

DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS

III

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LAURI LIPPING

The acidity of strong and superstrong
Brønsted acids, an outreach
for the “limits of growth”:
a quantum chemical study



TARTU UNIVERSITY PRESS

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Estonia

Dissertation is accepted for the commencement of the Degree of Doctor of
Philosophy in Physical and Analytical Chemistry on June 28th, 2011 by the
Doctoral Committee of the Institute of Chemistry, University of Tartu.

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Commencement: 9th of September 2011 in Room 1022, 14A Ravila
 Street, Tartu, at 14:00.

Publication of this dissertation is granted by University of Tartu

ISSN 1406–0299
ISBN 978–9949–19–836–8 (trükis)
ISBN 978–9949–19–837–5 (PDF)

Autoriõigus: Lauri Lipping, 2011

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr. 469

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LIST OF ORIGINAL PUBLICATIONS

- I** **Lauri Lipping**, Ilmar A. Koppel, Ivar Koppel and Ivo Leito. Some weakly coordinating anions based on carboranes. *Proc. Est. Acad. Sci. Chemistry*. **2006**, *55*, 145–154.
- II** **Lauri Lipping**, Ivo Leito, Ivar Koppel and Ilmar A. Koppel. Gas-Phase Brønsted Superacidity of Some Derivatives of Monocarba-*closo*-Borates: a Computational Study. *J. Phys. Chem. A* **2009**, *113*, 12972–12978.
- III** **Lauri Lipping**, Ivar Koppel, Ilmar A. Koppel, Alexander Kolomeitsev, Gerd-Volker Rösenthaller and Ivo Leito. Polytrifluoromethylation versus Polyfluorination of the Isomers of Kekule Benzene and Phenol: A Theoretical Study. *J. Org. Chem.* **2010**, *75*, 6436–6444.
- IV** **Lauri Lipping**, Agnes Kütt, Karl Kaupmees, Ivar Koppel, Peeter Burk, Ivo Leito and Ilmar A. Koppel. Acidity of Anilines: Calculations vs. Experiment. *J. Phys. Chem. A*: submitted.

Author's contribution

- Paper I** Main person responsible for preparing and writing the manuscript. Performed all of the theoretical calculations.
- Paper II** Main person responsible for preparing and writing the manuscript. Performed most of the theoretical calculations.
- Paper III** Main person responsible for preparing and writing the manuscript. Performed most of the theoretical calculations.
- Paper IV** Main person responsible for preparing and writing the manuscript. Performed significant part of the theoretical calculations.

ABBREVIATIONS

AU	Atomic Units
COSMO-RS	Conductor-like Screening Model for Real Solvents
DCSM	Dielectric Continuum Solvation Model
DFT	Density Functional Theory
DMSO	Dimethyl sulfoxide
ΔG_{acid}	Gas-phase acidity
FT-ICR	Fourier Transform Ion Cyclotron Resonance
GA	Gas-phase acidity
HA	Neutral acid
A^-	Conjugate base of the neutral acid HA
HPMS	High-Pressure Mass Spectrometry
NBO	Natural Bond Orbital
N_{imag}	The number of imaginary frequencies in DFT calculations
PA	Proton Affinity
pK_a	Negative logarithm of acid dissociation constant
rmsd	Root Mean Square Deviation
σ_F	constant for the substituent field-effect
σ_R	constant for the substituent resonance effect
σ_α	constant for the substituent polarizability effect

INTRODUCTION

An acid is a substance that reacts with a base by donating a proton. There are no bases without acids and vice-versa. The first scientific approach of acids and bases was formulated by a French natural scientist and nobleman Antoine Lavoisier in the second half of the 18th century. He thought that composition of acids always includes oxygen and named oxygen as the „acid former” (*oxyys*). This paradigm held until some decades later Sir Humphry Davy proved that acids without oxygen also exist. The shift of paradigm was finished by Justus von Liebig in 1830'ies who based on his extensive work with organic acids stated that an acid is a hydrogen-containing substance in which the hydrogen could be replaced by a metal. This theory remained dominant until the end of 19th century when 1880 Svante Arrhenius, a Swedish scientist provided the first modern definition for acids and bases: acids are substances that dissociate in aqueous solution to deliver hydrogen cations, and bases which give hydroxide ions to the solution. In 1923 Brønsted and Lowry generalized the definition by means of proton donation and accepting mechanism that manifested conjugate acid and base theory that is formally independent of solvent. Since then acidity and basicity have been considered as a dominant quantitative characteristics of chemical reactivity of compounds. Countless numbers of chemical processes, both, biological and technological, consider acid-base equilibria as a key aspect when obtaining desirable chemical results. Therefore, understanding the properties of acids and bases and how these properties depend on chemical structure is of fundamental importance. The basic approach and the first step on this way is to study the molecules in the gas phase where they are unaffected by the solvent molecules. Modern techniques like pulsed Ion Cyclotron Resonance (ICR), high-pressure mass-spectrometry (HPMS) and theoretical computational methods with constantly increasing computational capacity have provided an effective opportunity to study wide range of systems in terms of acid-base properties that under normal conditions might even not exist. The best of these computational methods, nowadays, allow predicting acidities and basicities with the precision of 1–2 kcal·mol⁻¹. The main goal of the present work is to study computationally the electronic structure and chemical properties of several classes of Brønsted acids of which some are expected to be super-acidic systems.

LITERATURE OVERVIEW

In the 1930's J. B. Conant¹ brought into use the name „superacid” for the systems more acidic than the conventional strong Brønsted acids. Later, R. J. Gillespie² introduced an arbitrary, but generally accepted definition that superacids are the systems whose acidity is stronger than that of the 100% sulfuric acid. Since then a still ongoing endeavor has been about for creating and finding more stronger and stable Brønsted acids^{3–13}. One of the main reasons for such an interest is because superstrong acids always come with the corresponding conjugate base, the weakly coordinating anion^{14,15} with important characteristics like extremely low nucleophilicity and strongly delocalized negative charge. This makes the suitable counterion for extremely acidic, electrophilic and/or oxidizing cations that bear great commercial interest in organic synthesis, petrochemical applications^{16–22}, electrochemical technologies (fuel cells^{23,24}, lithium batteries²⁵), etc. Therefore, creating more weakly coordinating anions is the way of creating stronger Brønsted acids. There are two parallel ways of achieving this: using substituents able to stabilize and withdraw negative charge of the anion^{6,10} and finding anions that along with having an acidic site (a) have a high degree of negative charge delocalization¹⁴, (b) have no points of local negative charge concentration or available lone electron pairs and bear only weakly basic sites, (c) respond well to the charge delocalizing ability of the substituents, (d) have sites for multiple substitution suitably conjugated with the reaction center. All over separate group of superacids are obtained from the complex-formation³ of Lewis acids (e.g., SbF₅, BF₃, SO₃, AlCl₃, etc.) with the Brønsted acids (e.g., HF, H₂SO₄, FSO₃H, H₂O, HCl, CF₃H, etc.). However, the gas-phase acidities of these complexes have never been measured experimentally.

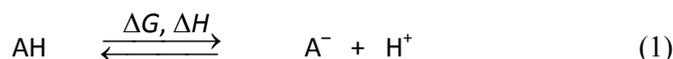
Finding and using more electron-withdrawing substituents has been the main trend¹⁰ in the design of new superstrong Brønsted acids. In the long list of substituents there are some which have become more widely used than others. Some of the most often occurring in the extreme cases of chemical reactivity are fluorine and fluorine containing substituents. Because the resulting compounds have many important qualities and the fluorination as a synthetical process is often relatively robust 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,²⁶ fluorinated catalysts,²⁷ self-assembling structures,²⁸ weakly coordinating anions,²⁹ ionic liquids³⁰ etc. 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.^{6,10,12,31} Although, the fluorine atom is considered as the most electronegative, the complicated interplay of different properties³⁴ of fluorine (i.e. resonance/hyperconjugation^{34–39}, electronegativity,

polarizability, field(inductive), p - π repulsion effect⁴⁰⁻⁴²) significantly depend on the position of the substitution center relative to the reaction site and the extent of a net delocalization of the anions 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 β -C-F bond's ability to delocalize the electron density of the carbanion lone pair to its energetically low-lying σ^* -orbital.^{36,38,39} The effects that are known to destabilize the conjugate bases^{42,43} 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 - π repulsion with geminal double bond orbitals.

An interesting group of polyfluorinated molecules are the polytrifluoromethylated molecules. Although, CF_3 group has field-inductive effect of similar³⁴ strength as F (σ_{F} of CF_3 and F are both 0.44), it is due to the hyperconjugation effect³⁵ that lets it act as a π -acceptor group,³⁷⁻³⁹ 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.³⁴⁻³⁹

Troughout most of the 20th century one of the main areas of research in physical organic chemistry have been substituents' effect on the physical and chemical properties of the compounds. Since the works of Ingold³² and Hammett³³ there has been made a tremendous effort to analyse several aspects of the rates and equilibria of different organic reactions in solution. Perhaps, the most substantial of them (at least from the perspective of the present dissertation) are the works³⁴ of R. W. Taft and co-workers about substituent effects (field-inductive, resonance, polarizability). Based on the substituent constants provided by Taft *et. al.* it is theoretically possible to predict the intrinsic gas-phase acidities and design new and more acidic series of Brønsted acids. However, recent^{6,13} research has shown, that the interdependence of the contributions of a number of effects including resonance/ hyperconjugation³⁴⁻³⁹, electronegativity, polarizability, field(inductive), p - π repulsion effect⁴⁰⁻⁴²) and also the position of the substitution center relative to the reaction site makes the precise prediction of acid-base properties of the systems rather complicated. Especially, if one considers that these effects are operative both in neutral and anionic forms, and often in opposite ways. Therefore, modern computational methods^{10,44,49} offer inexpensive, rather powerful and reliable alternatives to scout the ways for often rather complicated and expensive experimental field work.

