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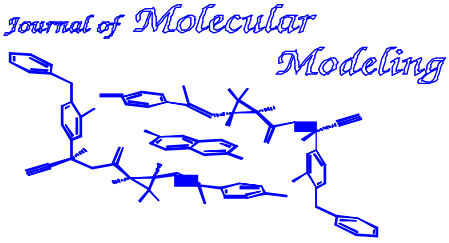

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The Source for the Difference Between Sulfhydryl and Hydroxyl Anions in Their Nucleophilic Addition Reaction to a Carbonyl Group: A DFT Approach.

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Abstract

Ab initio calculations show that sulfhydryl anion has a significantly lower potential than the hydroxide anion for stabilizing the products of its attack on carbonyl moieties – the tetrahedral complexes (*TC*). In this paper we analyze the factors that contribute to this phenomenon. Quantum mechanical MO *ab initio* calculations were used for studies of two reaction series, one for the attack of hydroxyl and one for the attack of sulfhydryl anion on different carbonyl compounds and their analogs. All of the anionic *TC*s formed by HS^- are characterized by higher charge transfer, but are significantly less stable than the relevant *TC* of HO^-. To explain the phenomenon we used a simple qualitative model based on Density Functional Theory (DFT). The crucial role of the occupied valence MOs is demonstrated in the process of electronegativity equalization between the donor and acceptor fragments in the final *TC* product. The sulfhydryl anion has significantly lower potential to stabilize *TC* products in comparison with the hydroxide anion because of the larger extent of electron back-donation from the electrophile's $HOMO_A$ to the nucleophile's $LUMO_D$. This electron back-donation thus reduces the stability of the anionic *TC* in the case of HS^- and may account for the calculational results. Applications of this work to enzyme reactions help in understanding the differences in mechanisms of serine and cysteine proteases and may be used to guide the design of inhibitors for these enzymes. In perspective, the back-donation phenomenon discussed here may be applied to the study of electron transfer processes involving oxidation-reduction enzymes.

Keywords: Nucleophilic addition to carbonyl group, Sulfhydryl anion, Hydroxyl anion, Tetrahedral Intermediate, Tetrahedral Complex, Density Functional Theory, MO *ab-initio* calculations.

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Introduction

Nucleophilic addition of an anionic nucleophile to a carbonyl group accompanied by $sp^2 \Rightarrow sp^3$ rehybridization of the atomic orbitals (AOs) on an electrophilic center results in the formation of a tetrahedral product, which in most cases is a reactive intermediate [1,2]. Hydrolysis of amides and esters are representative reactions of this type [3-5], and are the key process of the enzymatic catalysis provided by proteases [6]. The widely accepted terminology for the tetrahedral product is Tetrahedral Complex (*TC)* [6]. Howard and Kollman [7] showed that in its attack on a carbonyl species in the gas phase, a sulfhydryl nucleophile (SH^- or SR^-) does not form a stable covalent tetrahedral adduct. We address this paper to the question of why a sulfur nucleophile behaves differently than oxygen during nucleophilic attack on a carbonyl center. This understanding is important in relation to differentiation between hydrolytic enzyme mechanisms in serine and cysteine proteases [8]. The knowledge gained will provide clues for designing selective, mechanistic-based inhibitors for serine and cysteine proteases. Several attempts have been described to explain the different behavior of the hydroxyl and sulfhydryl nucleophiles. Cardy et al [9] applied the model of Heilbronner [10], who attempted to use molecular orbital (MO) theory to resolve this problem. However, the authors, considered only the occupied orbitals and neglected the charge-transfer process connected with the unoccupied MOs of the acceptor. The chemical nature of *TC* is predominantly covalent. Creation of a *TC* is accompanied by considerable donor-acceptor charge transfer, as will be discussed in detail below. A different interpretation [11] of the relative stability of carbanions and their isoelectronic analogs was based on hyperconjugation [12] and the anomeric effect, [11] where only frontier orbitals were considered. Neither approach alone can provide a comprehensive understanding of the reactions of hydroxyl and sulfhydryl anions with carbonyl species.

