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How weak an acid can be? Variations of H-bond and/or van der Waals Interaction of Weak Acids --Manuscript Draft--

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How weak an acid can be? Variations of H-bond and/or *van der Waals* Interaction of Weak Acids

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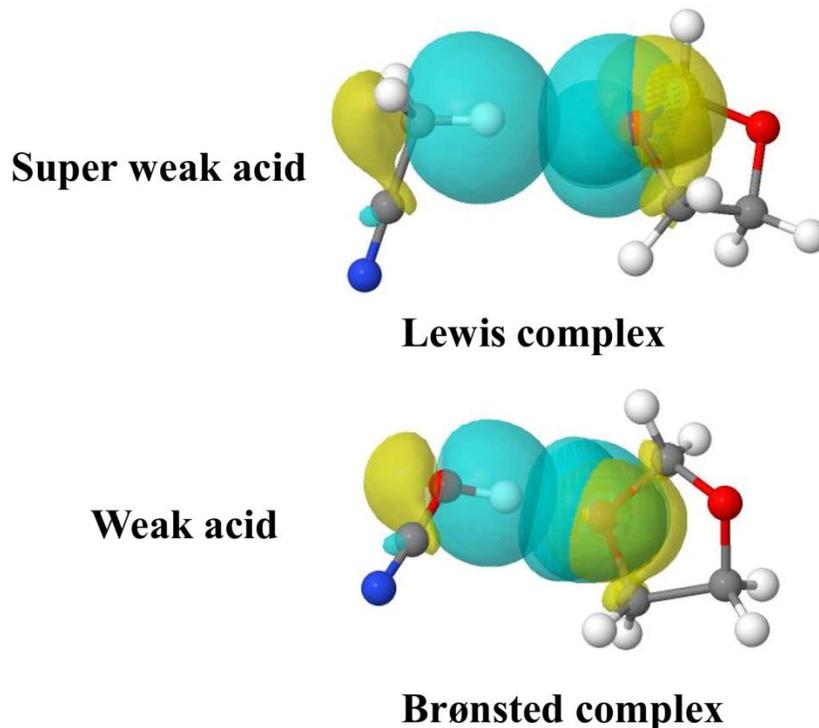
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Abstract

Complex formation ability and stability of both weak and super-weak acids was studied by mean of *in silico* determined thermodynamic data of the complexes. While weak acids act like Brønsted acids forming hydrogen bond type Brønsted complexes, super-weak acids form Lewis complexes *via* van der Waals interaction. Unlike in the former type, upon complexation, C-H distances changes insignificantly, yet the complex formation is energy driven in the terms of zero-point corrected Energies, $\Delta E_{zp} < 0$ kcal.mol⁻¹, which supports the Lewis complex formation, with the exception of CH₄, an extremely “weak acid”.

Graphical abstract



Selected NBOs of the complexes formed between NC-CH₂-H (Lewis acid) with dioxolane as well as NC-O-H (Brønsted acid) and dioxolane.

Introduction

From a historic point of view in 19th century the interest of chemistry focused on understanding the formation of chemical bond, the range of this dissociation energy falls in 20-100 kcalmol⁻¹ bond, covering a bond distance (d) between 0.9 -1.5 Å. The concept of the hydrogen bond was first mentioned by T.F. Winmill, and T.S. Moore in 1912 [1]. By the middle the 20th century, the discovery and atomic level description of natural products and bio-macromolecules (*e.g.* DNA, proteins) the significance of hydrogen bond formation emerged due to the fundamental role in the living systems [2]. Based on the X-ray diffraction (Photo 51) of DNA recorded by Rosaline Franklin, discovered not only that the DNA double helix hold together by H-bonds (and π - π stacking), but also that both replication, transcription and translation are driven by correct H-bond pairing mechanisms [3]. The wide range of criteria of H-bond properties as proton donors, acceptors, energies, distances are clearly summarized in work of Arunan et al. [4]. At the end of his report he gives a short definition of hydrogen bond: “*The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation*”. Depending on several factors and on the molecular environment H-bond energy falls in the range of 1-15 kcal.mol⁻¹ covering X-H...Y distance between 1.5-3 Å [5]. The suggestion of C-H...O hydrogen bonding has been first proposed by Glasstone as a logical extension of the X-H...Y concept [6]. Later Desiraju et al has defined quantitative criteria of the C-H..O hydrogen bond, as bond distance $D_{(C..O)} < 3.80\text{Å}$, angle $\theta_{(C-H..O)} 100^\circ < \theta < 180^\circ$ and bond energy $E \leq 4 \text{ kcal mol}^{-1}$ [5].

An extreme hydrogen bonded complex was shown between H₂O and CH₄, where the H₂O is the proton donor and CH₄ is the proton acceptor [7]. This can be considered as one case of CH₅⁺ formation. This interesting species of carbocations was earlier established by George Olah proving that even methane is suitable to be protonated as a base. Extending this concept to various protonated alkanes and explaining their formation, he founded the chemistry of superacids playing a significant role in boosting organic chemistry of the 20th century [8].

Recently, the focus of attraction has been extended to the area of super-weak acids and their complexing ability. Interaction concluding to C-H bond breakage was first considered significant in reactions such as the one described for example by *Stanislao Cannizzaron, namely Cannizzaro reaction*. However, this kind of C-H bond dissociation requests a strong base (beside additional structural prerequisites). By now the arsenal of well characterized organic reactions involving the dissociation of selected C-H covalent bonds fertilized many areas of modern synthetic organic chemistry [9-14]. Numerous X-ray structures have clearly indicated the existence of C-H...O interactions (**Figure 1**) even for cases where the acceptor O-atom is not a strong base [15]. Although such interactions are very weak, the sum of many of such contacts could lead to substantial stabilizations, holding even an entire crystal structure together. The magnitude of C-H...O interactions strongly depends on the actual molecular interaction type, geometrical properties, etc..

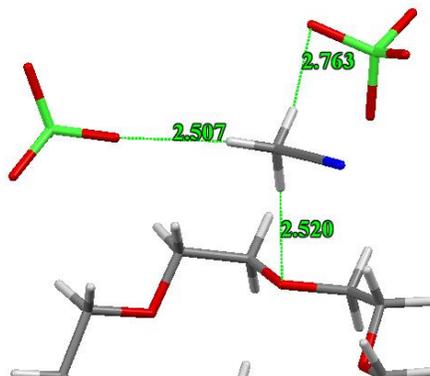


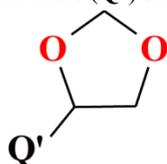
Figure 1. Three C-H...O weak bonds, formed between -CH₃ of acetonitrile and 4,4'-Oxydianilinium bis(1,4,7,10,13,16-hexaoxacyclooctadecane) diperchlorate (FECAW) hold the crystal structure together [15]. (Note that additional weak interactions *e.g.* C-H...N are present.)

Even in this example (**Figure 1**) the C-H bond in acetonitrile does not behave in a protonic fashion but, the whole group is involved in a van der Waals complex formation, making in fact a **Lewis complex**. Consequently, the -CH₃ group in acetonitrile acts as a super-weak, or rather a Lewis acid and not as a Brønsted one.

The electron withdrawing group(s) in the vicinity of the C-H...O interaction, might enhance the partial positive charge on the hydrogen of the proton donor, while electron donor groups increase the partial negative charge on the proton acceptor side of the complex.

Scope

The aim of the presented study is to better understand the qualitative background of different behavior of the C-H and O-H proton sources (in addition to the well-known difference in their electronegativities: $\chi_{(C)}=2.55$, $\chi_{(O)}=3.44$ [16]). The systematic change of substituents (**Q**) of the proton donors (**Q-CH₂-H** or **Q-O-H**) is a plausible approach to discover the main differences between these proton sources. In this study in the line of the *Hammett-Taft* concept, for the structure – reactivity relationship we used the σ_i values of the substituents to characterize their acidity or basicity [17-21]. For proton acceptors the oxygen of the substituted (**Q'**) 1,3-dioxolane was chosen as the proper partner for both **Q-CH₂-H** and **Q-O-H** proton-donors (**Figure 2**). Caused by different substituents (**Q'**) the oxygen of the 1,3-dioxolane ring has different basicity.