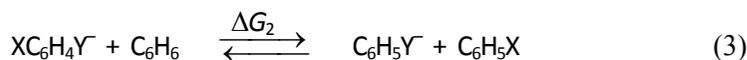
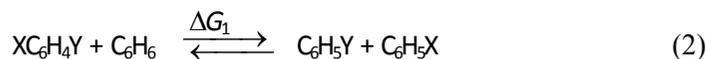
The intrinsic gas-phase acidity ($\Delta G_{\text{acid}} \equiv \text{GA} \equiv \Delta G$) calculations of the acid HA and proton affinities ($\text{PA}(\text{A}^-) \equiv \Delta H_{\text{acid}} \equiv \Delta H$) of the anionic base A^- follow the approach of Gibbs' free energy change on deprotonation of an acid according to the following equilibrium:



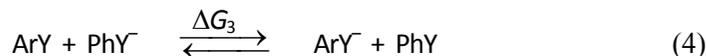
By definition, the gas-phase acidity of a neutral acid HA is equal to the gas-phase basicity towards the proton of its conjugate anion, A⁻. These quantities are of fundamental interest, and they provide valuable information about the inherent (intrinsic), solvent-independent properties of the acids. The current experimental gas-phase Brønsted acidity scale spans more than 130 kcal·mol⁻¹ from ethane (GA = 411.7 kcal·mol⁻¹)⁴⁵ to (C₂F₅SO₂)₂NH (GA = 283.7 kcal·mol⁻¹)⁶. Further computational studies have shown^{12,10} that intrinsic gas-phase acidities even below 200 kcal·mol⁻¹ can be expected for some novel classes of neutral superacids. The scale of Brønsted intrinsic gas-phase basicities is limited by ΔG_{base} = 35.5 kcal·mol⁻¹ for helium⁴⁶ and ΔG_{base} = 264.6 kcal·mol⁻¹ for EtN=P(NMe₂)₂NP(NMe₂)₃⁴⁷. There is a separate class of super-bases, alkali metal oxides, hydroxides, nitrides, alkali metals and alkaline earth metals that have been measured up to 337.5 kcal·mol⁻¹ for Cs₂O⁴⁶. The super-basicities of ylides, imides, phosphazenes, phosphines have been predicted to be in the same range⁴⁸.

For the deeper insight into the acid-base properties of the derivatives several approaches have been used. Based on electron structure for the neutral and anionic counterparts Natural Bond Orbital analysis⁴⁹ (NBO) can be performed. This computational tool mainly allows to quantify the electronic populations on the calculated orbitals, natural atomic charges, natural Lewis structure, stabilisation energies between natural bond orbitals, etc. Although, the bulk of information obtained from this analysis is large in case of the systems with strong resonance interactions the interpretation of the results is not satisfactory.

To perform further analysis of the computationally obtained results in terms of the effects of the substituents on the acidity of the derivatives there are two main approaches: isodesmic/homodesmotic^{34c,50-53} reaction series method and multilinear^{12,54} regression analysis of GA's and energies obtained from the isodesmic reactions against polar substituent constants. The latter helps recognizing which type of polar substituent effects are operational in different systems. The former allows obtaining often experimentally inaccessible data: the separation of substituents effects into those operational in anions and neutral forms. Furthermore, the separation of the meta, para and ortho substituents' effects into the components connected to the neutral or anionic form. As seen in Equations 2 and 3, Y and Y⁻ groups are separated from the substituent X into separate molecule which eliminates intramolecular interactions between the substituent X and neutral or deprotonated reaction center, Y or Y⁻. The ΔG₁ and ΔG₂ are the energies of the substituent effects in kcal·mol⁻¹.



The relative calculated acidities ΔG_3 refer to another isodesmic reaction 4



and are obtained as a difference of the free energy changes, ΔG_1 and ΔG_2 , for the isodesmic reactions 2 and 3 that is directly comparable with the respective experimental value:

$$\Delta G_3 = \Delta G_2 - \Delta G_1 \quad (5)$$

More sophisticated approach is needed if the effects of polysubstituted systems are analyzed:

$$\Delta G_{\text{acid}}(\text{C}_6\text{Y}_5\text{X}) = \Delta G_{\text{acid}}(\text{C}_6\text{H}_5\text{X}) + \Delta\Delta G_{\text{GAIE}} + \Delta\Delta G_{\text{S}} + \Delta\Delta G_{\text{RCC}} + \Delta\Delta G_{\text{RCX}} \quad (6)$$

The $\Delta\Delta G$ values in eq 6 are defined as follows:

$$\Delta\Delta G = \Delta G_{\text{anion}} - \Delta G_{\text{neutral}} \quad (7)$$

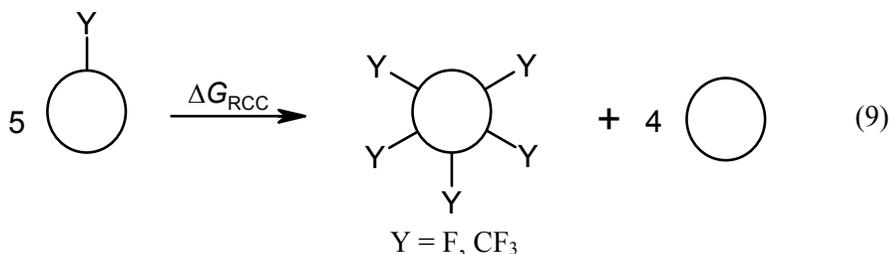
The ΔG values are defined as follows:⁵⁰

- ΔG_{GAIE} (defined via eq 8) 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: (a) in the pentakis-substituted derivative there can be simultaneously several CF_3 groups in the vicinity of X and (b) 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 series of reactions corresponding to eq 2 and 3 (neutral and anionic forms, respectively) where all possible positions for substituents are included. 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 -prismane:

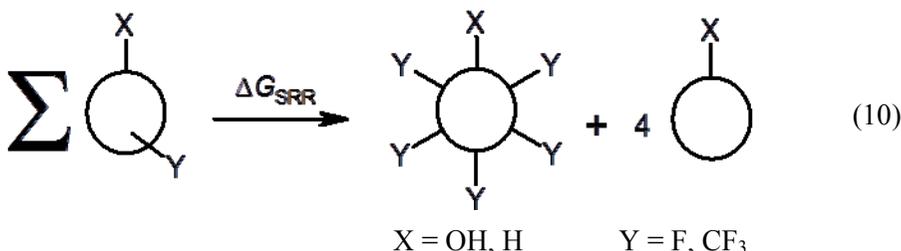
$$-\Delta G_{\text{GAI E}}(\text{neutral}) = \Delta G_1(1,2) + 2 \Delta G_1(1,3) + 2 \Delta G_1(1,5) \quad (8)$$

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



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 equations can be written for obtaining the remaining two ΔG contributions: the contributions $\Delta G_S + \Delta G_{\text{RCX}}$ can be in the framework of this isodesmic reaction approach estimated only jointly. The following series of reactions was used:



$\sum \text{C}_6\text{H}_4\text{XY}$ denotes for every compound in the sum of the five possible isomers of $\text{C}_6\text{H}_4\text{XY}$. The negative free energy change of these reactions can be expressed as follows:

$$\Delta G_{\text{SRR}} = \Delta G_S + \Delta G_{\text{RCC}} + \Delta G_{\text{RCX}} \quad (11)$$

From eqs 9 and 11 follows that:

$$\Delta G_S + \Delta G_{\text{RCX}} = \Delta G_{\text{SRR}} - \Delta G_{\text{RCC}} \quad (12)$$

As seen from above the isodesmic reactions method is also applicable to analyze the changes in energetic effects when substituent positions shift in or between molecules, calculate energetic effects rearranging the carbon skeleton of molecules, etc.

The fundamental issue concerning the acid-base properties of different types of compounds is the behavior when bringing them from the gas phase into

solution. This mainly concerns⁵⁵ polarity, polarizability and acid-base properties of solvents as the characteristics that most strongly influence the ionization of an acid in a solvent. Polarity of a solvent determines the overall solvation capability of the solvent that depends on the whole range of intermolecular interactions between solute and solvent molecules. The most common physical constant that describes the polarity of a solvent is relative permittivity ϵ_r . The relative permittivity of a material under given conditions reflects the extent to which it concentrates electrostatic lines of flux. The relative permittivity of a material for a frequency of zero is known as static relative permittivity or as dielectric constant. In solvents ϵ_r expresses the ability of a solvent to decrease the interactions between charged particles by orienting its dipoles and dissociating power of solvents. The relative permittivity of solvents range from pentane (in vacuum $\epsilon_r = 1$) to water ($\epsilon_r = 80$, at 20 °C).

