relative to the reaction site, and the extent of a net delocalization of the anion's lone pair determines the acid$-$base properties of the molecule. In the case of fluorinated organic molecules the acidity increase is mainly due to the stabilization of the carbanion's lone pair by the β-C$-$F bond's ability to delocalize the electron density of the carbanion lone pair to its energetically low-lying σ^*-orbital.[11,12b,13] The effects that are known to destabilize the conjugate bases[15,16] are p$-$p lone pair repulsion between the anionic center and fluorine atom, as well as the back-donating resonance effect of the fluorine electron pair and p$-\pi$ repulsion with geminal double-bond orbitals.

An interesting group of polyfluorinated molecules are the polytrifluoromethylated molecules. Although the CF_3 group has a field-inductive effect of similar[9] strength to F (σ_F of CF_3 and F are both 0.44), the hyperconjugation effect[10] lets it act as a π-acceptor group,[12,13] contrary to F, which acts as a resonance donor (σ_R 0.07 and -0.33, respectively). Also, CF_3 is more polarizable than F (σ_α -0.25 and 0.13, respectively) and has a tendency to stabilize β-bonds.[9-13] The introduction of multiple CF_3 substituents invokes a considerable steric strain. Compared to, for example, a CH_3 substituent, they have van der Waals volumes $CH_3 = 16.8$ Å^3 and $CF_3 = 42.6$ Å^3.[17] In the course of our recent work[18a] on the synthesis and properties of pentakis-CF_3-phenyl derivatives we observed (both experimentally and computationally) that the benzene rings of all $C_6(CF_3)_5$ compounds were significantly distorted from planarity. From these observations it is expected that $-$F and $-CF_3$ behave quite differently also in the aliphatic cage structures, and it is not easy to predict their effect on either acidity or structural stability. Nevertheless, all studied compounds were perfectly stable molecules: $C_6(CF_3)_5H$, $C_6(CF_3)_6$ and $C_6(CF_3)_5OH$ can be sublimed from sulfuric acid.

If one compares the acidities of, for example, phenols substituted with different patterns by CF_3 groups or F atoms, then in all cases the respective CF_3-substituted phenols are more acidic, both in the gas phase and in solution.[9b,c,18a] Thus, if speaking of acids, then polytrifluoromethylation is expected to lead to a more significant stabilization of the conjugate anion and acidity increase than fluorination. When π-systems are involved and the resonance effect is of importance, this is really the case. The situation with aliphatic cage-type acids is less straightforward.[6,19] In the systems with considerable strain in the ring elements the effect of various orbital overlappings can be operational in releasing the steric strain. Nevertheless, the possibility to prepare stable valence isomers of $C_6(CF_3)_6$ has been known[17,20,21] for a long time. It is known that polyfluoro and poly-CF_3 substitution can improve the kinetic and thermodynamic stability of these compounds via steric shielding and withdrawal of electron density.[17,18a] There are many studies about polyfluorinated cage compounds and aromatics, but the effect of polytrifluoromethylation on the stability of aliphatic cage systems, especially in comparison to polyfluorination, has not been thoroughly investigated. Even less is known about the respective anions. In the cage-type structures the efficiency of negative hyperconjugative stabilization is lower because of the less favorable orbital orientation.[6] In turn, the number of electron-withdrawing substituents bound to the reaction site is often higher. This can affect the stability in many ways.

Although Kekulé benzene is by far the most stable and common isomer corresponding to the formula C_6H_6, it is not the only one. There are three other nonaromatic isomers that have been experimentally prepared: benzvalene,[20] prismane,[21] and Dewar benzene[22] (Scheme 1). Choosing the isomers of benzene as the cage compounds is interesting for two reasons: (a) these are quite unstable molecules and it is interesting to see how polysubstitution affects their stability; (b) their identical elemental composition of the respective benzene derivatives allows direct comparisons of stability and acidity. Importantly, due to the geometry of **1**$-$**3**, the bulky substituents can in these molecules assume orientations significantly less interfering with each other than in the benzene ring. This led us to the idea to investigate the stability and acidity of polyfluorinated and polytrifluoromethylated

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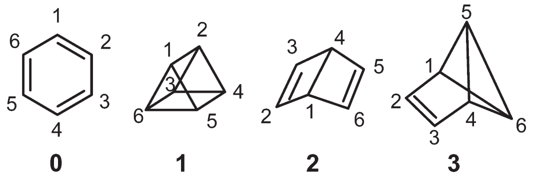
SCHEME 1. Structures of Benzene (0), Prismane (1), Dewar Benzene (2), and Benzvalene (3)



non-benzenoid isomers of C_6H_5H and C_6H_5OH and some related molecules.

The goals of this work were the following: (1) to investigate the thermodynamic stability and intrinsic acidity of the polyfluorinated and polytrifluoromethylated isomers of C_6H_5OH and C_6H_5H and the dependence of their acidity on the structure and (2) to elucidate and compare the acidifying effect and its mode of action in the case of the polytrifluoromethylation with that of the polyfluorination.

Methods

Computational Method. The gas-phase acidity ($\Delta G_{\mathrm{acid}} \equiv \mathrm{GA}$) of an acid HA and proton affinity [$\Delta H_{\mathrm{acid}} \equiv \Delta H \equiv \mathrm{PA}(\mathrm{A}^-)$] of the anionic base A^- refer to the following equilibrium:

$$\mathrm{HA} \overset{\Delta G_{\mathrm{acid}}}{\rightleftharpoons} \mathrm{A}^- + \mathrm{H}^+ \tag{1}$$

The ΔG_{acid} values were calculated in the usual way[8] taking into account zero-point energies, finite temperature (298 K) correction, and the pressure–volume work term. Density functional theory (DFT) calculations at the B3LYP 6-311+G** level were used. The Gaussian 09 system of programs was used.[23] Full geometry optimizations as well as the NBO analysis[23b] 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 the true minima, frequency calculations were run in all cases and the absence of imaginary frequencies ($N_{\mathrm{imag}} = 0$) was taken as the criterion of the stability of the species.