C1: Q' = CH₃, C2: Q' = H, C3: Q' = F

Figure 2. Schematic molecular structures of substituted (**Q'**) 1,3-dioxolanes.

For proton carrier two different types of molecule were selected, namely both a C-H and O-H type donor, however the same type of substituents (**Q**) were attached to central carbon atoms and oxygen in both cases. Substituents (**Q**) selected for this study of increasing electron donating and withdrawing effects are characterized here by their σ_i values [22-24]. The two species of proton carriers act indeed as two different types of acids (**Figure 3**).

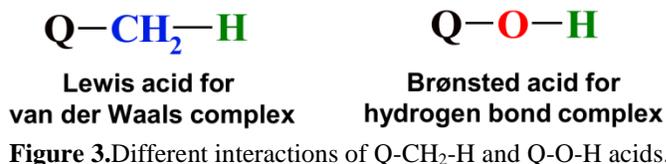


Figure 3. Different interactions of Q-CH₂-H and Q-O-H acids.

Methods

It has been shown that the acidity is predictable by using G3 computational scheme [25]. Vianello and co-workers have used the 6-311+G(2d,p) basis set to calculate the pK_a values of C-H acids for nitrile derivatives in gas phase and in DMSO [27]. All calculations were carried out using the Gaussian 09b01 software using Density Functional Theory (DFT) method with B3LYP functional and standard 6-311++G(d,p) basis set [26]. In some cases the proton donor moiety can interact with the substituent side to form a second (unwanted) interaction. To eliminate this effect, suitable redundant coordinates were chosen to restrict the reaction path. No imaginary frequencies were observed for the fully optimized (closed shell) geometries, except molecules calculated with redundant coordinates. To eliminate the basis set superposition error, Counterpoise Corrected calculations were carried out on all complexes while determining their thermodynamic parameters, namely “ E_{zp} , H and G ” (eqs. 1-3). For the above reasons the herein applied level of theory and associated computational method can be used with confidence.

Gas-phase reactions of the H-bonding thermodynamic parameters were calculated from the following equations:

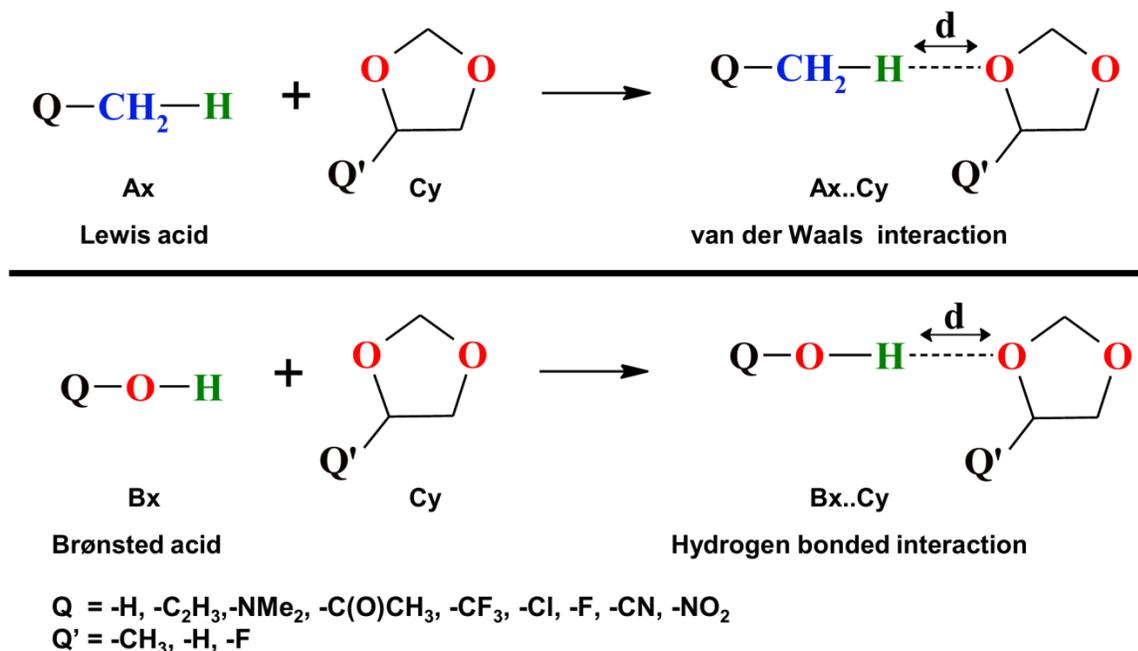
$$\Delta E = E_{zp(\text{Complex})} - [E_{zp(\text{Ax or Bx})} + E_{zp(\text{Cy})}] \quad (1)$$

$$\Delta H = H_{(\text{Complex})} - [H_{(\text{Ax or Bx})} + H_{(\text{Cy})}] \quad (2)$$

$$\Delta G = G_{(\text{Complex})} - [G_{(\text{Ax or Bx})} + G_{(\text{Cy})}] \quad (3)$$

Results and discussion

In the present *in silico* structure elucidation the stability values of the complexes (Ax..Cy and Bx..Cy) of proton carrier (Ax and Bx) and proton acceptor (Cy) molecules (**Scheme 1**) were calculated by suitable QM methods.

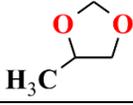
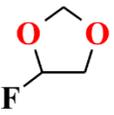


Scheme1: Complex formations between selected C-H and O-H acids with 1,3-dioxolane derivatives as suitable base.

The σ_i values of the used substituents (**Q** and **Q'**) are covering a large range of inductive effects from $\sigma_{i(\text{CH}_3)} = -0,01$ to $\sigma_{i(\text{N}_2\text{O})} = 0.67$ [24]. It has to be added that substituents -C(O)CH₃, -CN and -NO₂ exhibit also resonance effect, σ_r , but these values are significantly smaller than their σ_i values. These proton donors and acceptors are summarized in **Table 1**, together with the σ_i values of the substituents. The derived thermodynamic parameters from equation 1-3 are summarized in **Table 2**.

Table 1.Characteristic σ_i values of various proton carriers (**Ax** and **Bx**) and acceptors (**Cy**) (Scheme 1)

Proton carriers (Ax or Bx)				
Ax	CH - acids	Q (σ_i)	OH - acids	Bx
A1	H-CH ₂ -H	H (0)	H-O-H	B1
A2	H ₂ C=CH-CH ₂ -H	H ₂ C=CH (0.11)	H ₂ C=CH-O-H	B2
A3	Me ₂ N-CH ₂ -H	NMe ₂ (0.17)	Me ₂ N-O-H	B3
A4	H ₃ C-C(O)-CH ₂ -H	H ₃ C-C(O) (0.3)	H ₃ C-C(O)-O-H	B4
A5	F ₃ C-CH ₂ -H	CF ₃ (0.4)	F ₃ C-O-H	B5
A6	Cl-CH ₂ -H	Cl (0.47)	Cl-O-H	B6
A7	F-CH ₂ -H	F (0.54)	F-O-H	B7
A8	N≡C-CH ₂ -H	N≡C (0.57)	N≡C-O-H	B8
A9	O ₂ N -CH ₂ -H	N ₂ O (0.67)	O ₂ N -O-H	B9

Proton acceptors (Cy)		
Cy	1,3-dioxolane	Q' σ_i
C1		CH ₃ (-0.01)
C2		H (0)
C3		F (0.54)

The systematic variation of the above donors and acceptors (**Table 1**) makes possible the formation of 54 different complexes in total. The associated thermodynamic functions were determined from computed E_{zp} , H and G values. All changes in ΔE_{zp} , ΔH and ΔG values associated with the complex formation are summarized in **Table 2**. It has to be emphasized that the A1..C1, A1..C2 and A1..C3 complexes have positive of ΔE_{zp} energies which means they are insufficiently stable, consequently, their values were not considered when the thermodynamic function was formulated (values highlighted red in **Table 2**).