In this paper, we combine certain qualitative aspects of the molecular orbital approach and density functional theory (DFT) to analyze and explain the factors governing the *ab initio* calculated stability of *TC* products that are formed during nucleophilic attack on a carbonyl group by hydroxyl or sulfhydryl anions.

Results and Discussion

Two reaction series were calculated, one for the attack of hydroxyl and one for the attack of sulfhydryl on different carbonyl compounds and their analogs. Performing the calculations on a gas-phase model eliminates the effects of the media, so that intrinsic reactivity can be determined solely by the electronic and structural nature of the nucleophile and the carbonyl substrate. All structures were fully optimized at the HF/6-31+G*// HF/6-31+G* level, using the Gaussian 92 program [13].

Several geometrical and electronical changes are associated with the formation of a stable *TC*.

(a) The $sp^2 \Rightarrow sp^3$ rehybridization of the atomic orbitals (AOs) on an electrophilic center causes its pyramidalization and elongation of covalent bonds.

(b) The newly formed bond between the reactive centers (which is partially covalent and partially ionic) is usually longer and consequently weaker than an equivalent ordinary covalent bond [14], (see a comparison between calculated and corresponding experimental values of bond lengths in Table 1).

(c) A significant amount of charge transfer occurs from the nucleophile to the electrophile (shown in Table 1). The general reaction scheme for *TC* formation is presented in Fig. 1.

Energies

The reaction energy (E_{react}) for the formation of the tetrahedral covalent product – *TC* was calculated using eq 1.

$$E_{react} = E_{DA} - (E_D^o + E_A^o) \quad (1)$$

where E_D^o and E_A^o are the total energies of the isolated donor and acceptor molecules, and E_{DA} is the total energy of the nucleophilic addition product, the *TC*.

The original observations of Howard and Kollman [7] demonstrated at the *ab initio* MP2-FC/6-31*G//RHF/4-31G level of calculations that the hydrosulfide anion cannot form tetrahedral covalent adducts with formamide and formaldehyde. Our geometry optimizations using a higher level basis set including diffuse functions agree with their results. We found that for several substrates– formaldehyde CH_2=O, cyclopropenone $(CH)_2$C=O and urea $(NH_2)_2$C=O there is no minimum on the reaction potential surface corresponding to a *TC*. All tetrahedral complexes formed by HS^- are characterized by larger values of charge transfer, (see *ab initio* calculated values in Table 1) but are significantly less stable

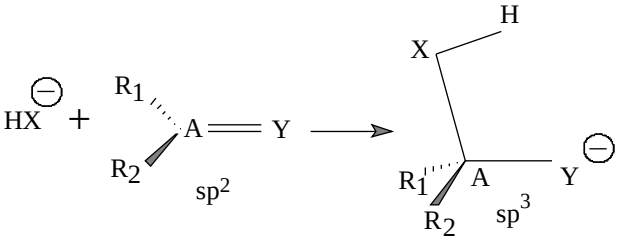

Figure 1. *The principal scheme of the formation of a TC from reagents. HX– is the anion (HO– or HS–), and R1 and R2 denote the variable substituents at the electrophilic center A on the carbonyl–like group. The varied atom A here is C or Si, and Y is O or S. The reaction is accompanied by the* $sp^2 \Rightarrow sp^3$ *rehybridization of the electrophilic center A.*