Isodesmic Reactions Analysis Method. [9c,18] The acidity of a pentafluoro (Y = F) or pentakis(trifluoromethyl) ($Y = CF_3$) substituted hydrocarbons **0** to **3** (X = H) or their hydroxy (X = OH) derivatives C_6Y_5X, denoted as $\Delta G_{\mathrm{acid}}(C_6Y_5X)$, can be calculated from the acidity of the unsubstituted compound, ΔG_{acid}-(C_6H_5X), and the acidifying/deacidifying effects of different interactions as follows:

$$\Delta G_{\mathrm{acid}}(C_6Y_5X) = \Delta G_{\mathrm{acid}}(C_6H_5X) + \Delta\Delta G_{\mathrm{GAIE}} + \Delta\Delta G_{\mathrm{S}} + \Delta\Delta G_{\mathrm{RCC}} + \Delta\Delta G_{\mathrm{RCX}} \tag{2}$$

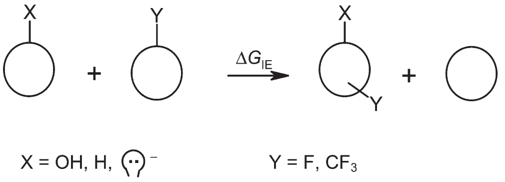
The $\Delta\Delta G$ values in eq 2 are defined as follows:

$$\Delta\Delta G = \Delta G(\mathrm{anion}) - \Delta G(\mathrm{neutral}) \tag{3}$$

The ΔG values are defined as follows:[18a]

- ΔG_{GAIE} (defined via eq 5) is the estimate of the gross additive interaction free energy between the reaction center and the substituents Y in the idealized pentasubstituted molecule where there are no steric or other interactions between the substituents themselves and the interactions between the substituents and the reaction center are just as strong as in the respective monosubstituted molecules. Possible steric interactions present in the monosubstituted molecules are also included in ΔG_{GAIE}.
- ΔG_{S} is the free energy contribution due to the saturation of the substituent effects of the F or CF_3 substituents interacting with the reaction center.
- ΔG_{RCC} is the free energy contribution due to the steric repulsion between the Y groups.
- ΔG_{RCX} is the free energy contribution due to the additional steric repulsion between the Y groups adjacent to the group X (or its deprotonated form). This additional contribution has two reasons: (1) in the pentakis-substituted derivative there can be simultaneously several CF_3 groups in the vicinity of X and (2) there may be other Y groups that reduce the flexibility of the Y groups in the vicinity of X.

The ΔG_{GAIE} contributions can be estimated from the following series of reactions (in this and the following equations the circle denotes one of the C_6H_6 isomers, **0** to **3**):

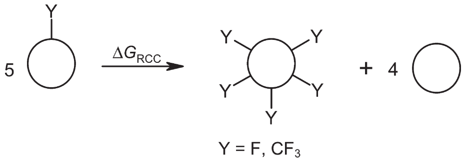


(4)

In order to obtain the ΔG_{GAIE}, the energy effects of this reaction with different substitution pattern are summarized taking into account the symmetry of the molecule. As an example, for 1-OH-Y_5-**1**,

$$\Delta G_{\mathrm{GAIE}} = \Delta G_{\mathrm{IE}}(1,2) + 2\Delta G_{\mathrm{IE}}(1,3) + 2\Delta G_{\mathrm{IE}}(1,5) \tag{5}$$

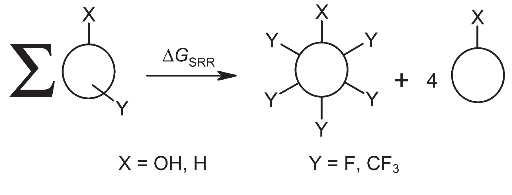
The ΔG_{RCC} is found via the following equation:



(6)

Since the group X is not involved in this reaction, this contribution is the same in the respective substituted hydrocarbon and hydroxy derivative.

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



(7)

The term to the left of the arrow denotes for every compound the sum of the five possible isomers of C_6H_4XY. The negative free energy change of these reactions can be expressed as follows:

$$\Delta G_{\mathrm{SRR}} = \Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCC}} + \Delta G_{\mathrm{RCX}} \tag{8}$$

From eqs 6 and 8 follows

$$\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}} = \Delta G_{\mathrm{SRR}} - \Delta G_{\mathrm{RCC}} \tag{9}$$

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TABLE 1. Results of Calculations of the Unsubstituted and Pentasubstituted Systems and Their Respective Acidifying Effects Relative to the Unsubstituted Compounds and Relative Stabilities toward the Corresponding Derivatives of Kekulé Benzene (all values in kcal·mol^{-1})