In the case of A4..Cy, A9..Cy, B4..Cy and B9..Cy complexes an extra O..H-C interaction type could have been obtained during complex optimization, where the O-atom of the substituents of the proton carrier might interact with a C-H of the 1,3-dioxolane ring. Redundant coordinates were used to eliminate these secondary (unwanted) interaction type. Furthermore, in the case of the B9..Cy complex even this approach failed and thus, the associated values have to be considered with caution. Due to the highly similar σ_i values of the substituents of C1 and C2, the formed Ax..C1, Bx..C1, Ax..C2 and Bx..C2 complexes are also similar. These phenomena are easily explained by the nature of their σ_i values: $\sigma_{i(H)} = 0$ and $\sigma_{i(CH_3)} = -0.01$, due to the similar inductive effects of -H and -CH₃ groups.

Table 2. Computed relative Stability* (Energy (ΔE_{zp}), Enthalpy (ΔH), and Gibbs free Energy (ΔG)) of the different 54 Ax..Cy and/or Bx..Cy complexes

codes		$\Delta E_{zp}(\text{kcal mol}^{-1})$			$\Delta H(\text{kcal mol}^{-1})$			$\Delta G(\text{kcal mol}^{-1})$		
		Cy								
		C1	C2	C3	C1	C2	C3	C1	C2	C3
Ax	A1	0.163	0.257	0.178	0.852	1.029	0.971	4.233	3.779	3.377
	A2	-0.060	-0.100	-0.063	0.820	0.275	0.319	5.981	6.940	6.992
	A3	-0.210	-0.045	-0.081	0.171	0.284	-0.275	6.877	7.819	9.112
	A4	-0.705	-0.531	-0.638	-0.497	0.234	0.198	7.958	6.273	6.710
	A5	-1.322	-1.182	-0.940	-1.056	-0.936	-0.603	7.385	8.097	7.435
	A6	-0.949	-0.817	-0.727	-0.740	-0.639	-0.457	6.376	7.578	6.451
	A7	-0.623	-0.701	-0.402	-0.402	-0.468	0.465	6.241	6.113	4.265
	A8	-1.683	-1.317	-1.007	-1.543	-1.178	-0.198	6.211	7.276	5.021
	A9	-1.879	-2.107	-1.404	-1.775	-1.387	-1.194	7.349	5.112	6.842
Bx	B1	-3.283	-3.134	-1.743	-3.406	-3.264	-2.200	4.036	4.251	5.921
	B2	-5.198	-5.279	-3.374	-4.842	-4.898	-2.843	3.195	3.226	4.064
	B3	-3.734	-3.396	-2.436	-3.341	-3.960	-2.313	5.413	7.472	6.006
	B4	-6.112	-6.046	-4.840	-5.614	-5.565	-4.251	2.632	3.129	3.794
	B5	-8.370	-8.583	-5.993	-7.984	-8.206	-5.495	-0.093	0.575	2.614
	B6	-5.872	-6.026	-3.955	-5.718	-5.863	-3.672	2.300	2.178	3.735
	B7	-6.610	-6.710	-4.418	-7.073	-7.162	-4.679	2.920	2.732	4.133
	B8	-10.194	-10.466	-7.175	-10.211	-11.025	-7.576	-1.595	-0.493	2.403
	B9	-8.199	-8.364	-5.969	-7.808	-7.992	-5.472	0.683	0.892	2.985

*Stabilization energies

The relationship of the different stability terms (ΔE_{zp} , ΔH and ΔG) of **Table 2** are graphically presented in **Figure 4**.

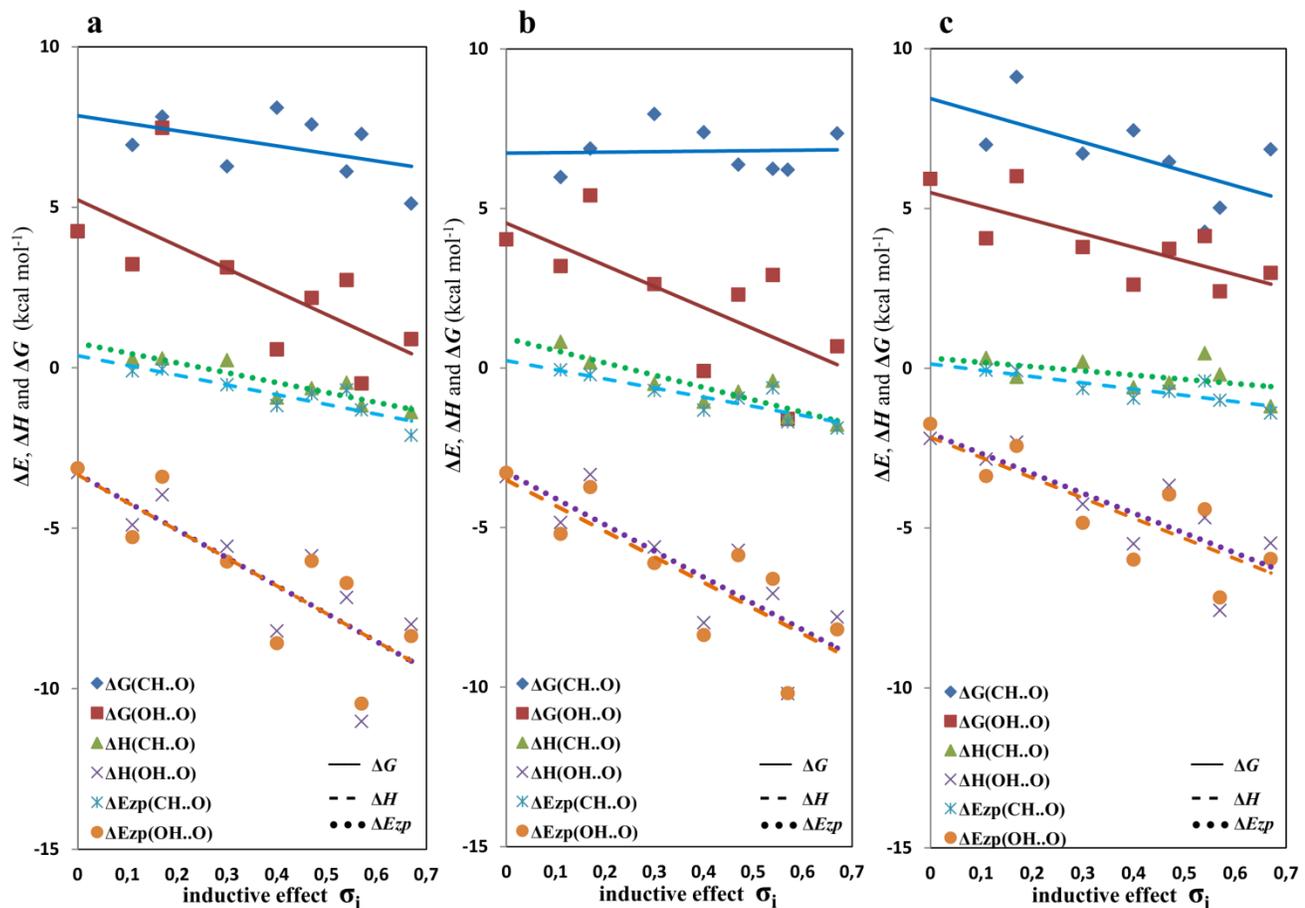


Figure 4. Variations of the relative stabilities (ΔE_{zp} , ΔH and ΔG) correlated with inductive effects, for Ax..C1 and Bx..C1 (a), Ax..C2 and Bx..C2 (b) Ax..C3 and Bx..C3 (c) complexes.