The polarizability, α expresses how submissile is the electron cloud of a molecular entity towards the electric field of a nearby charge center. Because of the stronger dispersional interactions between solute and solvent molecules, solvents with high polarizability are good solvators for large and polarizable anions. This also affects directly the vapor pressure of solutions.

The acid-base properties of solvents are mainly important in terms of autoprotolysis constant K_{ap} (ref. 55, pp. 88–89) that determines the absolute pK_a range for a solvent. Self-ionizing solvents possess both acid and base characteristics and are called amphiprotic solvents. The opposites are called aprotic solvents. As the ionization of an acid depends on the basicity of the solvent, i. e. proton affinity of the medium and the strongest acid that can exist in a solvent is the lyonium ion then the less protic is the solvent the larger range of acid or base strengths can exist in the solvent.

The progressive reduction of computational cost and evolution of quantum chemical methods has made it possible to predict acidities also in solvents. In the recent years from different quantum chemical methodologies available for the computation of pK_a values the dielectric continuum solvation methods (DCSMs) have become quite popular since they are able to describe accurately long range electrostatic interactions of solutes at moderate computational cost in the context of quantum chemical programs⁵⁶. Despite the well-known deficiencies of DCSM methods, (i.e. the neglect of hydrogen bonding and the inadequate treatment of the short range electrostatics which can be much stronger in ions than in neutrals and thus can introduce a large asymmetry to the solvation energy of an acid compared to its conjugate base) it is possible to correlate the quantum chemical dissociation free energy of a solvated molecule via a linear free energy relationship. COSMO-RS (Conductor-like Screening Model for Real Solvents)⁵⁷ goes beyond the DCSM concept in that it combines the electrostatic advantages and the computational efficiency of the DCSM COSMO with a statistical thermodynamics method for local interaction of surfaces, which takes into account local deviations from dielectric behavior as well as hydrogen bonding.

THE GOALS OF THE INVESTIGATION

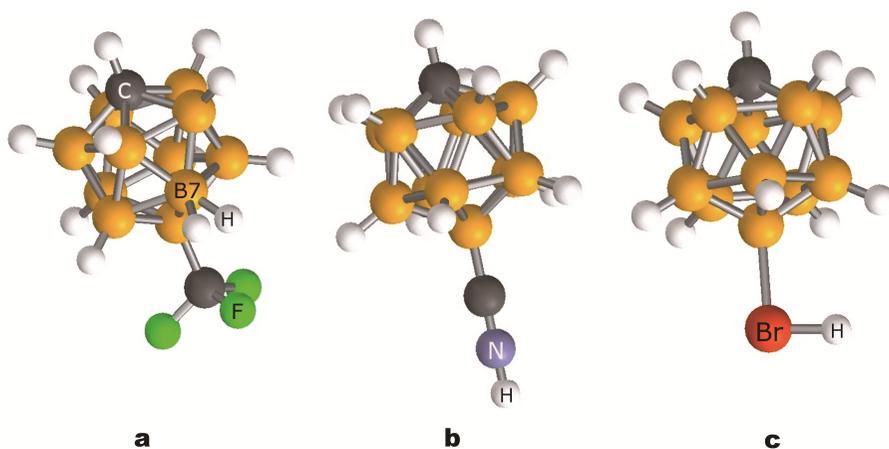
The major goals of the present study are:

- extension towards higher acidities of the computational intrinsic gas-phase acidity scale using high level density functional theory (DFT) and *ab initio* G3(MP2) calculations of mono-carborane based superacid derivatives with a wide range of substituents of different nature.
- investigating the thermodynamic stability and intrinsic acidity of the polyfluorinated and polytrifluoromethylated strained isomers of C₆H₅OH and C₆H₅H and the dependence of their acidity on the structure.
- calculating the gas-phase acidities over a wide range of substituted anilines. The computational acidities of this class of NH acids are compared with their experimental gas-phase acidities and pK_a values in DMSO.
- analyzing the substituent effects separately in the neutral acid molecules and in their deprotonated forms using the isodesmic reactions in order to elucidate the reasons for the high acidity.

RESULTS AND DISCUSSION

I. The gas-phase Brønsted superacidity of some derivatives of monocarba-*closo*-borates

For some time^{10,14,15,58–62} it has been accepted that monocarba-*closo*-borates, the derivatives of $\text{CB}_{11}\text{H}_{12}^-$ (Scheme 1) present a new class of extremely inert, superweakly coordinating anions whose conjugate acids are Brønsted acids of unprecedented strength. These deductions are based on extensive and convincing, but mostly qualitative and often indirect evidence of different origin. For the first time $\text{CB}_{11}\text{H}_{12}^-$ was synthesized by Knoth in 1960s⁷². Later, the synthesis method was improved and simplified^{73,74}. Although the chemistry of carborane anions has a long history the first actual carborane-based “weighable and measurable” superacids (i.e., conjugate acids of carborane anions) were synthesized and liberated by C. Reed *et al* in 2000^{60,61,65}. The first, preliminary, computational evidence^{10,11,63} that the intrinsic (gas-phase) superacidity of conjugate acids of carborane anions can exceed that of the “classical” strong inorganic acids by many powers of ten was published by Koppel *et al* about a decade ago. Preliminary calculations^{10,71} made with density functional theory (DFT) using the B3LYP exchange-correlation functional at 3–21+G* and 6–31+G* level and the PM3 semi-empirical method showed that adding some electronegative substituents generally increases acidity, but in some cases introduces protonation centers that lead to decrease of acidity. In some cases substitution also increases the tendency of the fragmentation of the boron cage.



Scheme 1. Some Examples of Monosubstituted Monocarba-*closo*-dodecaborane Derivatives. Colours of Atoms Correspond to the Following Chemical Elements: Black – Carbon, Green – Fluorine, White – Hydrogen, Brown – Boron, Blue – Nitrogen, Red – Bromine.

Because of the fundamental challenges and interest in measuring the acidity of super strong acids, there have been recently published several investigations that have concentrated on estimating either theoretically^{10,62,71} or experimentally the intrinsic or solution-phase acidity of 1-carba-*closo*-dodecaborate-based superacids^{15,61,68} or developing methods for ranking them according to their strength. The solution-phase superacidity has been evaluated indirectly by Reed *et al* using the NH stretching frequency shifts of Oct₃NH⁺ in CCl₄ induced by H-bond formation between the latter proton donor and the super weak anionic base^{63,65}. The protonation-induced ¹³C NMR shifts of mesityl oxide in liquid SO₂ have been used for acid strength ranking of some superacids⁶⁵ as well. Also, a theoretical approach was introduced recently that attempts to evaluate the intrinsic acidity order by means of analyzing molecular electrostatic potential surfaces⁶⁶. Although, the solid and gas-phase structures of CB₁₁Cl₁₁H₁H have been determined⁶⁸, no direct and reasonably precise measurements of Brønsted acidity of these acids neither in solution nor in the gas phase have been performed so far. The reasons are fundamental. Direct equilibrium acidity determinations require a known reference acid within a few kcal·mol⁻¹ of the compound of interest. The effort closest to measuring the acidities of carborane acids in the gas phase was made by Meyer⁶⁷ *et al*. They quantified the gas-phase deprotonation enthalpy experimentally by ranking the H-carborane bond dissociation energy of CHB₁₁Cl₁₁H. The resulting rough estimate $\Delta H^{\circ}_{\text{acid}} = 241 \pm 29 \text{ kcal}\cdot\text{mol}^{-1}$ is considered to be the strongest experimental gas-phase acidity to date.

Nevertheless, an extensive research on finding even more weakly coordinating anions is going on^{10,11,14,15,60-63}, and one of the main trends has been the introduction of suitable strong electron-acceptor substituents that are capable of extensive negative charge delocalization from the anionic protonation center. These results with some modern concepts^{10b,69} have been considered as a route of making less basic anions. Central in this paradigm is the design of a more or less well-defined anionic protonation site whose basicity reduction is carried out with the introduction of a limited number of substituents. As the carborane cage's many vertexes pose a possibility to introduce a large number of groups, the chemical properties of already inherently very weakly basic and chemically extremely stable monocarba-*closo*-borate anions could be significantly modified by substituents of different kind. Although this feature poses a great prospect of creating application-specific counter ions in terms of solubility and reactivity⁷⁰, the introduction of the substituents can change the location of the most basic site of the anion considerably.

The analysis of electron structure and properties of the compounds under consideration was approached flowingly. The density functional theory (DFT) calculations were carried out on CB₁₁X_nH_{12-n}H (X = CN, F, Cl, CF₃, etc.; n = 0, 1, 6, 11, 12), CB₄X_nH_{5-n}H, CB₅X_nH_{6-n} (X = F, Cl or CF₃) and CB₂₁H₂₂H⁷¹ cages mostly at B3LYP/6-311+G** level with Gaussian 03 or 09 system of programs⁴⁹. Full geometry optimizations as well as vibrational analyses were

carried out for all anions and their conjugated acids. The ΔG_{acid} values (at 298 K) were calculated taking into account the zero-point energies, finite temperature (0 to 298 K) correction and the pressure-volume work term pV . The absence of imaginary frequencies ($N_{\text{imag}} = 0$) was considered as the criterion of a true minimum. In cases where the thermodynamically most stable protonated system was partially decomposed (i.e., a substituent or part of it was abstracted by proton), the next stable protonated form was used.