				relative stabilities				
			acidifying effect	neutral	neutral	anion	anion	
acid	PA(A−)	GA	ΔGA	*H*	*G*	*H*	*G*	comments
H-**0**	400.7	393.3						
H-F_5-**0**	354.4	346.5	−46.8					
H-$(CF_3)_5$-**0**	341.9	332.4	−60.9					
H-**1**	402.6	394.7		122.1	122.6	124.0	124.1	
H-F_5-**1**	343.1	335.6	−59.2	131.2	131.0	119.9	120.1	
H-$(CF_3)_5$-**1**	341.8	334.9	−59.8	82.2	77.9	82.1	80.4	
1-H-**2**	390.0	382.2		82.9	82.8	72.3	71.7	
1-H-F_5-**2**	358.1	350.0	−32.2	70.7	70.3	74.4	73.8	
1-H-$(CF_3)_5$-**2**	327.8	319.9	−62.3	46.4	41.1	32.3	28.6	
2-H-**2**	397.7	389.9		82.9	82.8	80.0	79.4	
2-H-F_5-**2**	362.4	354.5	−35.4	70.1	69.8	78.1	77.8	
2-H-$(CF_3)_5$-**2**	344.1	336.3	−53.6	47.4	43.3	49.6	47.2	
1-H-**3**	401.5	393.6		80.1	80.4	80.9	80.7	
1-H-F_5-**3**	355.1	347.2	−46.4	93.1	92.8	93.7	93.6	
1-H-$(CF_3)_5$-**3**	346.2	338.3	−55.4	51.2	47.7	55.5	53.6	
2-H-**3**	401.0	393.2		80.1	80.4	80.4	80.2	
2-H-F_5-**3**	362.2	354.3	−38.9	92.8	92.6	100.5	100.3	
2-H-$(CF_3)_5$-**3**	346.9	339.8	−53.4	51.7	48.3	56.7	55.7	
5-H-**3**	391.4	383.5		80.1	80.4	70.8	70.6	
5-H-F_5-**3**	345.4	337.6	−45.9	91.5	91.4	82.5	82.5	
5-H-$(CF_3)_5$-**3**	333.6	326.1	−57.4	54.8	52.0	46.5	45.7	
OH-**0**	346.8	339.2						
OH-F_5-**0**	323.5	315.7	−23.5					
OH-$(CF_3)_5$-**0**	297.8	290.2	−49.0					
OH-**1**	357.6	350.0		124.1	124.6	135.0	135.4	
OH-F_5-**1**				133.3	132.9			anion: C1−C5 broken
OH-$(CF_3)_5$-**1**	305.4	298.0	−52.0	79.8	75.3	87.3	83.0	
1-OH-**2**	361.3	353.5		85.5	85.4	100.1	99.7	
1-OH-F_5-**2**				68.7	68.4			anion: C1−C4 broken
1-OH-$(CF_3)_5$-**2**				44.3	38.5			anion: C1−C4 broken
2-OH-**2**	343.6	336.2		80.4	80.1	77.2	77.1	
2-OH-F_5-**2**	314.7	307.2	−29.1	64.9	64.5	56.1	55.9	
2-OH-$(CF_3)_5$-**2**	296.5	288.5	−47.8	34.0	30.0	32.8	28.2	
1-OH-**3**	358.5	350.7		83.9	84.1	95.6	95.5	
1-OH-F_5-**3**				94.9	94.5			anion: changed the order of C's
1-OH-$(CF_3)_5$-**3**				49.5	46.0			anion: bond broken
2-OH-**3**	350.9	342.9		81.3	81.6	85.4	85.3	
2-OH-F_5-**3**	324.4	317.0	−26.0	93.5	92.9	94.4	94.2	
2-OH-$(CF_3)_5$-**3**	303.9	296.2	−46.7	42.7	39.4	48.8	45.3	
5-OH-**3**	351.0	343.1		82.6	82.8	86.8	86.7	
5-OH-F_5-**3**				93.0	92.2			anion: bond C5−C6 broken
5-OH-$(CF_3)_5$-**3**	298.7	290.5	−52.6	52.1	49.2	52.9	49.5	

Results

The proton affinities [PA(A^-)] and inherent gas-phase acidities (GA) together with calculated acidifying and substituent additivity effects as well as the relative stabilities of the systems that remained intact are presented in Tables 1 and 2. The corresponding Hartree−Fock energies, enthalpies, and free energies (HF, ΔH, ΔG) of all systems calculated are presented in the Supporting Information.

All neutrals calculated were stable with respect to the geometry optimization of the used computational method. However, in some of the anions significant bond elongations or bond ruptures took place. The monosubstituted 5-F and 5-CF_3 and also pentafluoro hydroxy anions of **1** went through a C(5)−C(6) bond cleavage. The pentafluorinated and pentakis-trifluoromethylated 1-hydroxy anions of **2** underwent rearrangement (rupture of the 1−4 bond) to give the corresponding phenolate derivatives. Several anions of the monosubstituted 1-OH and 5-OH derivatives as well as 1-OH persubstituted and 5-OH pentafluoro derivatives of **3** also rearranged into the respective phenolate ions.

As seen from the results in Supporting Information, the rupture of the bonds in the anions is accompanied by a significant release of steric strain and the additional stabilization of the system. Because this process is not a reversible Brønsted acid−base equilibrium, such acidities can only be called apparent. In order to carry out the analysis of substituent effects according to the above presented scheme, it is necessary that all the neutral and anionic species involved in eqs 4, 6, and 8 can be computed and that no bond ruptures take place. If a species with a disrupted bond (and thus with several tens of kcal·mol^{-1} extra stabilization) were included in the analysis, the whole analysis would be immediately meaningless. Given the bond rupture problems outlined above, it was possible to carry out the analysis of isodesmic reactions only for H-$(CF_3)_5$-**1**, H-F_5-**1**, 1-H-$(CF_3)_5$-**2**, 1-H-F_5-**2**, 2-H-$(CF_3)_5$-**2**, 2-H-F_5-**2**, 2-OH-$(CF_3)_5$-**2**, 2-OH-F_5-**2**, 1-H-$(CF_3)_5$-**3**, 1-H-F_5-**3**, 2-H-$(CF_3)_5$-**3**, 2-H-F_5-**3**, 5-H-$(CF_3)_5$-**3**, 5-H-F_5-**3**, 2-OH-$(CF_3)_5$-**3**, and 2-OH-F_5-**3** species.