The negative values of ΔE_{zp} (Zero-point corrected Energies) show that the complex formation is associated with some stability (energy) gain and thus, complex formation is possible: a spontaneous thermodynamically driven procedure not necessarily manifesting in term of ΔH and/or ΔG . The fact of complex formation can easily be explained by $n \rightarrow \sigma^*$ (HOMO-LUMO) interaction types, in line with the well-established MO theory.

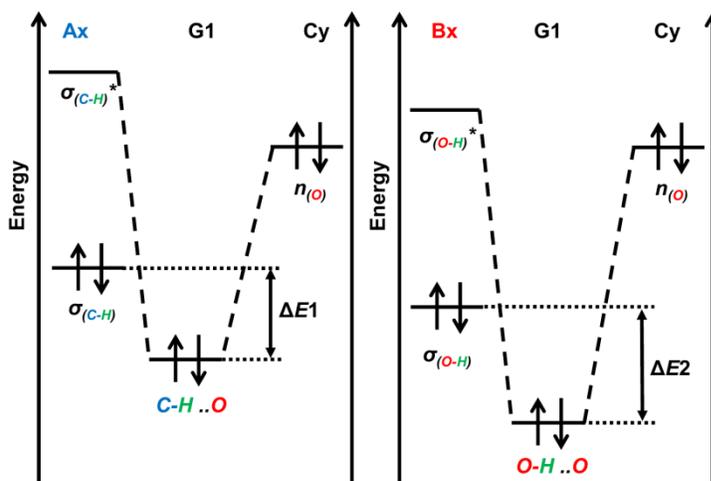


Figure 5. MO scheme of energy gain (ΔE) from the complex formation of either Ax..Cy (G1) or Bx..Cy (G2).

As was expected the energy level of the complex is always lower than that of non-bonding n orbital of the oxygen atom of the acceptor and that of the σ -bond orbital of the donor moieties. The energy gain ($\Delta E1$ or $\Delta E2$) is the difference between the level of the σ bond (C-H or O-H) and that of the complex bond (C-H..O or O-H..O) in both cases. It is essential this gain is always larger in the O-H..O than in the C-H..O complex (schematically demonstrated in **Figure 5**).

The values of thermodynamic functions (ΔE_{zp} , ΔH as well as ΔG) decreases as the σ_i values increase (**Figure 4**). The slope of these lines clearly indicates that the effect of the σ_i of the acids is less pronounced if the basicity of the 1,3-dioxolane oxygen is reduced by the fluorine substituent. As it is well known from the *Hammitt – Taft* relationship, a linear correlation is to be observed with increasing values of σ_i if a uniform and “single interaction” is operative. The parameters of the linear fits are summarized in **Table 3**.

Table3. Linearity (m , b and R^2) of selected thermodynamic ΔE_{zp} , ΔH and ΔG and values with substituents

Code Bx.Cy	$\Delta G(Q-OH)$			Code Ax.Cy	$\Delta G(Q-CH_2-H)$		
	R^2	m	b		R^2	m	b
Bx.C1	0.487	-7.151	5.229	Ax.C1	0.212	-2.349	7.849
Bx.C2	0.489	-6.612	4.539	Ax.C2	0.0021	0.1628	6.731
Bx.C3	0.572	-4.275	5.496	Ax.C3	0.372	-4.549	8.44
	$\Delta H(Q-OH)$				$\Delta H(Q-CH_2-H)$		
	R^2	m	b		R^2	m	b
Bx.C1	0.675	-8.691	-3.318	Ax.C1	0.803	-3.071	0.763
Bx.C2	0.692	-8.228	-3.268	Ax.C2	0.795	-3.872	0.935
Bx.C3	0.657	-6.215	-2.047	Ax.C3	0.233	-1.337	0.322
	$\Delta E_{zp}(Q-OH)$				$\Delta E_{zp}(Q-CH_2-H)$		
	R^2	m	b		R^2	m	b
Bx.C1	0.672	-8.641	-3.343	Ax.C1	0.777	-3.038	0.376
Bx.C2	0.671	-8.034	-3.513	Ax.C2	0.738	-2.867	0.228
Bx.C3	0.669	-6.331	-2.161	Ax.C3	0.696	-1.965	0.135

From data tabulated in **Table 3** it looks obvious, that while the trends shown in **Figure 4** due exist, the maximum correlating (*Pearson*) coefficient is limited ($R_{max} = 0.8$). It is more important to compare the slope (m) of the lines as these are the measures to indicate changes in complex stability following the increasing inductive effect, σ_i , of substituents. As expected most of the slopes are negative signaling that acidity increases by the inductive effect of the substituent. Values are

more negative in the cases of Q-O-H family than they are for Q-CH₂-H. These differences make the formers (Q-O-H) weak, while the latter's (Q-CH₂-H) **super-weak acids**.

One may expect to see some geometrical deviation of the two type of complexes with 1,3-dioxolanes (Q' = CH₃, H, F) due to the differences between Lewis (C-H) and Brønsted (O-H) acids (**Figure 6**). The C-H bond length (d) in C-H...O complexes slightly changes ($\Delta d \sim 0$) with increasing inductive effects (σ_i) of the substituents. In contrast to that the O-H bond length (d) in an O-H...O complex exhibits an increase with increasing (σ_i) values of the substituent.

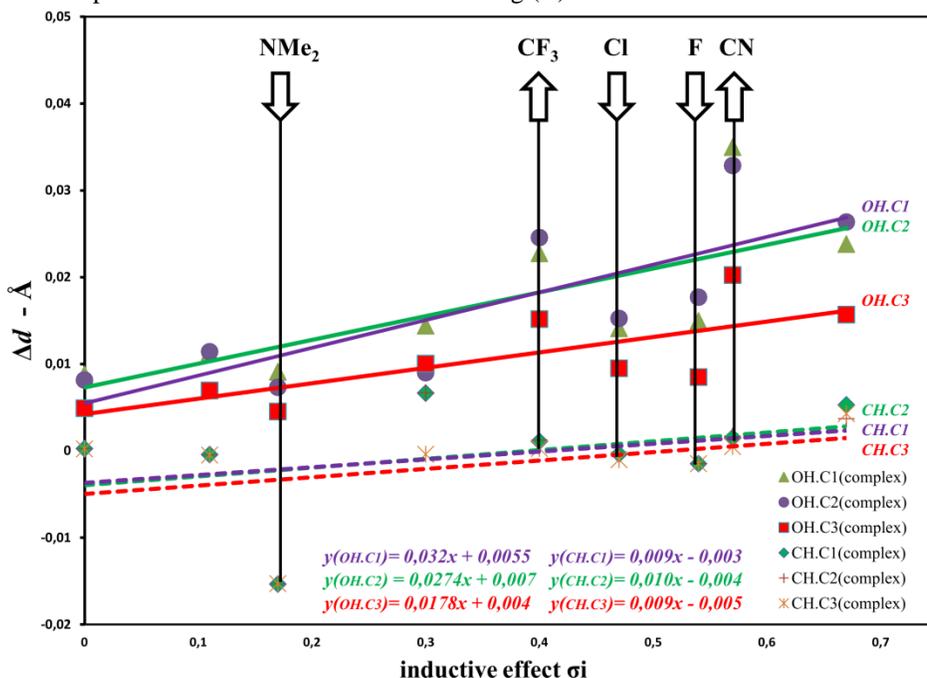


Figure 6: Changes of C-H and O-H bond length (Δd) correlated to the inductive effect of Qs.