The parent carborane acid $\text{CB}_{11}\text{H}_{12}\text{H}$ and several of its derivatives were calculated also with the *ab initio* G3(MP2) theory. For some species, where there was a hypothetical possibility of a significant negative charge accumulation on hydrogen atoms, also the 6-311++G** basis set was used. As iodine is not parameterized in the 6-311G range of basis sets, modified SDD basis set was used for this specific atom.

When modeling, the boron clusters were viewed as the belts of vertexes: 1 : 5 : 5 : 1, 1 : 4 : 1, etc. Replacement of hydrogen atoms with substituents was done systematically belt wise, starting from the vertex antipodal to carbon, i.e. position 12, 6 or 5. For most of the carborane anions A^- several input geometries of different protonation sites were composed to determine the most basic one. The intrinsic gas-phase acidity (ΔG_{acid}) of a neutral acid HA was calculated according to the standard thermodynamic heterolysis equilibrium (1).

The interplay between the substituent effects is complex because of the strong dependence on the molecular structure that can either support or suppress them. In view of this DFT calculations were made to estimate the influence of the substituent effects on the protonation site by comparing the acidities of hypothetical monosubstituted monocarba-*closo*-dodecaborate acids in isostructural series in which a single substituent is in the position 1, 2 or 7 and the protonation site is fixed at the same position as in the case of the unsubstituted carborane acid (B_{12}). The $\Delta\Delta G_{\text{acid}}$ values for these hypothetical derivatives, where $\Delta\Delta G_{\text{acid}} = \Delta G_{\text{acid}}(\text{CB}_{11}\text{H}_{11}\text{X}_1\text{H}) - \Delta G_{\text{acid}}(\text{CB}_{11}\text{H}_{12}\text{H})$ were statistically analyzed in the framework of the multilinear correlation equation:

$$\Delta\Delta G_{\text{acid}} = a_0 + b_1\sigma_{\text{F}} + b_2\sigma_{\alpha} + b_3\sigma_{\text{R}}^-, \quad (13)$$

where σ_{F} , σ_{R}^- and σ_{α} express the corresponding substituent constants³⁴.

For the unsubstituted (parent) compound $\text{CB}_{11}\text{H}_{12}\text{H}$ the calculations at three different levels of theory (DFT B3LYP 6-311+G**, DFT B3LYP 6-311++G** and *ab initio* G3(MP2)) resulted in geometry which resembles structure where the loosely bound H_2 molecule is attached to the B_{12} atom of the $\text{CB}_{11}\text{H}_{11}^-$ cage (B_{12}H and H – H distances 1.35 and 0.82 Å, respectively) and provided the ΔG_{acid} values 266.5 (265.5 ref. 10), 265.5 and 265.2 kcal·mol⁻¹, respectively. These are in a reasonable agreement with each other. The close agreement of the results using different levels of theory was also noticed for different mono- and multi-substituent systems for which DFT 6-311+G** (or 6-311++G**) and *ab initio* correlated G3(MP2) calculations were made for comparison. In all

cases the differences between GA values calculated at those levels of theory agreed within 1–3 kcal·mol⁻¹, except for the CF₃SO₂-substituted system ($\Delta\Delta G_{\text{acid}} = 3.9$ kcal·mol⁻¹).

The results of the computational predictions of basicity of the carborane anion with a single substituent (CB₁₁H₁₁X₁) placed on the B₁₂ vertex ranked the systems according to the increasing GA values (decreasing acidity): CF₃ → Br ≈ Cl → I → F → CMe₃ ≈ CH₃ → H → CN → CF₃SO₂ → NO₂ → NH₂ → NMe₂. The most stable protonated forms of monosubstituted F, Cl, CF₃ and CH₃ derivatives have very similar geometry. Both hydrogen atoms attached to B₇ are equidistant from it and 0.831–0.834 Å from each other. The small distance between the hydrogen nuclei supports the idea of some charge transfer^{75–81} (covalent) character and could be viewed as an expression of a partial “two electron three center bond” character in the BH₂ fragment. Their conjugate acids display the increasing acidity order (kcal·mol⁻¹): CH₃ (261.2) → F (257.2) → Cl (255.3) → CF₃ (253.1) where the derivative with more electronegative fluorine substituent is less acidic than the chlorine counterpart. The proportions of the effects are system-dependent and complex, thus it is reasonable to look at their influence from a qualitative point of view in the context of average acidity increase per substituent: CH₃ → F → I → Cl ≈ Br → CF₃. In the case of the single-atom halogen derivatives the proton-affinity on the B₇ vertex decreases with the increasing size of the halogen substituent atom. But as the electronic polarizability of the substituent in this sequence increases the most favorable protonation site does not remain on the B₇ vertex, but in the case of the Br and I derivatives it shifts onto the substituent (0.7 and 2.2 kcal·mol⁻¹ lower in energy compared to B₇ vertex, respectively). Although, NO₂, CN and CF₃SO₂ have been considered extremely potent in reducing anion basicity, attractive protonation sites on sp² oxygen or sp nitrogen atoms make the mono-triflyl-, -nitro- and -cyano-derivatives less acidic than the unsubstituted compound.

Diverse protonation site geometries were observed with the derivatives of CB₁₁H₆X₆H. In the Cl-, Br- and I-substituted systems proton interacts with the substituent in the position 12 and is chelated by the substituent in the position 7. In terms of negative charge distribution, the hexafluoro carborane acid CB₁₁F₆H₆H represents a unique system. Although, the one-atom halogen substituents appear to supply the most favorable protonation site in the form of intramolecular hydrogen bridge between two substituents and H, lower polarizability makes the proton interaction with the fluorine-shield unsustainable. Preferred protonation sites with rather insignificant 0.5 kcal·mol⁻¹ differences in energies can be found near the boron cage above the facets 7 – 8 – 12 and 2 – 3 – 7. The protonation site on the B₂ vertex is only by 1 kcal·mol⁻¹ less favorable i.e., practically indistinguishable from that of the two previous sites. In the hexakis-CF₃ derivative the most favorable protonation site (which do not lead to HF elimination) is on the B₂ vertex that is probably “as near as it gets” to C₁, yielding the GA of 211.7 kcal·mol⁻¹.

Undeca-Br- and -I-, undeca- and dodeca-Cl-derivatives as well as the corresponding fluoro systems, each have several protonation sites of very close basicity, all of them with proton forming a hydrogen bridge between the substituents on the antipodal polyhedron ($\text{HCB}_{11}\text{X}_{11}\text{H}$, $\text{X} \equiv \text{F}$; Cl: $\text{F}_{12}\text{-H--F}$ 0.974/1.781 Å; $\text{Cl}_{12}\text{-H--Cl}$ 1.379/2.000 Å). Although the undeca- and dodeca-fluoro carboranes have several orders of magnitude stronger acidity compared to the rest of the corresponding halide systems, protonation of their corresponding anions is accompanied also by a greater degree of distortion that is expressed by 16.5° tilt of the F_{12} - and about 12° of the F_7 -substituent towards proton, compared with the respective angles in the anions. Thus the large number of “hard” electron-withdrawing groups attached directly to the cage vertexes weakens the bonding between the boron atoms, making the whole molecule more susceptible to distortions and fragmentation.⁶⁴ The distortions, though on a smaller scale, are also visible in Cl-, Br- and I-systems.

The $(\text{CF}_3)_{11}$ -system had the most stable protonation site (characterized by $N_{\text{imag}} = 0$) above the 7 – 8 – 12 facet of the boron cage which resembled the polysubstituted CH_3 -derivatives. The calculated basicity of the protonation site was 172.7 kcal·mol⁻¹. This would make the system by about 94 powers of ten more acidic than the parent compound. Breaking any “limits of growth” of intrinsic super-acidity by the derivatives of the carborane acids is clearly shown on Fig. 1., where these systems are compared with other strong acids of different structure and landmark acidity values.

Interesting results are displayed by the CN-derivatives. With a protonated lone pair of electrons on the nitrogen, the monosubstituted acid is by 8.5 kcal·mol⁻¹ weaker than $\text{CB}_{11}\text{H}_{12}\text{H}$. With 6, 11 and 12 substituents, the GA value decreases considerably reaching 225 kcal·mol⁻¹ making $\text{CB}_{11}(\text{CN})_{12}\text{H}$ by 4.3 kcal·mol⁻¹ more acidic, than $\text{CB}_{11}\text{Cl}_{12}\text{H}$. Introducing electron-withdrawing groups does not alter the location of the most favorable protonation site on the CN-substituted carborane derivatives, thus the acidity increase is achieved in a similar way as with the “common” Brønsted acids, by reducing the electron density of a well-defined protonation center.