TABLE 2. Results of the Analysis of Substituent Effects According to eqs 5−9 (all ΔG values in kcal·mol^{-1})

	neutral				anion				
	ΔG_{GAIE}	ΔG_{SRR}	ΔG_{RCC}	$\Delta G_{\mathrm{S}}+\Delta G_{\mathrm{RCX}}$	ΔG_{GAIE}	ΔG_{SRR}	ΔG_{RCC}	$\Delta G_{\mathrm{S}}+\Delta G_{\mathrm{RCX}}$	additivity (%)
H-F_5-**0**	0	24.0	24.0	0	−48.2	25.4	24.0	1.4	97.1
H-F_5-**1**	0	19.0	19.0	0	−54.7	14.6	19.0	−4.4	108.1
1-H-F_5-**2**	0	16.9	16.9	0	−35.3	19.9	16.9	3.0	91.4
2-H-F_5-**2**	0	14.0	14.0	0	−47.8	26.5	14.0	12.4	74.0
1-H-F_5-**3**	0	16.7	16.7	0	−45.2	15.5	16.7	−1.2	102.6
2-H-F_5-**3**	0	17.1	17.1	0	−43.1	21.3	17.1	4.2	90.2
5-H-F_5-**3**	0	17.6	17.6	0	−48.3	19.9	17.6	2.3	95.1
H-$(CF_3)_5$-**0**	0	56.0	56.0	0	−68.5	63.6	56.0	7.6	88.9
H-(CF3)5-**1**	0	28.9	28.9	0	−75.6	44.6	28.9	15.8	79.1
1-H-$(CF_3)_5$-**2**	0	24.2	24.2	0	−77.1	39.0	24.2	14.8	80.8
2-H-$(CF_3)_5$-**2**	0	26.1	26.1	0	−65.1	37.6	26.1	11.5	82.3
1-H-$(CF_3)_5$-**3**	0	31.4	31.4	0	−69.5	45.6	31.4	14.2	79.6
2-H-$(CF_3)_5$-**3**	0	30.5	30.5	0	−67.1	44.2	30.5	13.7	79.6
5-H-$(CF_3)_5$-**3**	0	34.7	34.7	0	−72.3	49.6	34.7	14.8	79.5
OH-F_5-**0**	3.7	26.0	24.0	2.1	−19.2	25.4	24.0	1.5	102.6
2-OH-F_5-**2**	2.3	14.8	14.0	0.7	−26.6	14.6	14.0	0.6	100.6
2-OH-F_5-**3**	10.1	11.9	17.1	−5.2	−22.9	18.9	17.1	1.8	78.7
OH-$(CF_3)_5$-**0**	3.8	61.1	56.0	5.0	−56.5	72.4	56.0	16.3	81.3
OH-$(CF_3)_5$-**1**[a]	3.2	29.9	28.9	1.0	−57.8	38.9	28.9	10.1	85.2
2-OH-$(CF_3)_5$-**2**	−4.3	28.6	26.1	2.5	−60.0	36.6	26.1	10.4	85.7
2-OH-$(CF_3)_5$-**3**	−1.2	30.4	30.5	−0.1	−63.0	45.5	30.5	15.0	75.6

[a] For the position 5 the energies of the corresponding anion with a substituent in position 2 were used.

OH-$(CF_3)_5$-**1** was also included with certain reservations. The single-substituted anion with a substituent in position 5 had a bond rupture, so the energies of the corresponding derivative with a substituent in position 2 were used instead. Results of the analysis of substituent effects using the isodesmic reactions approach described above are presented in Table 2.

The gross additive interaction effect among the fluorinated valence isomers of Kekulé benzene is higher than in the case of **0** only in case of prismane (by 6.5 kcal·mol^{-1}) and significantly lower (12.9 kcal·mol^{-1}) in the case of 1-H-F_5-**2**. The respective trifluoromethyl derivatives had up to 7.1 kcal·mol^{-1} higher ΔG_{GAIE} when the reaction center was not on the bridgehead of the double bond. If the gross additive interaction effects among hydrocarbons and hydroxy derivatives are compared, then the effect among the latter ones was markedly lower. Nevertheless, in the cases where the HO systems remained intact, the isomerization improved the gross additive interaction effect. The ΔG_{RCC} parameters followed the pattern where the strongest repulsion was detected between the substituents of **0** and other isomers were ordered as follows: prismane > benzvalene > Dewar benzene. The $\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}}$ values were noted generally larger in the case of the CF_3-substituted systems. For all but 2-H-F_5-**2** (12.4 kcal·mol^{-1}) of the fluorine derivatives they remained below 5 kcal·mol^{-1}. Two of them were even negative. In several cases very low values of substituent effect saturation were accompanied by additivity rates above 100%.

Discussion

Since acidities refer first of all to Gibbs free energies, the discussion below uses Gibbs free energies (unless specifically stated otherwise). Using enthalpies leads in all cases to the same conclusions.

The stability of the calculated derivatives is evaluated with respect to the corresponding isomeric benzene derivatives.

Stability of the Derivatives of 1−3. The unsubstituted hydrocarbons **1**−**3** are significantly less stable than benzene (**0**). The prismane is the most strained of them and is even 123 kcal·mol^{-1} less stable than benzene. Relative stabilities of the pentafluorinated **1** and **3** as well as the corresponding alcohols with respect to pentafluorobenzene and pentafluorophenol, respectively, are even less stable with strain energies of 131.0 kcal·mol^{-1} in the case of 1-H-F_5-**1** and 132.9 for 1-OH-F_5-**1**. The latter is predicted as the least stable compound investigated in this work. For the Dewar benzene and benzvalene the relative (in)stabilities are 82.8 and 80.4 kcal·mol^{-1}, respectively.

In most cases the relative stabilities of the parent (fluoro)-hydrocarbons and the corresponding alcohols are fairly similar. This cannot be generalized to their anions. As opposed to the deprotonated hydrocarbons, deprotonated OH derivatives of **1**−**3** can be significantly destabilized if the OH group is not attached at a double bond, e.g., 11 to 28 kcal·mol^{-1} lower relative stabilities toward the respective derivatives of **0** than the respective deprotonated hydrocarbons, and were accompanied by significant (> 0.1 Å) C(α)−C(β) bond lengthening. This was also observed with $C_{10}H_{15}O^-$ derivatives in ref 19. In two cases (OH-$(CF_3)_5$-**1** and 5-OH-$(CF_3)_5$-**3**), when CF_3 substituents were used, the X = H/OH difference of relative stabilities remained under 4 kcal·mol^{-1}. The rest of the deprotonated fluoro and CF_3 derivatives of 1-OH and 5-OH alcohols were unstable, as indicated by the cleavage of a C(α)−C(β) bond from the X.