Figure 6 shows the cases in which the anion charge leads to destabilization, marked by arrows, showing downward to a smaller d value. In contrast to that, the substituents where the negative charge of the anion is stabilized either by inductive (F₃C-) or inductive and conjugative (NC-) effects are marked by arrows showing upward to a larger than observed values of d . Thus, the deviation from the linear correlations is attributed to the structural possibility of destabilization or stabilization by the substituent on the negative charge: the total anionic structure suggests two classes, proposed on **Figure 7**.

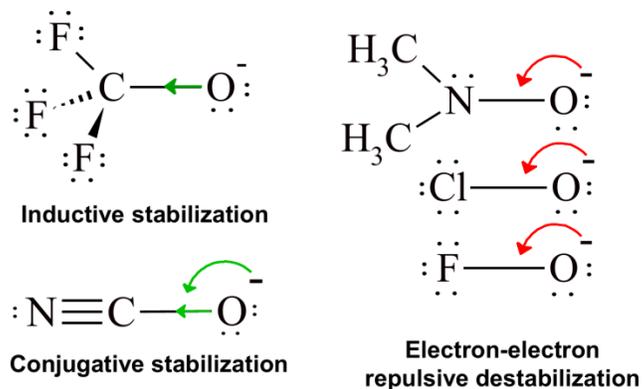


Figure 7: Stabilizing and destabilizing structures of anionic electron pairs.

It seems therefore that the difference between weak acids (R-O-H) and super-weak acids (R-CH₂-H) has been manifested in terms of thermodynamic changes as well as in characteristic shifts in bond lengths. Clearly the super-weak

acids behave as Lewis acid in spite of the fact that they have hydrogen atoms, of very low “mobility” and thus their pKa(s) are large figures.

Conclusion:

The territory of the acids extends from George Olah’s super acids, as strongest species to the weak acids. Furthermore, the latter’s can be divided to two subtypes: **weak acids** and **super-weak acids**, which differ not only in the range of bond energies, but also changes in the bond length (Δd). For better understanding the problem of the difference between weak acids and super-weak acids we performed *in silico* QM calculations supplemented with an MO-approach. The calculated thermodynamic functions established that in the case of O-H acids the Δd values increase parallel with the σ_i values, which is typical of Brønsted acids. On the other hand, the Δd values of C-H acids in C-H..O complexes are practically zero, *i.e.*, they behave like Lewis acids as no significant changes are seen. Consequently, super weak acids Q-CH₂-H can be regarded as exceptional Lewis acids bearing a proton suitable for C-H..O complex formation. This consideration might help in explaining unexpected cases of organo-catalysis, or organo-inhibition and crystal structure formation.

Acknowledgments

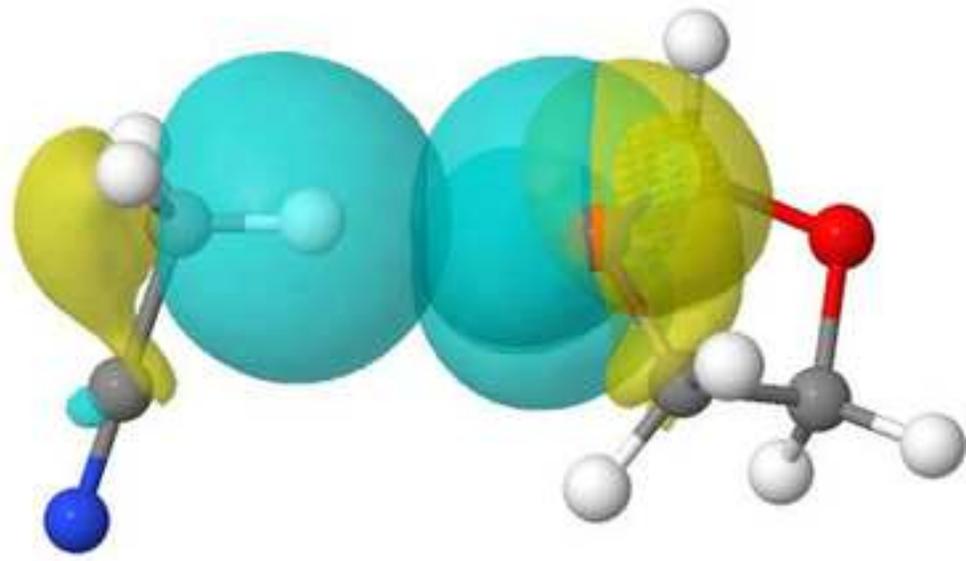
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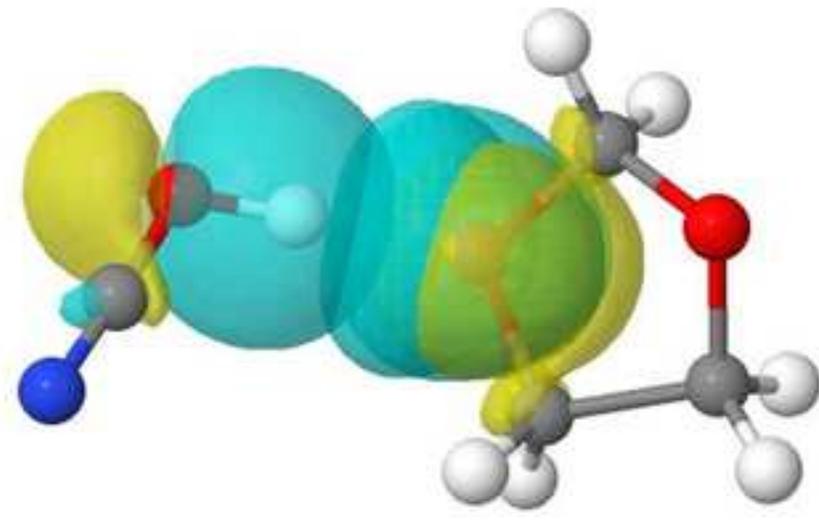
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Super weak acid