The multilinear regression analysis within the isostructural series of hypothetical monosubstituted carborane acids in which a single substituent is in the position 1, 2 or 7 and the protonation site is fixed at the same position (B_{12}) according to the equation 13 the basicities of the anions of C_1 -substituted derivatives were best described by the σ_{F} and σ_{R}^- terms ($R^2 = 0.995$, $s = 0.517$ kcal·mol⁻¹). The exclusion of more-deviating points gave no improvement and there was no notable and statistically significant dependence of $\Delta\Delta\text{G}$ on polarizability effect as measured by σ_{α} . When the set of B_2 -substituted derivatives' gas-phase acidities were set against the σ_{F} and σ_{R}^- constants, the exclusion of CF_3SO_2^- and CH_3 -derivatives improved the correlation coefficient ($R^2 = 0.990$). σ_{α} constant, again, had no notable influence on the result. In the case of the series of B_7 -positioned substituents (i.e. in the α -position to the reaction

center on the B₁₂ vertex) besides the field-inductive and resonance effects also the inclusion of σ_a , polarizability constants somewhat improved the overall correlation. It is evident that the contribution of the field-inductive effect into the overall substituent effect is dominant for all three series of positions, B₇, B₂ and C₁. The share of the $b_1\sigma_F$ term for the substituents with significant σ_F values was 7–36 times larger than the corresponding $b_2\sigma_a$ and 3–16 times larger than $b_3\sigma_R$. Statistically important contribution belongs also to the resonance-effect term, whereas it is difficult to find similar proof for the polarizability effect for the positions B₂ and C₁. With some probability, the polarizability effect could be present in the case of B₇-positioned substituents, thus one could recognize a pattern similar to the correlation of gas-phase acidities of 4-substituted benzoic acids⁸², where the contributions of the field-inductive as well as resonance effect were found to be dominant.

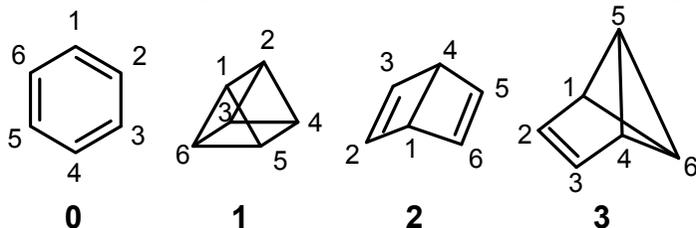
If the computational results for carborane-based systems with different sizes of the boron cage [CB₄X_nH_{5-n}H, CB₅X_nH_{6-n} (X ≡ F, Cl or CF₃) and CB₂₁H₂₂H⁷¹] are set against each other, it is possible to outline the following trends. With the increasing volume of the anion the basicity-reducing effect of larger surface area decreases. The monocarba-*closo*-dodecaborane derivatives stand on a kind of borderline where single-substituent systems still have the acidity ranking similar to the monocarba-*closo*-penta- and -hexa-boranes: F → Cl → CF₃ whereas in the case of the corresponding 22-vertex F- and Cl-derivatives the intrinsic gas-phase acidities are nearly equal (246.5 kcal·mol⁻¹).

If the corresponding increases of acidities, ΔG_3 are compared across the single-substituted carboranes of different sizes the acidity increase with CF₃ group in CB₄H₅H and CB₅H₆H systems (19.5 and 16.3 kcal·mol⁻¹, respectively) is larger than in case of the CB₁₁H₁₂H (13.4 kcal·mol⁻¹), opposite to the Cl and F substituents. The absolute acidities of the former derivatives where all hydrogen atoms are substituted by CF₃ have been predicted to reach the acidity values of 227 kcal·mol⁻¹ for CB₅(CF₃)₆H and 246 kcal·mol⁻¹ for CB₄(CF₃)₅H. For comparison, the acidities of the respective unsubstituted compounds are 305.1 and 319.6 kcal·mol⁻¹.

II. Polytrifluoromethylation vs polyfluorination of the strained isomers of Kekulé benzene and phenol

Although Kekulé benzene is by far the most stable and common isomer corresponding to the formula C₆H₆, it is not the only one. There are strained – non-aromatic – isomers that have been experimentally prepared: benzvalene⁸³, prismane⁸⁴, and Dewar benzene⁸⁵ (Scheme 2). Choosing the isomers of benzene as the cage compounds is interesting for two reasons: (a) because of steric strain 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 in some cases assume orientations significantly less interfering with each other than in the benzene ring.



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

If one compares the acidities of, e.g., phenols substituted with different patterns by CF_3 -groups or F atoms then in all cases the respective CF_3 -substituted phenols^{34, 50} are more acidic, both in the gas phase and in solution. 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. This is really the case when π -systems are involved and the resonance effect is of importance. Situation with aliphatic cage-type acids is less straightforward.^{6,86} In the systems with considerable strain in the ring elements various effects of orbital overlapping can be operational in releasing the steric strain. Nevertheless, the possibility to prepare stable valence isomers of $\text{C}_6(\text{CF}_3)_6$ has been known^{83,84,87} 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.^{87,50} There are many studies about polyfluorinated cage compounds and aromatics but the effect of poly-trifluoromethylation 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.

Table 1. The Results of Calculations of the Unsubstituted and Penta-substituted Systems and Acidifying Effects of the Substituents Relative to the Unsubstituted Compounds and Relative Stabilities Towards the Corresponding Derivatives of Kekulé Benzene (all values in $\text{kcal}\cdot\text{mol}^{-1}$).

Acid	GA	Acidifying effect ΔGA	Relative Stabilities		Comments
			Neutral G	Anion G	
H-0	393.3				
H-F ₅ -0	346.5	-46.8			
H-(CF ₃) ₅ -0	332.4	-60.9			
H-1	394.7		122.6	124.1	

Acid	Relative Stabilities				Comments
	GA	Acidifying effect Δ GA	Neutral	Anion	
			G	G	
H-F ₅ -1	335.6	-59.2	131.0	120.1	
H-(CF ₃) ₅ -1	334.9	-59.8	77.9	80.4	
1-H-2	382.2		82.8	71.7	
1-H-F ₅ -2	350.0	-32.2	70.3	73.8	
1-H-(CF ₃) ₅ -2	319.9	-62.3	41.1	28.6	
2-H-2	389.9		82.8	79.4	
2-H-F ₅ -2	354.5	-35.4	69.8	77.8	
2-H-(CF ₃) ₅ -2	336.3	-53.6	43.3	47.2	
1-H-3	393.6		80.4	80.7	
1-H-F ₅ -3	347.2	-46.4	92.8	93.6	
1-H-(CF ₃) ₅ -3	338.3	-55.4	47.7	53.6	
2-H-3	393.2		80.4	80.2	
2-H-F ₅ -3	354.3	-38.9	92.6	100.3	
2-H-(CF ₃) ₅ -3	339.8	-53.4	48.3	55.7	
5-H-3	383.5		80.4	70.6	
5-H-F ₅ -3	337.6	-45.9	91.4	82.5	
5-H-(CF ₃) ₅ -3	326.1	-57.4	52.0	45.7	
OH-0	339.2				
OH-F ₅ -0	315.7	-23.5			
OH-(CF ₃) ₅ -0	290.2	-49.0			
OH-1	350.0		124.6	135.4	
OH-F ₅ -1			132.9		Anion: C1-C5 broken
OH-(CF ₃) ₅ -1	298.0	-52.0	75.3	83.0	
1-OH-2	353.5		85.4	99.7	
1-OH-F ₅ -2			68.4		Anion: C1-C4 broken
1-OH-(CF ₃) ₅ -2			38.5		Anion: C1-C4 broken
2-OH-2	336.2		80.1	77.1	
2-OH-F ₅ -2	307.2	-29.1	64.5	55.9	
2-OH-(CF ₃) ₅ -2	288.5	-47.8	30.0	28.2	
1-OH-3	350.7		84.1	95.5	
1-OH-F ₅ -3			94.5		Anion: changed the order of C's
1-OH-(CF ₃) ₅ -3			46.0		Anion: bond broken
2-OH-3	342.9		81.6	85.3	
2-OH-F ₅ -3	317.0	-26.0	92.9	94.2	
2-OH-(CF ₃) ₅ -3	296.2	-46.7	39.4	45.3	
5-OH-3	343.1		82.8	86.7	
5-OH-F ₅ -3			92.2		Anion: Bond C5-C6 broken
5-OH-(CF ₃) ₅ -3	290.5	-52.6	49.2	49.5	

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. In the present case the relative thermodynamic stabilities of the valence isomers of Kekulé benzene were significantly lower than that of the aromatic cycle. 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-CF₃- 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. The rupture of the bonds in the anions is accompanied by a significant release of steric strain and 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 can be computed and that no bond ruptures take place. If a species with 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-(CF₃)₅-**1**, H-F₅-**1**, 1-H-(CF₃)₅-**2**, 1-H-F₅-**2**, 2-H-(CF₃)₅-**2**, 2-H-F₅-**2**, 2-OH-(CF₃)₅-**2**, 2-OH-F₅-**2**, 1-H-(CF₃)₅-**3**, 1-H-F₅-**3**, 2-H-(CF₃)₅-**3**, 2-H-F₅-**3**, 5-H-(CF₃)₅-**3**, 5-H-F₅-**3**, 2-OH-(CF₃)₅-**3** and 2-OH-F₅-**3** species. OH-(CF₃)₅-**1** was also included with certain reservations. The single-substituted anion with substituent in position 5 had a bond rupture, so the energies of the corresponding derivative with substituent in position 2 were used instead.