The situation is quite different if the OH group is in position 2. Especially in the fluorinated and trifluoromethylated structure of Dewar benzene this position seems to favor the stabilizing orbital interactions between the $^{-}$O fragment and substituents. The anion of 2-OH-F_5-**2** had 21.2 kcal·mol^{-1} better relative stabilization against $^{-}$O−F_5-**0** than the unsubstituted **2** against phenolate anion $^{-}$O-**0**. One reason is obviously the resonance between the $^{-}$O−center and the unsaturated part that is visible from the stability of the anions of both **2** and **3**. It is also confirmed by the results of NBO calculations, where the *E*(2) energy of the oxygen lone pair interaction with the C(2)−C(3) antibonding orbital is in the range of 100 kcal·mol^{-1}. This resonance interaction is visible also with the neutrals of the respective hydroxy compound, resulting in $E(2)$ energies around 30 kcal·mol^{-1}.

It has been demonstrated that the polyfluorination stabilizes the anions of strained alcohols.[19] First of all this occurs via the partial transfer of electron density from the nonbonding orbitals of the $-O^-$ center to the σ^*-orbitals of the adjacent C−C bonds of the hydrocarbon skeleton. This effect causes elongation of the C−C bonds and partial release of the steric strain. In derivatives of **1**−**3** the exact stabilizing effect significantly depends on the orientation and distance between interacting substituent, functional group, and C−C bond acceptor orbitals as well as the position of the double bond relative to the reaction center. Certain substitution patterns can easily result in decomposition of the molecular structure.

The substituted hydrocarbons are generally slightly less stable than the corresponding hydroxy derivatives. Nevertheless, the former are less favored to decompose on deprotonation. In many cases the relative stabilities even improve considerably with deprotonation: H-F_5-**1** (−10.9 kcal·mol^{-1}), 1-H-**2** (−11.1 kcal·mol^{-1}), 1-H-$(CF_3)_5$-**2** (−12.5 kcal·mol^{-1}), and the derivatives of 5-**3** (−6.3 to −9.8 kcal·mol^{-1}). Notable exceptions are the pentasubstituted derivatives with the −H at the bridgehead of a double bond, where deprotonation results in ca. 8 kcal·mol^{-1} lower relative stability.

As already mentioned, the H and HO derivatives with the same substitution pattern mostly had similar (−5 to +3 kcal·mol^{-1}) stabilities toward the respective derivatives of **0**. The exceptions were 2-X-$(CF_3)_5$-**2** and 2-X-$(CF_3)_5$-**3**, in which cases the corresponding alcohol was markedly more stable.

If compared with fluorination, introducing CF_3 substituents changes the stability differences from the derivatives of **0** in a more straightforward way. With the compounds that remained intact in all cases the relative stability was improved by substitution. The $(CF_3)_5$-prismane is found to be 77.9 kcal·mol^{-1} less stable than $(CF_3)_5$-**0**, and 1-H-$(CF_3)_5$-**2** and 2-H-$(CF_3)_5$-**2** are 41.1 and 43.3 kcal·mol^{-1} less stable than $(CF_3)_5$-**0**. For the different isomers of $(CF_3)_5$-**3** these differences range from 47.7 to 52.0 kcal·mol^{-1}. The same relative stability energies for the respective hydroxy derivatives $C_6(CF_3)_5OH$ of **1** to **3** are even a couple of kcal·mol^{-1} less positive. This can be due to the destabilizing interaction energy of 3.8 kcal·mol^{-1} in the neutral 1-OH-$(CF_3)_5$-**0**.[18a] Thus, the introduction of the substituents into **1**−**3** invokes a smaller increase of steric strain than introducing the same substituents into a benzene ring.[18a] The reason is that the somewhat globular shape of **1**−**3** allows the substituents to take such orientations that they are directed away from each other.

The differences in the stability of anions and neutrals of the derivatives of **1** to **3** relative to the respective derivatives of benzene translate directly into the differences of their acidities.

Acidity of the Substituted Hydrocarbons 1−3. As seen in Table 1, similarly to benzene the unsubstituted hydrocarbons **1** to **3** are weak acids. Nevertheless, 1-H-**2** and 5-H-**3** are ca. 10 kcal·mol^{-1} more acidic than benzene. Pentafluoro substitution increases the acidity of benzene by 46.8 kcal·mol^{-1}.[18a] From the corresponding hydrocarbons **1**−**3** the acidifying effect of pentafluoro substitution is higher only in the case of the **1**. The most acidic isomers of C_6F_5H are 1-H-F_5-**1** (335.6 kcal·mol^{-1}) and 5-H-F_5-**3** (337.6 kcal·mol^{-1}). The following factors are responsible for the stabilizing/destabilizing effects of pentafluoro-substituted anions of **0**−**3**:

1. Fluorine as a substituent has a strong field-inductive effect ($\sigma_F = 0.57$[9]), but is at the same time a resonance *donor* group ($\sigma_R = -0.33$[9]). In the aromatic ring both effects are operational, have opposite direction, and partially cancel. In the predominantly aliphatic structures **1**−**3** the field-inductive effect mostly works and is not counterbalanced by the resonance-donative effect.
2. The geometric arrangement of the F substituents in pentafluorobenzene is not the best possible. The efficiency of the field-inductive effect decreases rapidly when distance from the reaction center increases, thereby reducing the activity of 3-F and 4-F substituents. At the same time the 2-F substituents that otherwise are in a good position are, due to the geometry of the benzene ring, bent quite near the acidic proton (F−H distance 2.618 Å) and thus also near the lone pair of the anionic center. This causes a lone pair−lone pair repulsion in the pentafluoro benzenide anion. Contrary to this, the geometry of the derivatives of **1** to **3** permits the F substituents to be arranged in a very efficient way. In particular, in both 1-H-F_5-**1** and 5-H-F_5-**3** there are three F substituents in the alpha-position to the reaction center, but all of them are bent away: distances between H and the nearest F atoms are slightly longer than 3 Å. This minimizes the lone pair−lone pair repulsion in the anions. In 1-H-F_5-**3** the F−H distance from fluorine in the 2 position is 2.85 Å, and this acid is ca. 10 kcal·mol^{-1} weaker than 5-H-F_5-**3**. Also, the greater s character in the C−H bond of 5-H-F_5-**3** compared to the 1-H derivative could be one reason for higher acidity.
3. At first sight in the carbanions studied here the charge from the anionic center cannot be delocalized by the negative hyperconjugation effect. This is because the geometry of the acids is nonplanar and cannot be planarized in the anions because of Bredt's rule[6] and because in the cage-like structures achieving a planar geometry would require major rearrangements. In a pyramidal carbanionic center hyperconjugation is normally not effective, because of the poor overlap between the lone pair electrons of the anionic center and the σ^*-orbitals of the β-CF bonds.

Indeed, from the NBO analysis no significant lone pair delocalization to the substituents' antibonding orbitals can be detected from any of the derivatives **1**−**3**. Instead, ca. 16 kcal·mol^{-1} LP−BD* interactions with double bonds are present in 1-H-**2** and 1-H-F_5-**2** anions. The energetic effect of this delocalization in the case of 1-H-$(CF_3)_5$-**2** is more than 60 kcal·mol^{-1}. In the 1-H-**3** derivatives this effect is nonexistent. Also, notable stabilization of the 1-H-$(CF_3)_5$-**2** anion comes from delocalization of the lone electron pair to the antibonding orbitals of the following bonds: C(1)−C(2) and C(1)−C(6) (43 kcal·mol^{-1}), as well as C(1)−C(4) (25 kcal·mol^{-1}). This is accompanied by the shortening of the C(1)−C(2) and C(1)−C(6) bonds by 0.06 Å. These interactions,

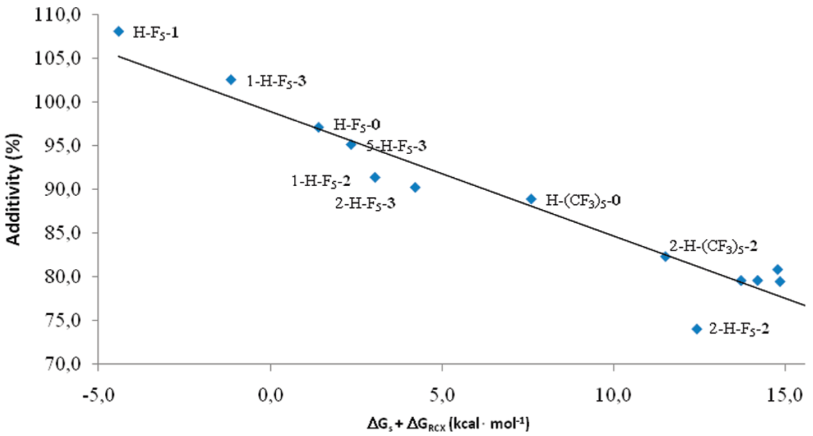

FIGURE 1. $\Delta G_s + \Delta G_{RCX}$ (anion) vs substituent additivity. $y = -1.4247x + 98.955$, $R^2 = 0.924$.

unique in the present set of systems, result in the strongest CH acidity among the benzene isomers, 319.9 kcal·mol^{-1}. At the same time, studying, for example, in pentakis(trifluoromethyl)prismane the bonds C(1)−C(2), C(1)−C(5), and C(1)−C(6) reveals slight elongation upon deprotonation. In the corresponding pentafluoro derivative the shortening of the C(1)−C(5) and C(1)−C(6) bonds on deprotonation and slight deformation of the C(1) carbon toward planarity is evident.

No substantial increase in acidity was observed if $(CF_3)_5$-**0** and $(CF_3)_5$-**1** isomers are compared, differently from the corresponding F derivatives. Although, the acidifying effect of CF_3 is higher in nearly all isomers of **1**−**3**, the additivity surpasses that of fluorine's only in the case of 2-H-$(CF_3)_5$-**2**. Nevertheless, somewhat surprisingly the substitution of **1** by five CF_3 groups leads to a similar acidity increase as in the case of five fluorine substituents. Although, CF_3 is a reasonably strong electron acceptor group due to its hyperconjugation effect ($\sigma_R = 0.09^9$), its field-inductive effect ($\sigma_F = 0.46^9$) is weaker than that of the F substituent. As opposed to F this set of properties can make CF_3 a very efficient group in acidifying compounds with an aromatic ring. At the same time in the cage-type aliphatic structures of **1**−**3** it is suboptimal due to the loss of the resonance acceptor effect.

The intrinsic gas-phase acidity of pentakis-substituted CF_3-hydrocarbons studied in this work is mostly around 330 kcal·mol^{-1}, i.e., comparable to the acidity of the open-chain hydrocarbon $(CF_3)_3CH$.[6] The only exception is 1-H-$(CF_3)_5$-**2**. This acid is only about 3 kcal·mol^{-1} less acidic than 1-H-perfluoroadamantane[24] and is expected to be significantly outperformed only by $[(CF_3)_3C]_3CH$ (this work, 300.4 kcal·mol^{-1}, see Supporting Information pp 236−238), which is estimated to be the strongest fluorinated hydrocarbon CH acid currently known. Notable for its nearly planar carbanionic center is that differently[6] from $(CF_3)_3C^-$ NBO calculations it does not show any lone pair orbital on the central carbon atom but rather strong BD−BD* and BD*−BD* delocalization from a β C−C bonding orbital to the unfilled molecular orbital of the respective α-bond with an interaction energy of up to 323 kcal·mol^{-1}. Similar expressions of stabilizing orbital interactions (LP*−LP*, LP*−BD*) have been earlier found in compounds with electron-deficient bonds, such as carboranes.[7] Apparently, describing such delocalization with this method has its limits.