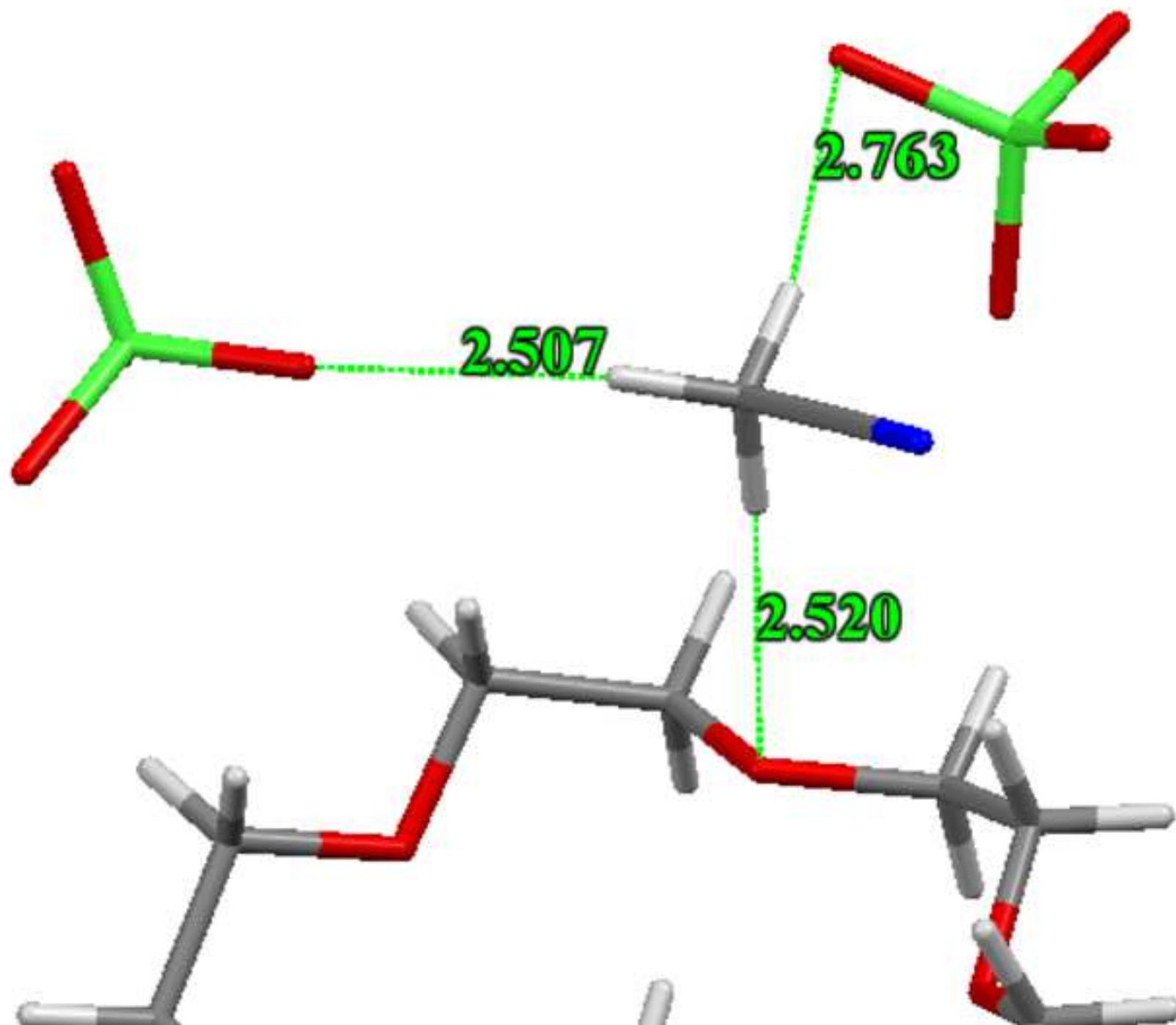


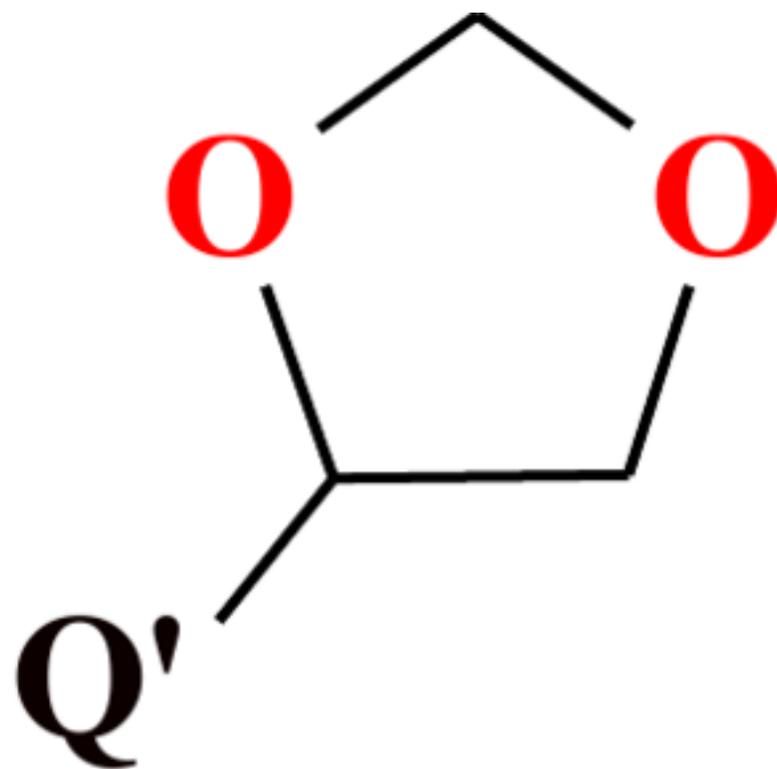
Lewis complex

Weak acid



Brønsted complex





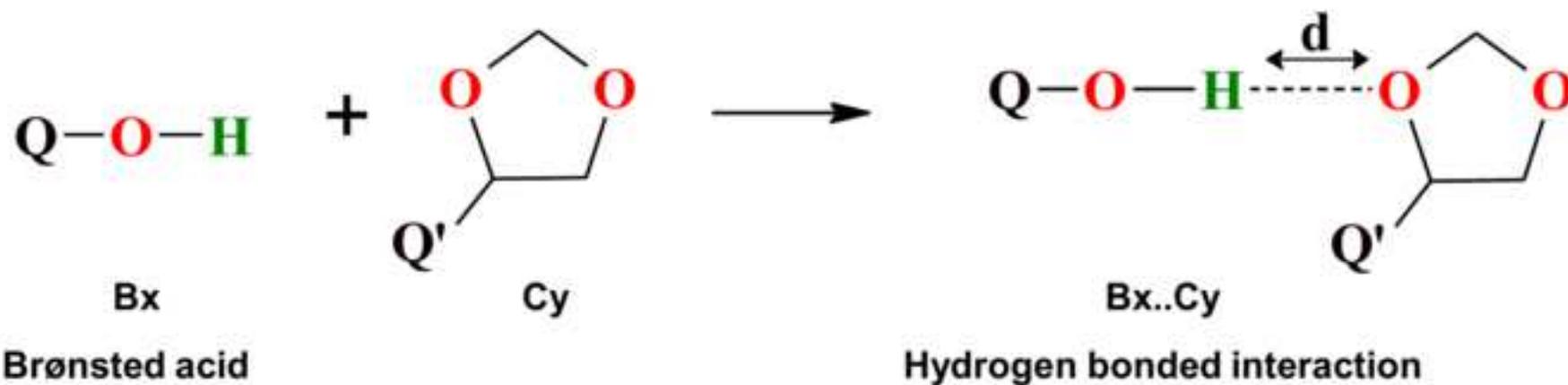
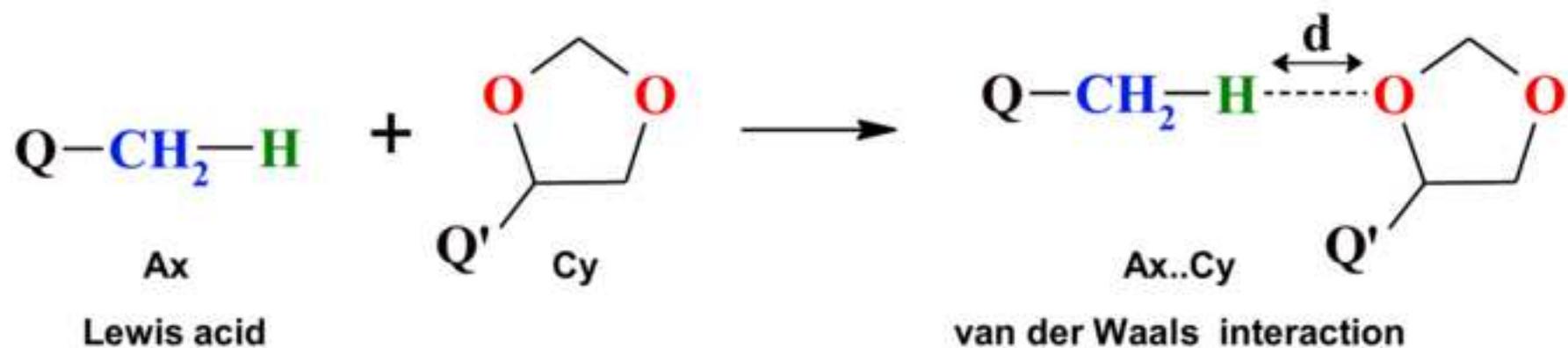
C1: Q' = CH₃, C2: Q' = H, C3: Q' = F