The unsubstituted hydrocarbons **1–3** (Table 1) are significantly less stable than benzene (**0**). The prismane is the most strained of them and is even by 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-F₅-**1** and 132.9 for 1-OH-F₅-**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

towards the respective derivatives of **0** than the respective deprotonated hydrocarbons and were accompanied by significant (>0.1 Å) C(α) – C(β) bond lengthening. The situation is quite different if 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 $\bar{\text{O}}$ -fragment and substituents. The anion of 2-OH-F₅-**2** had 21.2 kcal·mol⁻¹ better relative stabilization against $\bar{\text{O}}$ -F₅-**0** than the unsubstituted **2** against phenolate anion $\bar{\text{O}}$ -**0**.

The substituted hydrocarbons are generally slightly less stable than the corresponding hydroxy derivatives. Nevertheless, the former are less likely to decompose on deprotonation. In many cases the relative stabilities even improve considerably with deprotonation. Notable exceptions are the penta-substituted derivatives with the H at the bridgehead of a double bond where deprotonation results in ca 8 kcal·mol⁻¹ lower relative stability. If compared with fluorination, introducing CF₃-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 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. Similarly to benzene the unsubstituted hydrocarbons **1** to **3** are weak acids. Nevertheless, 1-H-**2** and 5-H-**3** are by ca 10 kcal·mol⁻¹ more acidic than benzene. Pentafluoro substitution increases the acidity⁵⁰ of benzene by 46.8 kcal·mol⁻¹. From the corresponding hydrocarbons **1**–**3** the acidifying effect of pentafluoro substitution is higher only in the case of **1**.

No substantial increase in acidity was observed if (CF₃)₅-**0** and (CF₃)₅-**1** isomers are compared, differently from the corresponding F-derivatives. Although, the acidifying effect of CF₃ is higher in nearly all isomers of **1**–**3**, the additivity surpasses that of fluorine's only in the case of 2-H-(CF₃)₅-**2**. Nevertheless, somewhat surprisingly, the substitution of **1** by five CF₃ groups leads to a similar acidity increase as in the case of five fluorine substituents. Although, CF₃ is a reasonably strong electron acceptor group due to its hyperconjugation effect ($\sigma_{\text{R}} = 0.09^{34}$), its field-inductive effect ($\sigma_{\text{F}} = 0.46^{34}$) is weaker than that of the F-substituent. As opposed to F this set of properties can make CF₃ a very efficient group in acidifying compounds with aromatic ring. At the same time in the cage-type aliphatic structures of **1** to **3** it is suboptimal due to the loss of the resonance acceptor effect.

The intrinsic gas-phase acidity of pentakis-substituted CF₃-hydrocarbons studied in this work is mostly around 330 kcal·mol⁻¹, i.e., comparable to the acidity of the open-chain hydrocarbon (CF₃)₃CH⁶. The only exception is 1-H-(CF₃)₅-**2**. This acid is only about 3 kcal·mol⁻¹ less acidic than 1-H-perfluoroadamantane⁸⁸ and is expected to be significantly outperformed only by [(CF₃)₃C]₃CH¹³ (300.4 kcal·mol⁻¹), which is estimated to be the strongest fluorinated hydrocarbon CH-acid currently known.

The analysis of the acidifying effect of the poly-CF₃-substitution with the isodesmic reactions approach for (CF₃)₅-**1** in comparison to (CF₃)₅-**0** leads to the following conclusions. Although, the gross additive interaction effect of the five CF₃ substituents in (CF₃)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 (CF₃)₅-**1**. The main reason is the saturation of the effects of the five CF₃ groups which is in (CF₃)₅-**1** by 8 kcal·mol⁻¹ more intense than in (CF₃)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 case of the 1-H-(CF₃)₅-**2**. This is in accordance with its higher acidifying effect. Among the derivatives of (CF₃)₅-**3** the lowest substituent saturation and steric repulsion effects are in case of the 2-H-system, but the gross additive interaction effect is also the lowest. This results in the lowest acidifying effect. Similar pattern is also observed with the fluorine derivatives where the acidifying effect is affected by a largest part by the gross additive interaction effect. However, the analysis of the different energy contributions of poly-substitution shows a notable linear relationship between $\Delta G_S + \Delta G_{RCX}$ and the extent of substituent additivity (Figure 2). The R²-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.

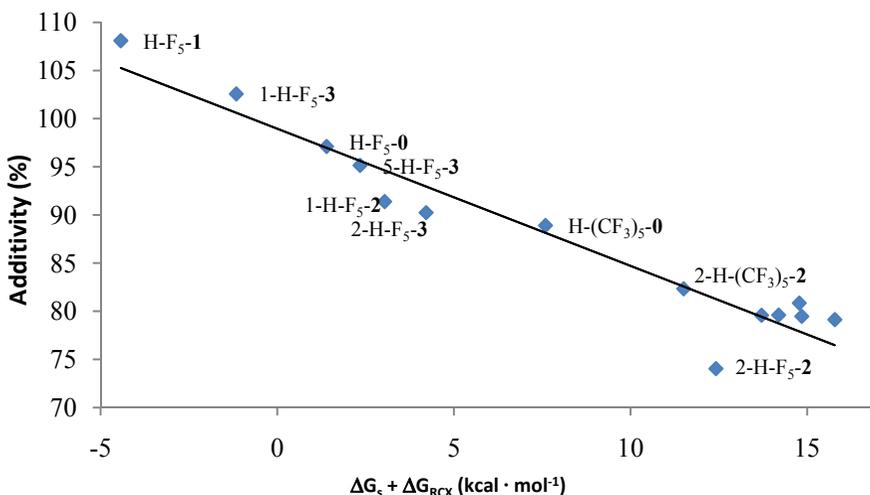


Figure 2. $\Delta G_S + \Delta G_{RCX}$ (Anion) vs Substituent Additivity. $y = -1.4247x + 98.955$, $R^2 = 0.924$.

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. 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 relatively high acidity of 5-OH-**3** is unexpected.

Substituting all five hydrogen atoms by fluorine atoms increases the acidity of phenol by 23.5 kcal·mol⁻¹. Out of all the hydroxy compounds studied in this work 2-OH-F₅-**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-adamantanol⁸⁶ ($GA_{\text{exp}} = 315.6$ kcal·mol⁻¹, $GA_{\text{DFT B3LYP 6-311+G**}} = 308.2$ kcal·mol⁻¹). The 2-OH-F₅-**2** can rival this position.

The acidifying effect of pentakis-CF₃-substitution in phenol is by more than two times larger than the effect of a similar fluorination. By their intrinsic acidities the OH-(CF₃)₅-isomers can be considered as superacids in the gas phase. The strongest of them is 2-OH-(CF₃)₅-**2** (288.5 kcal·mol⁻¹) that is 1.5 kcal·mol⁻¹ more acidic, than the OH-(CF₃)₅-**0**. Notable is the 28.2 kcal·mol⁻¹ relative stability of the 2-O⁻-(CF₃)₅-**2** that makes this anion the most stable compared with the anion of OH-(CF₃)₅-**0**.

The analysis of the acidifying effect of the poly-CF₃-substitution with isodesmic reactions for 1-OH-(CF₃)₅-**1** in comparison to 1-OH-(CF₃)₅-**0** (ref. 50) leads to the following conclusions: the gross additive interaction effect of the five CF₃ substituents in the two cases is practically the same. The acidifying effect in 1-OH-(CF₃)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-(CF₃)₅-**1** is still by 8 kcal·mol⁻¹ less acidic than 1-OH-(CF₃)₅-**0**. The ΔG_{GAIE} is in case of the 2-OH-(CF₃)₅-**2** and -**3** even slightly higher and although, the substituent saturation and repulsion are stronger in case of the **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 $\Delta G_{\text{S}} + \Delta G_{\text{RCX}}$ is with lower quality ($R^2 = 0.465$, $y = -1.0821x + 95.714$). The most strongly deviating point is 2-OH-F₅-**3**, if left out the $R^2 = 0.931$ ($y = -1.5686x + 102.59$) over six trend points. The reason for such non-linearity is again the strong p- π and p-p lone pair repulsion.

III. Acidity of Anilines: Calculations vs Experiment

The introduction of phenyl substituent into ammonia increases its intrinsic gas-phase acidity by 37.0 kcal·mol⁻¹. Further introduction of substituents into phenyl ring of aniline results in mono- or polysubstituted anilines whose experimentally measured or predicted gas-phase acidities span^{6,89,90} almost 60 kcal·mol⁻¹ (44 powers of ten): from 359.1 kcal·mol⁻¹ down to almost as acidic as a milestone 300 kcal·mol⁻¹. Some aniline derivatives have been predicted to reach even much stronger gas-phase acidities.⁵⁰ Several formal

models have been suggested and used in the literature³⁴ to take into account the substituent effects in aromatic as well as in aliphatic reaction series and other processes.

In this work quantum chemical calculations have been used to predict gas-phase acidities of substituted anilines. Based on previous experience^{6,44,50,51,90}, the Density Functional Theory approach using B3LYP hybrid functional was used. Full geometry optimization and vibrational analyses were performed at 6-311+G** level with the Gaussian 09 system of programs⁴⁹ and acidities calculated as described above (eq. 1). COSMO-RS (Conductor-like Screening Model for Real Solvents)⁵⁷ method was used to predict the acidities in DMSO. Isodesmic reactions scheme (eq. 2 - 5) was used for the separation of the meta, para, or ortho substituents effects into the components connected to the neutral aromatic amine ArNH₂ and its anionic form, ArNH⁻, respectively.