The analysis of the acidifying effect of the poly-CF_3 substitution with the isodesmic reactions approach (Table 2) for $(CF_3)_5$-**1** in comparison to $(CF_3)_5$-**0** (ref 18a) leads to the following conclusions. Although the gross additive interaction effect of the five CF_3 substituents in $(CF_3)_5$-**1** is larger by 7 kcal·mol^{-1}, the actual acidifying effect is weaker by 1 kcal·mol^{-1}, leading to ca. 2.5 kcal·mol^{-1} weaker acidity of $(CF_3)_5$-**1**. The main reason is the saturation of the effects of the five CF_3 groups, which in $(CF_3)_5$-**1** is 8 kcal·mol^{-1} more intense than in $(CF_3)_5$-**0**. In the case of the respective 1-H- and 2-H-Dewar benzene derivatives the energy contributions of the substituents are more favorable in the case of 1-H-$(CF_3)_5$-**2**. This is in accordance with its higher acidifying effect. Among the derivatives of $(CF_3)_5$-**3** the lowest substituent saturation and steric repulsion effects are in the case of the 2-H-system, but the gross additive interaction effect is also the lowest. This results in the lowest acidifying effect. A similar pattern is also observed with the fluorine derivatives, where the acidifying effect is largely affected by the gross additive interaction effect. However, the analysis of the different energy contributions of poly substitution (Table 2) shows a notable linear relationship between $\Delta G_S + \Delta G_{RCX}$ and the extent of substituent additivity (Figure 1). The R^2 value in the case of hydrocarbons is 0.924 ($y = -1.4247x + 98.955$). The factors responsible for deviations of some compounds from the additivity trend could be mostly associated with resonance (positive) or p (lone pair) − π repulsion (negative) effects.

Acidity of the Hydroxy Derivatives of 1−3. Hydroxy derivatives of **1** to **3** are distinctly more acidic than the respective hydrocarbons themselves and have acidities similar to that of phenol. The strong resonance interaction between the aromatic ring and the $-O^-$ center that stabilizes the phenolate anion is eliminated or significantly reduced in the predominantly aliphatic hydroxy derivatives of unsubstituted **1** to **3**. Hence, one would expect lower acidities of their hydroxy isomers. Table 1 reveals that this is indeed the case with most of them. The 11−14 kcal·mol^{-1} weaker acidities of 1-OH-**1**, -**2**, and -**3** are reasonable, but the

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[24] Abboud, J.-L. M.; Mishima, M.; Sonoda, T. *Proc. Est. Acad. Sci. Chem.* **2005**, *54*, 60–69.

relatively high acidity of 5-OH-**3** is unexpected. The deprotonation of 5-OH-**3** results in a 0.109 Å lengthening of the C(1)−C(5) and C(4)−C(5) bonds and ca. 0.025 Å lengthening of the C(5)−C(6) bond with the respective LP−BD* interaction energies of 27.8 and 23.6 kcal·mol^{-1}.

Although the 2-OH-**2** and -**3** isomers have significantly weaker oxygen lone pair resonance interactions with the double bonds compared with **0**, the ΔG_{acid} differences remain in the range of ±4 kcal·mol^{-1}. A large part of the stabilization obviously comes from the extensive release of steric strain, which in the case of the C(α)−C(β) aliphatic bond of the 2-O$^-$-**2** ion is 0.069 Å. Also, the double bonds, in both **2** and **0**, are 0.055 Å longer than in the corresponding neutrals. For comparison, the lengthening of the similar bonds on deprotonation of 2-OH-**3** was 0.055 and 0.053 Å, respectively. Part of the stabilization in the anions of **2** and **3** can be caused by the lower p−π repulsion. The C(3)−C(2)−O bond angles in **2** and **3** are 140.1° and 135.5°, compared with 123.1° in phenolate. This could also be the reason that the anion of 2-OH-**2** is better stabilized than 2-OH-**3**.

Substituting all five hydrogen atoms by fluorine atoms increases the acidity of phenol by 23.5 kcal·mol^{-1}. A somewhat larger acidity increase is observed in the case of the pentafluoro derivatives of the investigated alcohols that remained intact, namely, 2-OH-F_5-**2** and -**3**, from which 2-OH-F_5-**2** is 8.5 kcal·mol^{-1} more and 2-OH-F_5-**3** is 1.3 kcal·mol^{-1} less acidic than pentafluorophenol. Out of all the hydroxy compounds studied in this work 2-OH-F_5-**2** was the only one that was significantly more acidic than its phenol counterpart. The most acidic experimentally measured alcohol currently known is perfluoro-1-adamantanol ($\mathrm{GA_{exp}}$ = 315.6 kcal·mol^{-1}, $\mathrm{GA_{DFT\ B3LYP\ 6\text{-}311+G^{**}}}$ = 308.2 kcal·mol^{-1}).[19] The 2-OH-F_5-**2** can rival this position.