**Lewis acid for
van der Waals complex**

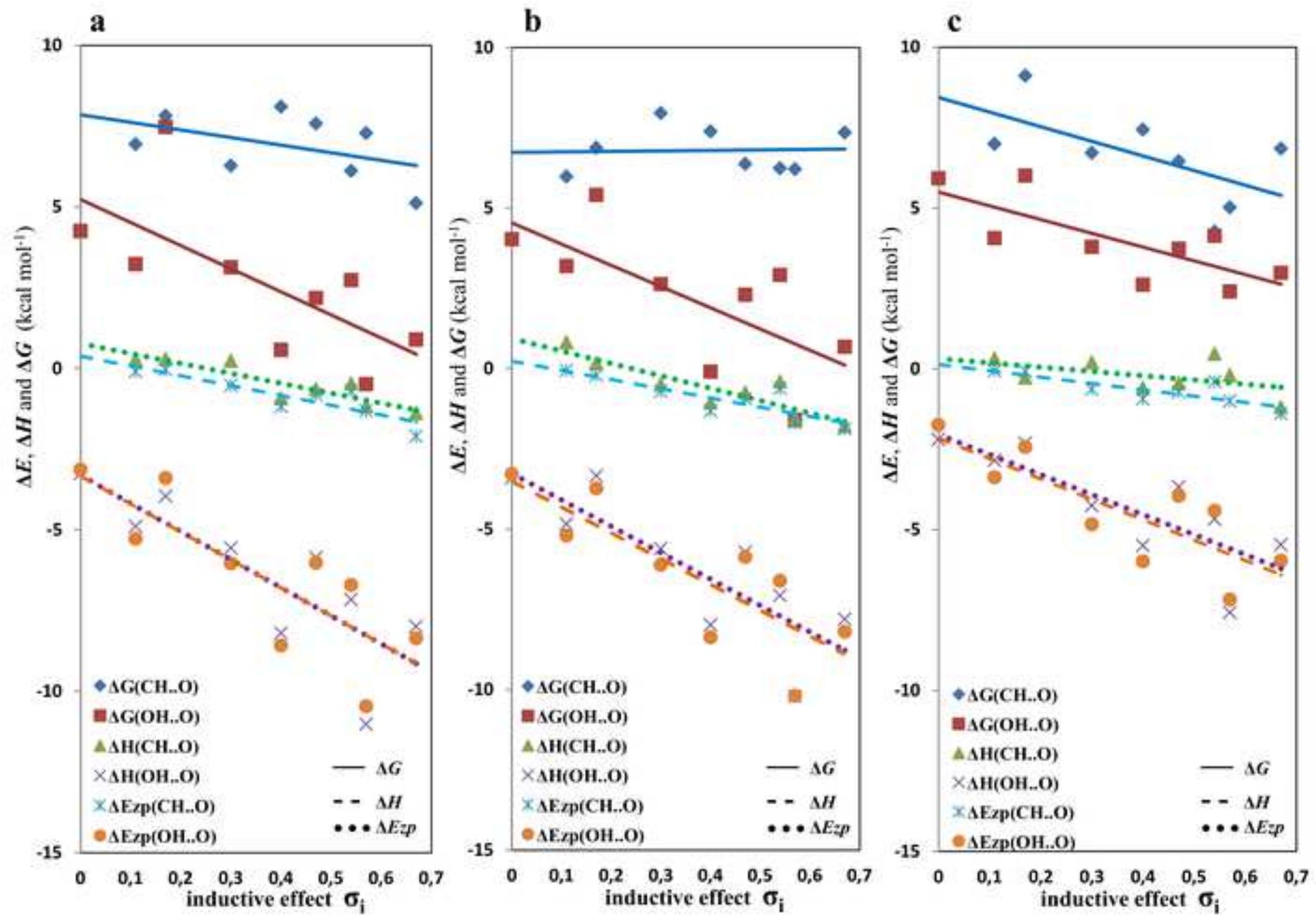


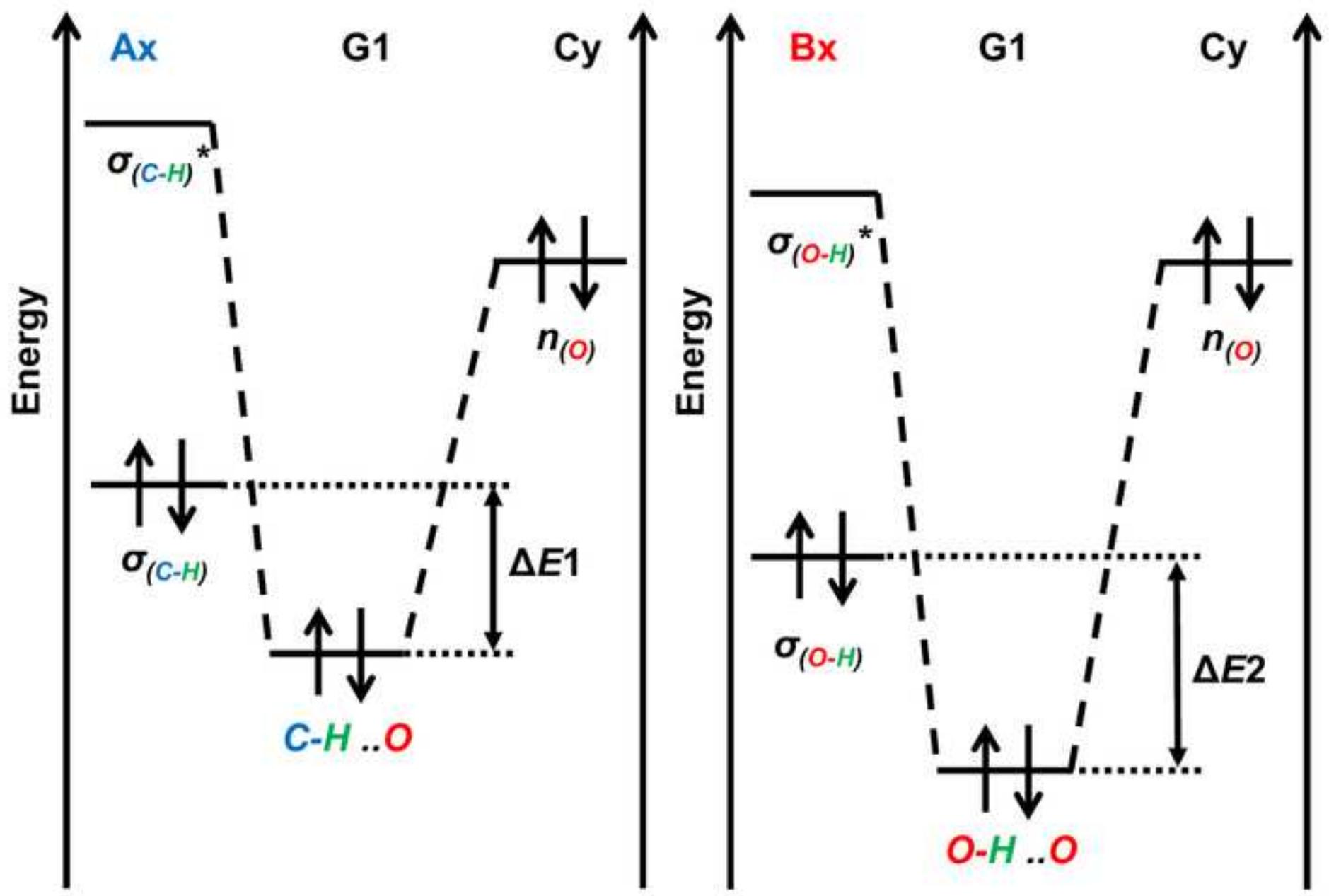
**Brønsted acid for
hydrogen bond complex**