Table 1. *Electronic and geometric characteristics of a stable TC.*

no.	Tetrahedral complex (TC)	Values of charge-transfer			Charges on reactive centers				X–A [*a,b*]
		ab initio Mulliken	*ab initio* NAO	*eq. 2*	Mulliken *X*	Mulliken *A*	NAO *X*	NAO *A*	
1	$HO–CH_2–O^-$	0.6417	0.5563	0.3720	-0.8337	0.2381	-0.9257	0.3584	1.470
2	$HO–CF_2–O^-$	0.6053	0.6348	0.3883	-0.8893	1.3604	-0.8623	1.3537	1.396
3	$HO–CH_2–S^-$	0.7168	0.6261	0.4124	-0.7728	-0.0734	-0.8708	-0.2104	1.428
4	$HO–(CH)_2C–O^-$	0.6865	0.6107	0.3733	-0.8002	0.4608	-0.8818	0.6563	1.438
5	$HO–(NH_2)_2C–O^-$	0.6618	0.5823	0.2683	-0.8283	0.6777	-0.9073	0.9485	1.459
6	$HO–(NH_2)_2C–S^-$	0.7827	0.6401	0.3801	-0.7229	0.1011	-0.8654	0.4687	1.421
7	$HO–SiH_2–O^-$	0.4639	0.2914	0.4207	-1.0296	1.1723	-1.2062	1.9172	1.705
8	$HO–SiH_2–S^-$	0.5670	0.3140	0.4346	-0.9354	0.8547	-1.1943	1.4206	1.692
9	$HS–CF_2–O^-$	0.8109	0.8634	0.3623	-0.2650	0.7802	-0.2492	1.0459	1.915
10	$HS–CH_2–S^-$	0.8813	0.9634	0.3832	-0.2286	–0.4190	-0.1702	-0.7127	1.861
11	$HS–(NH_2)_2C–S^-$	0.8746	0.9669	0.3428	-0.2160	-0.0346	-0.1640	0.1308	1.897
12	$HS–SiH_2–O^-$	0.5673	0.4821	0.3959	-0.5042	0.8339	-0.6445	1.5987	2.248
13	$HS–SiH_2–S^-$	0.6420	0.55731	0.4087	-0.4476	0.6188	-0.5814	1.0107	2.225

[a] *The experimental values [14] of bond lengths for the relevant ordinary covalent bonds in Å are: O–C (1.42), O-Si (1.63), S–C (1.81), S–Si (2.14).*

[b] *The bond lengths in Å for the relevant ordinary covalent bonds in neutral species* ab initio *calculated in this work with full geometry optimization in the 6-31$^+$G* basis set are O–C (1.382) in $HOCH_2OH$; O–Si (1.637) in $HOSiH_2OH$; S-C (1.803) in $HSCH_2OH$; S–Si (2.134) in $HSSiH_2OH$.*

than the relevant tetrahedral products of HO^-, as is shown in Table 2.

Density Functional Theory

Our strategy emerged from analyzing the MOs of the *TC* and combining the results with simple concepts from DFT that relate to donor-acceptor (D-A) interactions [15,16]. The charge transfer energy ΔE_{CT} can be expressed either as a function of electronegativity and hardness or as the energy gap between the donor-acceptor frontier orbitals [15,16]. Hence, a quantitative functional relation between the stabilization energy E_{react} resulting from charge transfer and an expression of the energies of HOMO-LUMO orbitals of the reactants can be obtained. The concept and the novelty of our approach lies in a surprising result, presented in the following section, which we obtained by straight forward merging of two DFT equations. The result is that back donation of electrons occur from the electrophile's $HOMO_A$ to the nucleophile's $LUMO_D$. The extent of back donation relates on the nucleophile's type and affects the stability of the tetrahedral product.

The value of the donor-acceptor charge transfer ΔN_{CT} for the simplest DFT model, using a fixed external potential, is presented in eq 2 [15,16].

$$\Delta N_{CT} = (\chi_A - \chi_D) / 2(\eta_A + \eta_D) \quad (2)$$

The energy-change term ΔE_{CT} contributed by the charge transfer can be calculated according to eq 3 [15,16].

$$\Delta E_{CT} = (E_A - E_A^0) + (E_D - E_D^0) =$$

$$-1/4\,(\chi_A - \chi_D)^2 / (\eta_A + \eta_D) \quad (3)$$

where χ_D, η_D and χ_A, η_A represent the absolute electronegativity and hardness for the donor *D* and the acceptor *A*. E_D^0, E_A^0 are the respective ground-state energies of the isolated donor and acceptor, and E_D, E_A are the respective energies of the donor and acceptor in the new valence states corresponding to the complex, *D:A*. Equation 2 shows that (a) the differences in electronegativity drive the electron transfer, and (b) the sum of the absolute hardness inhibits electron transfer.