The acidifying effect of pentakis-CF_3 substitution in phenol is more that 2 times larger than the effect of a similar fluorination. In the case of the structures of 2-OH-**2** and -**3** the CF_3 substitution is slightly less efficient, whereas in OH-$(CF_3)_5$-**1** and 5-OH-$(CF_3)_5$-**3** the pentasubstitution results in ca. 3 kcal·mol^{-1} higher acidifying effect than in OH-$(CF_3)_5$-**0**. The intrinsic gas-phase acidities of the OH-$(CF_3)_5$ isomers can be considered as superacidic. The strongest of them is 2-OH-$(CF_3)_5$-**2** (288.5 kcal·mol^{-1}), which is 1.5 kcal·mol^{-1} more acidic than OH-$(CF_3)_5$-**0**. Notable is the 28.2 kcal·mol^{-1} relative stability of 2-O$^-$-$(CF_3)_5$-**2**, which makes this anion the most stable compared with the respective isomer of **0**.

The analysis of the acidifying effect of the poly-CF_3 substitution with isodesmic reactions (Table 2) for 1-OH-$(CF_3)_5$-**1** in comparison to 1-OH-$(CF_3)_5$-**0** (ref 18a) leads to the following conclusions: the gross additive interaction effect of the five CF_3 substituents in the two cases is practically the same. The acidifying effect in 1-OH-$(CF_3)_5$-**1** is larger by 3 kcal·mol^{-1} because of the lower substituent saturation effect. However, due to the significantly higher acidity of phenol compared to 1-OH-**1**, 1-OH-$(CF_3)_5$-**1** is still 8 kcal·mol^{-1} less acidic than 1-OH-$(CF_3)_5$-**0**. The ΔG_{GAIE} in the case of the 2-OH-$(CF_3)_5$-**2** and -**3** is even slightly higher, and although the substituent saturation and repulsion are stronger in the case of **3**, the acidifying effects are nearly the same. Thus, again the acidity is determined mostly by the properties of the parent compound.

In the case of the hydroxy compounds the relationship between the additivity and $\Delta G_{\mathrm{S}} + \Delta G_{\mathrm{RCX}}$ is of lower quality (R^2 = 0.465, $y = -1.0821x + 95.714$). The most strongly deviating point is 2-OH-F_5-**3**; it left out the R^2 = 0.931 ($y = -1.5686x + 102.59$) over six trend points. The reason for such nonlinearity is again the strong p−π and p−p lone pair repulsion.

Conclusions

According to the isodesmic reaction analysis approach, the most important factor in determining the acidifying effect of the pentasubstituted derivatives of **1**−**3** is the gross additive substituent effect (ΔG_{GAIE}). Minor alterations come from the saturation and substituent repulsion effects. These factors contain a complicated interplay of different interactions between the hydrocarbon structure, substituents, and reaction site. The most influential part of these interactions on the stabilities and acidities of the systems can be described with Taft substituent parameters,[9] the interactions[15,16] of lone pairs with the surrounding moiety, and hyperconjugation effects.[11,12b,13] The ΔG_{GAIE} is mostly structure dependent; thus the strongest interactions could be expected from the hydrocarbon systems with CF_3 substituents. In the case of the respective fluorine compounds these interactions are more than 17 kcal·mol^{-1} weaker. In the case of the fluorinated hydroxy derivatives the value of ΔG_{GAIE} can be more than 3 times smaller. By the substituent repulsion energies the structures of the isomers can be ordered as follows: Kekulé benzene > prismane > benzvalene > Dewar benzene. Although in the unsaturated systems CF_3 groups are usually significantly more efficient in increasing the acidities of the compounds, they also have a larger tendency for substituent effect saturation. In turn, for fluorine atoms as substituents one could expect a significantly better additivity effect, in some cases even exceeding 100%. This is possible because of relatively low saturation effects.

The valence isomers **1**−**3** of Kekulé benzene are under much higher steric strain, and this is observable also in the thermodynamic relative stabilities. The neutrals of OH and H derivatives have similar relative stabilities toward the parent isomer, although there is a tendency of OH derivatives to be slightly less stable when the OH group is not placed at the bridgehead of the double bond and no substituents are present. In the case of the substituted derivatives of the respective anions the $^-$O systems are much more favored to decompose on deprotonation by means of the rupture of a C(α)−C(β) bond, with the exception of the above-mentioned systems, which have oxygen lone pairs stabilized by a double bond. Unlike hydroxy compounds, deprotonation of the CH acids did not cause any bond ruptures. Rather, there was an interesting result concerning the relative stabilities of the neutrals and anions of H-**1** and 5-H-**3**. Upon fluorination, the relative stability of the neutral decreased and, at the same time, the relative stability of the fluorinated form was increased by deprotonation. The 1-H-F_5-**1** had even higher relative stability than the unsubstituted compound. This illustrates well the fact that not only the stabilization of the anion is important in increasing the acidity. Even more so, the acidities of the hydrocarbon structures compared with the respective hydroxy compounds by isomerization are generally more likely to increase. The loss of aromaticity is a major deacidifying factor for the hydroxy isomers. The only exception is pentafluorinated 2-OH-Dewar benzene (DFT B3LYP: 307.2 kcal·mol^{-1}), which is expected to rival the gas-phase acidity of perfluoro-1-adamantanol (exptl: 315.7 kcal·mol^{-1}, DFT B3LYP: 308.2 kcal·mol^{-1}),[19] currently the most acidic experimentally measured perfluorinated alcohol. Some of the compounds investigated in this study are predicted to have even stronger inherent gas-phase acidities, e.g., some pentakistrifluoromethylated alcohols, which in the case of 2-OH-$(CF_3)_5$-**2** are expected to reach an acidity of 288.5 kcal·mol^{-1}, or the hypothetical pertrifluoromethylated hydrocarbon acid $[(CF_3)_3C]_3CH$, whose gas-phase acidity of 300.4 kcal·mol^{-1} is predicted to be slightly stronger than that of sulfuric acid.

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Supporting Information Available: Full details of quantum chemical calculations of Table 1 (Tables S21, S23−S205); full details of the calculations of the isodesmic reactions approach in Table 2 (Tables S1−S20); relative stabilities and acidifying effects of monosubstituent derivatives (Table S22); complete ref 23. This material is available free of charge via the Internet at http://pubs.acs.org.