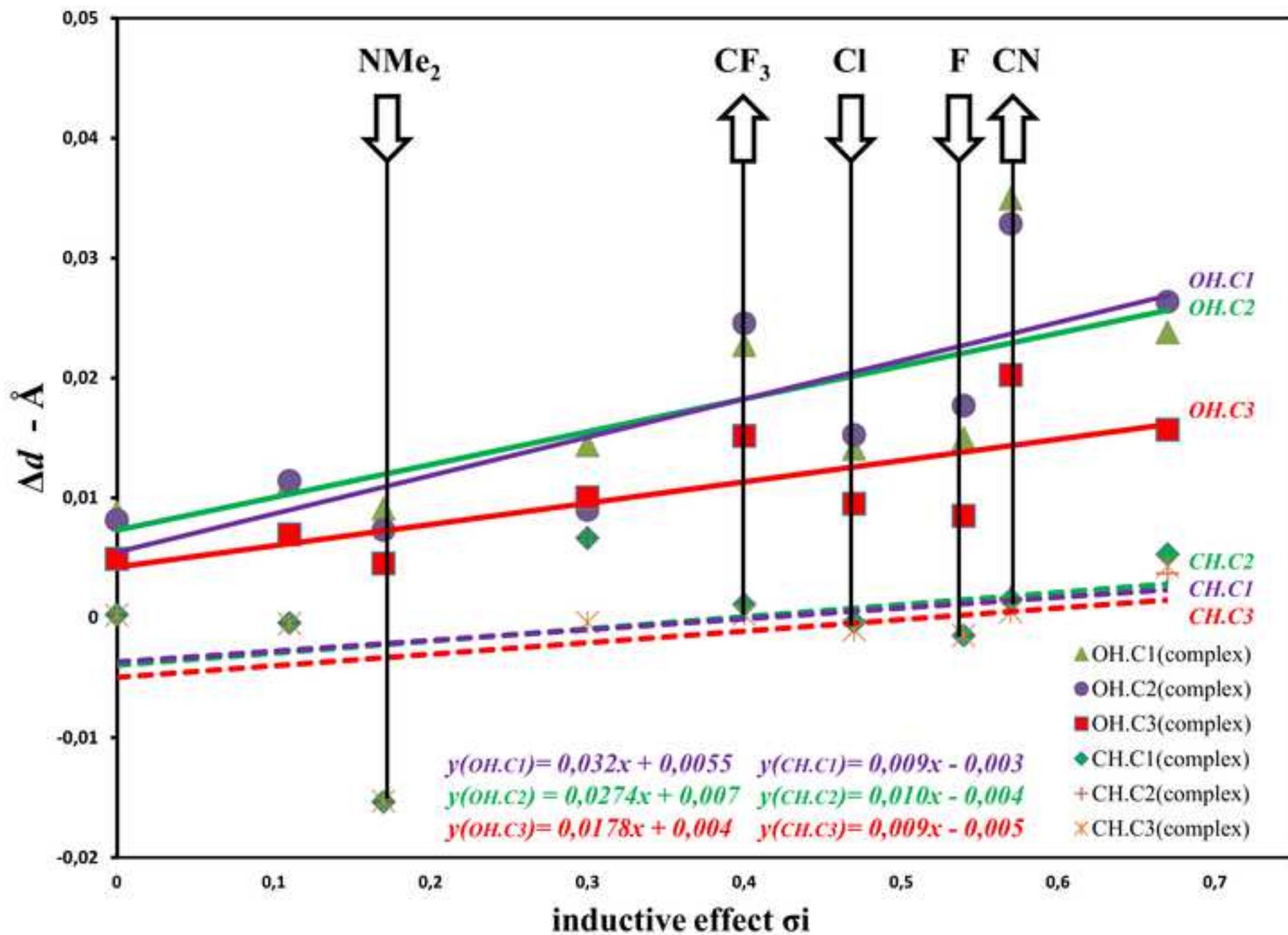


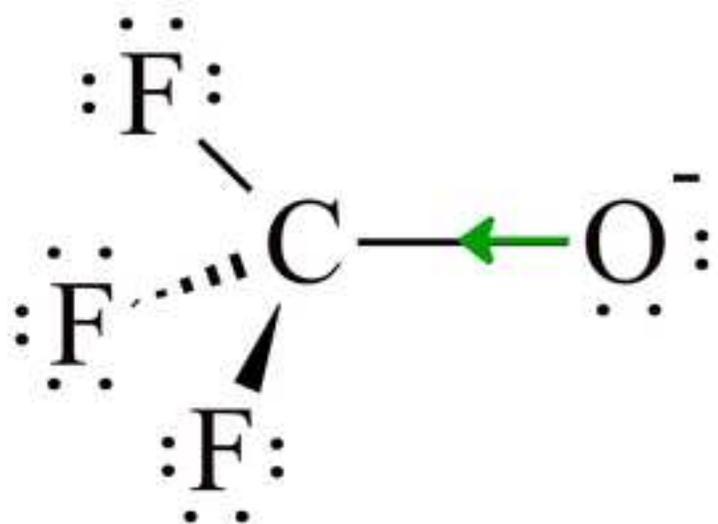
Q = -H, -C₂H₃, -NMe₂, -C(O)CH₃, -CF₃, -Cl, -F, -CN, -NO₂

Q' = -CH₃, -H, -F

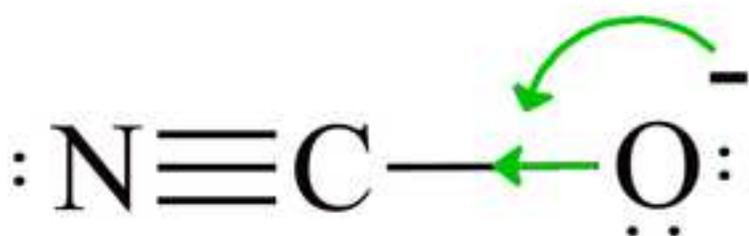




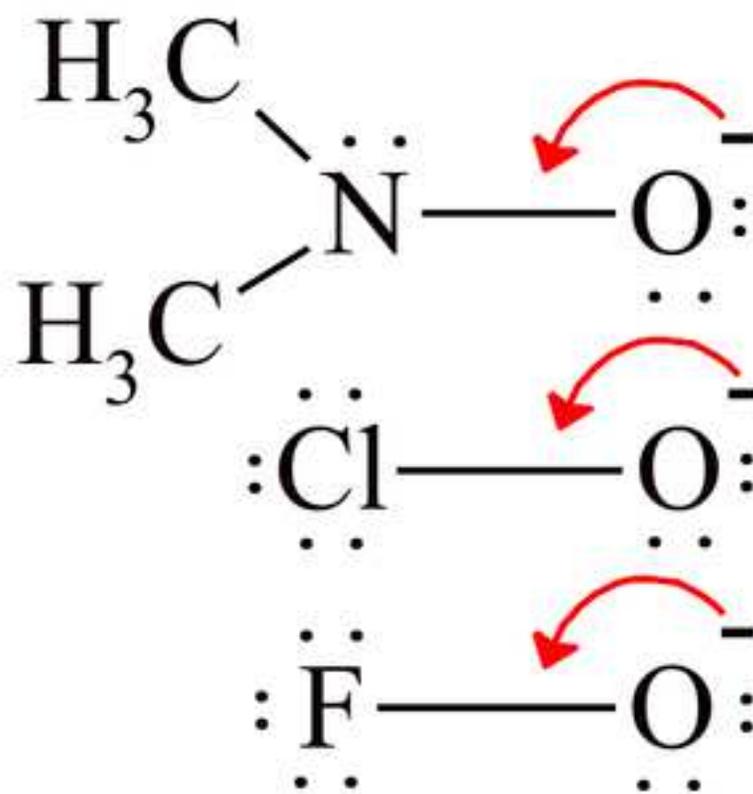




Inductive stabilization



Conjugative stabilization



**Electron-electron
repulsive destabilization**