Table 2. The Results of Calculation of Gas-Phase Acidities (GA, kcal·mol⁻¹) of Substituted Anilines at DFT B3LYP/6-311+G** Level.

Substituents	4-Substituted GA	3-Substituted GA	2-Substituted GA
H	359.4	359.4	359.4
F	356.7	353.4	354.6
Cl	352.9	351.4	352.1
Br	351.7	350.4	351.1
CF ₃	345.0	348.7	347.1
C(CF ₃) ₃	343.4	346.7	342.2
SO ₂ CF ₃	331.6	339.5	336.1
CN	340.5	345.8	342.9
CH ₃	360.9	359.6	358.3
SO ₂ CH ₃	340.2	344.9	343.7
COCH ₃	342.9	351.7	350.9
C(CH ₃) ₃	359.0	358.9	353.7
CHO	340.4	349.5	348.1
NO ₂	333.3	344.1	338.5
SF ₅	336.2	339.8	338.4
NH ₂	362.9	360.6	357.1
SO ₂ F	331.4	339.4	335.6
SOF ₃	327.6	337.3	333.9
N(CH ₃) ₂	359.8	361.1	359.8
NO	333.1	346.8	339.1
S(=O)(=NSO ₂ CF ₃)CF ₃	322.5	331.4	

The quality of the computational gas-phase acidity data can best be judged from the root mean square deviation (rmsd) of the differences between the experimental and computational values. The rmsd of all computed ΔG_{acid} values for which experimental data are available for comparison is 2.61 kcal·mol⁻¹ (n=29; o-, m- and p-anilines where X = H are considered as one). The rmsd values are 0.84 (n=7), 2.81 (n=11) and 2.85 (n=13) for the families of ortho-, meta- and

para-substituted anilines, respectively. However, closer look at the families of substituted anilines reveals that there are only two markedly deviating compounds: 4-S(=O)(=NSO₂CF₃)CF₃ and 3-SF₅ aniline. Although, both of the systems remained intact in DFT calculations in case of the SF₅ group there is a tendency towards ruptures by ejecting HF that can explain the difference between the experimental and predicted value. For the highly polar supersubstituent S(=O)(=NSO₂CF₃)CF₃ similar complications with NSO₂CF₃-group are possible. Eliminating 4-S(=O)(=NSO₂CF₃)CF₃ and 3-SF₅ aniline leads to the rmsd 1.05 kcal·mol⁻¹ (n = 27). This very good agreement validates the use of the computational acidities for the analysis of substituent effects in mono-substituted anilines.

In neutral anilines the interaction energies ΔG_1 are small and their absolute values remain between -9 kcal·mol⁻¹ and 6 kcal·mol⁻¹ for 2-substituted, -2.4 kcal·mol⁻¹ and 4.1 kcal·mol⁻¹ for 4-substituted and around 1 kcal·mol⁻¹ for 3-substituted derivatives.

In anilide anions the effects are dramatically stronger with all positions. In 3-substituted anilides ΔG_2 values span above to 15 kcal·mol⁻¹ for a number of substituents. In 4-substituted anilides the effects are even stronger reaching 20–30 kcal·mol⁻¹ for the most powerful -I /-R groups. The largest effect 42.0 kcal·mol⁻¹ is displayed by the 4-CF₃S(O)(=NSO₂CF₃) supersubstituent followed by the computationally estimated effect of 35.3 kcal·mol⁻¹ for a relatively unknown⁹¹ SOF₃ group. If compared with meta- and para-positions ΔG_2 values with systems substituted in position 2 tend to be in the middle range. Thus, in most cases the best stabilization for the anions comes from the substituents in position 4. It should be pointed out that the interaction energies are dependent, both, on the combinations of substituent resonance and field-inductive effects and their positions in the ring. To estimate the correlation of ΔG_1 , ΔG_2 , ΔG_{acid} , etc. of different mono-substituent aniline derivatives with the sigma constants³⁴ the multilinear regression analysis according to the equation (14) could be used.

$$\Delta G = \Delta G^0 + \rho_F \sigma_F + \rho_R \sigma_R + \rho_\alpha \sigma_\alpha \quad (14)$$

According to the calculation scheme (14) the best correlation between interaction energies and substituent σ -constants in position 4 is obtained for resonance effect with small contribution from field-inductive effect ($R^2 = 0.950$). In case of the respective anilide ions the R^2 value is slightly lower ($R^2 = 0.926$) and the contribution of the field-inductive effect is somewhat higher. For 3-substituted neutral anilines the correlation coefficients are lower, but for the anilides (anions) the results show the highest correlation ($R^2 = 0.962$) from the sets of ΔG_1 and ΔG_2 R^2 -coefficients where all involved substituents were present. In this case the σ_F constant is nearly the only statistically important contributor ($\Delta G_2 = \Delta G^0_2 + \rho_F \cdot \sigma_F$, $R^2 = 0.900$). The largest deviator is the SF₅ substituent.

In case of the 2-substituted anilines no significant correlation between ΔG_1 and σ -constants was detected. At the same time the ΔG_2 energy had a correlation coefficient according to the multilinear relationship $\Delta G_2 = \Delta G_2^0 + \rho_F \cdot \sigma_F + \rho_R \cdot \sigma_R^-$ around 0.85. The most deviating points were NO, C(CF₃)₃, NMe₂, NH₂ and NO₂ that tend to have stronger lone pair repulsion between the substituent and reaction center. In case of the ΔG_1 the differences in energies are relatively small and the scale of the absolute values so contracted that the possibility to find any linear relationships is hindered.

The energetic effects of the substituents in neutral anilines and anilide ions are quantitatively summed up by ΔG_3 that is directly connected with the acidifying effect and thus the gas-phase acidity. The predicted and experimental absolute values of ΔG_3 of the whole series are in excellent linear correlation ($R^2 = 0.991$, $s = 0.77$ kcal·mol⁻¹, 3-SF₅ and 4-CF₃S(O)(=NSO₂CF₃) excluded). Similarly good results are obtained when predicted ΔG_3 and ΔG_2 are set against each other ($R^2 = 0.994$, $s = 0.61$ kcal·mol⁻¹). However, ΔG_3 vs. ΔG_1 results in rather modest $R^2 = 0.800$ ($s = 3.6$ kcal·mol⁻¹). This gives another proof that the stabilization of the anion by the substituent largely determines the acidity of anilines and the neutral forms have relatively small and inconsistent effect on the gas-phase acidities of aniline derivatives.

Aniline is a weak acid in the gas phase: $\Delta G_{\text{acid}} = 359.1$ kcal·mol⁻¹. Because the acidity center in anilines is directly conjugated to the aromatic ring their acidity is quite sensitive to substitution: the acidities of anilines substituted with conventional substituents are in the range of 30 kcal·mol⁻¹ reaching down to the value of 331.6 kcal·mol⁻¹ for 4-SO₂CF₃ aniline. The intrinsic gas-phase acidity of the exceptional 4-S(=O)(=NSO₂CF₃)CF₃-substituted aniline has been predicted to be 322.5 kcal·mol⁻¹ (Table 2) from which the acidity of 4-SOF₃ system remains only 5 kcal·mol⁻¹ weaker demonstrating the potential of creating super-strong organic acids by means of stronger charge-acceptor groups or multi-substituent⁵⁰ systems. The gas-phase acidities of polysubstituted anilines have been predicted to test 300 kcal·mol⁻¹ level (i.e. 300.4 kcal·mol⁻¹ for (NO₂)₅C₆NH₂, DFT B3LYP 6-311+G**).

Interpretation of the intrinsic gas-phase acidifying effects, ΔG_3 in terms of substituent constants was carried out via regression analysis according to the calculation scheme (14). The linear relationships are reasonably good for meta- and para-positions. The largest deviators among para-anilines were 4-NO- and 4-NMe₂-aniline and among meta-anilines the 3-SF₅-aniline. Removing those three compounds brings the R^2 values of the regression analysis for all positions above 0.94 and for position 3-substituted anilines even up to the excellent 0.99. Again, the most important contributors are σ_F and σ_R^- . Inclusion of the polarizability constant does not improve the correlation in most cases. However, the acidity of 2-substituted anilines was not so well-described by the polar substituent constants.

The pK_a values of most singly substituted anilines lie in the range of 25 to 30 in DMSO. In the lower end there is p-aniline with super-substituent

$\text{S(=O)(=NSO}_2\text{CF}_3\text{)CF}_3$ and the weakest measured value is of 3- CH_3 aniline origin (31.0). When correlating experimental $\text{p}K_{\text{a}}$ values with the calculated gas-phase acidities according to equation $\text{p}K_{\text{a}}^{\text{obs}} = a + b\Delta G_{\text{calc}}$, the correlation coefficient $R^2 = 0.875$ is obtained ($n = 30$, $\text{rmsd} = 3.18 \text{ kcal}\cdot\text{mol}^{-1}$). As from the linear regression analysis of $\text{p}K_{\text{a}}$ values obtained experimentally vs. COSMO-RS correlation coefficient $R^2 = 0.980$ was obtained ($n = 26$, $\text{rmsd} = 2.49 \text{ kcal}\cdot\text{mol}^{-1}$). Therefore, COSMO-RS could be considered as reasonably good in predicting $\text{p}K_{\text{a}}$ values of missing compounds in series for which experimental data are available. However, the absolute $\text{p}K_{\text{a}}$ values found by COSMO-RS deviated systematically from the respective experimentally measured values.

SUMMARY

The goal of the present work was to investigate computationally the electronic structure and superacidic properties of the mono- and poly-substituted derivatives of different classes of Brønsted acids. The work has three parts each dissecting one class of basic chemical structures: carboranes, Kekulé benzene's valence isomers (prismane, benzvalene, Dewar benzene), and anilines.

The first part, focusing on carborane acids, considers four different cage-types of *closo*-monocarboranes based on: $\text{CB}_4\text{H}_5\text{H}$, $\text{CB}_5\text{H}_6\text{H}$, $\text{CB}_{11}\text{H}_{12}\text{H}$ and $\text{CB}_{21}\text{H}_{22}\text{H}$. The intrinsic gas-phase acidities of the 42 derivatives of these systems calculated at DFT B3LYP 6-311+G** level of theory span from $319.6 \text{ kcal}\cdot\text{mol}^{-1}$ down to less than the groundbreaking $200 \text{ kcal}\cdot\text{mol}^{-1}$ thus pushing the "limits of growth" of acidity of neutral acids. The most acidic of them, $\text{HCB}_{11}(\text{CF}_3)_{11}\text{H}$ is predicted to be by more than 94 powers of ten stronger acid than the "classic" H_2SO_4 .

For each of them, both, neutral and anionic forms with several protonation sites were calculated to find the most basic site in the conjugate base. Some $\text{CB}_{11}\text{H}_{12}\text{H}$ derivatives with 1 and 6 substituents were also investigated with *ab initio* G3(MP2) method for the validation of the results.

The substituent effects of dodecaborate derivatives were analyzed in terms of a multilinear regression analysis against the substituent sigma constants (σ_{F} , σ_{R} , σ_{a}) by calculating the gas-phase acidities of the hypothetical derivatives with varying position of substituent over the vertexes of the carborane cage and considering the effect of substituent's position on the change of acidity.

The second part disserts the effects of F and CF_3 substituents on the stability and acidity of the derivatives of the valence isomers of Kekulé benzene and phenol where the number of the non-hydrogen substituents was five or none and the acidities of the reaction sites on all vertexes were calculated. The acidities of benzene and phenol valence isomer derivatives are in the range between $394.7 \text{ kcal}\cdot\text{mol}^{-1}$ and $288.5 \text{ kcal}\cdot\text{mol}^{-1}$. With the help of NBO and isodesmic reactions analysis method the substituent's effects on the electronic structure, acidity and stability were described. In the course of this work some of the strongest organic CH and OH acids were calculated.

In the third part the main attention is on the acidities of monosubstituted anilines. The intrinsic gas-phase acidities of ca. 60 monosubstituted aniline derivatives were calculated (with acidity span of almost $50 \text{ kcal}\cdot\text{mol}^{-1}$) and found to be in excellent correlation with the experimental results. Again, the effects of the substituents on acidities of the derivatives were under observation and for the first time using homodesmotic isodesmic reactions approach the substituent effects were separately analyzed in the respective anionic and neutral forms. Also the results of COSMO-RS method for calculating $\text{p}K_{\text{a}}$ values in DMSO were considered and found to be useful in predicting $\text{p}K_{\text{a}}$ trends of aniline acids.

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SUMMARY IN ESTONIAN

Tugevate ja ülitugevate Brønsted'i hapete happelisused, „kasvupiiride” avardamine: arvutuskeemiline uurimus

Käesoleva uurimistöö eesmärgiks oli arvutuslikult uurida mono- ja polüasendatud erinevate Brønsted'i hapete derivaatide happelisi ja superhappelisi omadusi ning elektronstruktuuri. Tööle läheneti kolmes jaos, millest iga osa käsitles ühte põhilist keemilist alusstruktuuri: karboraanid, Kekulé benseeni valentsisomeerid (prismaan, bensvaleen, dewari benseen) ning aniliinid.

Esimene osa tööst, mis keskendub karboraanhapetele, käsitleb nelja erinevat *closo*-karboraani struktuuri tüüpi, mis baseeruvad ühenditel: $\text{CB}_4\text{H}_5\text{H}$, $\text{CB}_5\text{H}_6\text{H}$, $\text{CB}_{11}\text{H}_{12}\text{H}$ and $\text{CB}_{21}\text{H}_{22}\text{H}$. Neile derivaatidele omased gaasifaasilised happelisused, mis arvatati DFT B3LYP 6-311+G** tasemel algavad väärtusest $319.6 \text{ kcal}\cdot\text{mol}^{-1}$ ning ulatuvad allapoole happelisuse kasvu “maagilist” piiri $200 \text{ kcal}\cdot\text{mol}^{-1}$ ja hõlmavad 42 erinevat ühendit. Tugevaim gaasifaasiline happelisuus kuulub süsteemile $\text{HCB}_{11}(\text{CF}_3)_{11}\text{H}$, mis on ennustatud 94 suurusjärku happelisemaks kui väävelhape.

Et leida happelisused arvatati iga ühendi kohta neutraalse ja anioonse vormi energiad. Süsteemi happelisuseks loetava kõige stabiilsema protoneeritud vormi leidmiseks prooviti iga derivaadi jaoks läbi läbi mitmed võimalikud geomeetriad. Mõnede ühendite happelisused arvatati kontrolliks ka *ab initio* G3(MP2) meetodiga.

Dodekaboraatderivaatide asendusrühmade efekte analüüsiti multilineaarse regressiooni analüüsi meetodiga sigma konstantide suhtes. Selleks arvatati happelisused hüpoteetilistele süsteemidele, kus reaktsioonitsenter jäeti paigale ja varieeriti selle suhtes asendusrühma asekohta. Saadud happelisuste muutusi võrreldi vastavate σ -konstantidega.

Töö teises osas vaadeldi F ja CF_3 asendajate mõju Kekulé benseeni ja fenooli valentsisomeeride stabiilsusele ja happelisusele. Uuriti isomeeride asendamata ja viie asendajaga derivaate ning nende happelisusi igale süsiniktiple vastavas reaktsiooni tsentris. Käesolevate benseeni ja fenooli valentsisomeeride derivaatide happelisused asuvad vahemikus $394.7 \text{ kcal}\cdot\text{mol}^{-1}$ ja $288.5 \text{ kcal}\cdot\text{mol}^{-1}$. Arvutuskeemilise NBO ja isodesmiliste reaktsioonide analüüsi meetodite abil kirjeldati asendusrühmade efekte süsteemide elektronstruktuurile, happelisusele ja stabiilsusele. Töö käigus disainiti mõned tugevamatest orgaanilistest CH ja OH hapetest.

Kolmandas osas oli peatähelepanu monoasendatud aniliinide happelisustel. Arvutusi sooritati kokku ca. 60 derivaadiga. Monoasendatud aniliinide gaasifaasiliste happelisuste skaala ulatuseks saadi peaaegu $50 \text{ kcal}\cdot\text{mol}^{-1}$ ning leiti, et arvutustulemused on väga heas kooskõlas eksperimendiga. Jällegi uuriti asendusrühmade efektide mõju happelisustele ning esimest korda analüüsiti homodesmiliste isodesmiliste reaktsioonide abil asendajate mõju vastavatele neutraalsetele ja anioonsetele vormidele. Samuti uuriti mainitud ühendite $\text{p}K_a$ väärtusi DMSO's kasutades COSMO-RS programmide süsteemi. Leiti, et COSMO-RS võimaldab rahuldavalt ennustada aniliinide happelisuste trende DMSO keskkonnas.

ACKNOWLEDGMENTS

Foremost, I would like to express my deepest gratitude to my supervisor Professor Ilmar A. Koppel for his patience, faith, professional guidance and persistence in turning a wilder-student into a beginner scientist.

I deeply appreciate my supervisor Professor Ivo Leito for his professional and always diplomatically presented advice. Also, one should not underestimate the fact that he was the one who introduced me the first basics about computational chemistry.

I would like to thank my supervisor Senior Research Fellow Dr. Ivar Koppel and Professor Peeter Burk for helping me out with computational issues when ever I had questions.

I am very grateful to the co-authors and co-students Dr. Agnes Kütt and Karl Kaupmees for their help with a paper and being good colleagues through all these years of study.

I am indebted to my supervisor Mr. Tarmo Laht at AS A. Le Coq for accepting and supporting my studies all since 2002 when I became employed as a B.Sc. student. Similarly important have been the support, motivation and example of my parents, Maie and Tõnu Lipping as well as my brother Hardi, sister Kadri, friendly neighbours Oliver, Katrin, Hando and friend Dr. Tarmo Tamm.

Finally, I cannot express enough how thankful I am to my family: Mari and little Laura Lotta for giving me energy and support and giving up the time I spent for the studies.

The financial support for this work came from the Estonian Science Foundation Grants Nos 6701, 8162, 7374.

PUBLICATIONS

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