Table 2. *Reaction energies E_{react} of the TCs and the values of energy gaps α and β between the frontier MOs of the reagents.*

no.	Tetrahedral complex (TC)	E_{react} [kcal/mol]	α a.u.	β a.u
1	HO–CH_2–O^-	–35.2	0.1792	0.8608
2	HO–CF_2–O^-	–69.8	0.1697	0.9772
3	HO–CH_2–S^-	–69.6	0.1389	0.7701
4	HO–$(CH)_2$C–O^-	–24.6	0.1618	0.8107
5	HO–$(NH_2)_2$C–O^-	–19.4	0.1666	0.8323
6	HO–$(NH_2)_2$C–S^-	–41.4	0.1518	0.7359
7	HO–SiH_2–O^-	–111.9	0.1258	0.8638
8	HO–SiH_2–S^-	–118.7	0.1118	0.7802
9	HS–CF_2–O^-	–9.8	0.1606	0.8203
10	HS–CH_2–S^-	–22.2	0.1298	0.6132
11	HS–$(NH_2)_2$C–S^-	15.4	0.1427	0.5790
12	HS–SiH_2–O^-	–56.2	0.1167	0.7069
13	HS–SiH_2–S^-	–62.0	0.1027	0.6233

The following operational definitions of χ and η are useful for calculating several experimental values [15,16]:

$$\chi = (I + A) / 2 \qquad \eta = (I - A) / 2 \qquad (4)$$

where I is the ionization potential, and A is the electron affinity of the system. I and A can be extracted directly from the output of quantum mechanical calculations.

According to Koopman's theorem [17] , eq. 4 may be rewritten in terms of the energies of frontier orbitals (HOMO and LUMO) [18], where the frontier orbitals are given by:

$-\varepsilon_{HOMO} = I$ and $-\varepsilon_{LUMO} = A$.

$$\chi = -(\varepsilon_{HOMO} + \varepsilon_{LUMO}) / 2; \quad \eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) / 2 \qquad (5)$$

The values of χ and η estimated in eq 5, however, are only rough estimates compared with the values in eq 4. Therefore, before using eq 5 for further applications, we compared the values of χ and η derived by both eq 4 and eq 5 for our series of calculated reagents. The results are presented in Table 4. I and A used in eq 4 were determined according to eq 6 [15,16].

$$I = E(N - 1) - E(N); \qquad A = E(N) - E(N + 1) \qquad (6)$$

E(N) is the total energy of a starting system with N electrons and charge q; $E(N-1)$ and $E(N+1)$ are the total energies of the same species going (on ionization) from the charge q to the charge $q+1$ or to the charge $q-1$ (accepting one additional electron), respectively. The calculations were done with a frozen geometry for the initial system (vertical I and A values). All energetic values were estimated with second order Møller-Plesset correlation corrections implemented in the standard Gaussian 92 program [13], using restricted Hartree-Fock calculations MP2//RHF/6-31+G* for closed shell - and unrestricted MP2//UHF/6-31+G* for open shell species. As can be seen from Table 4, the two sets of values for χ and η are well correlated, so we may use eq 5 for our development. Hence, a quantitative function of the relation between the value of ΔE_{CT} resulting from charge transfer and an expression of the energies of HOMO-LUMO orbitals of the reactants can be obtained.

The value of ΔE_{CT}, derived from eq 3, is always negative and roughly approximates the stabilization energy E_{react} of *TC*, as calculated by eq 1. E_{react} comprises several components: charge-transfer energy, the energy of formation of the covalent bond between the reactive centers, and the nuclear repulsion energy.

We use eq 3 as a working tool for a qualitative analysis of how the intrinsic properties of distinct isolated chemical species D and A (energies of their frontier MOs) determine the

Table 3. *Values of ε_{HOMO}, ε_{LUMO}, I, A (in a.u.) calculated for the reagents.*

no.	Comp.	ε_{HOMO}	ε_{LUMO}	I [a]	A [a]
1	HO^-	–0.10333	0.41779	0.0589	–0.3902
2	HS^-	–0.09416	0.26090	0.0660	–0.2444
3	CH_2=O	–0.44295	0.07593	0.4046	–0.0577
4	CF_2=O	–0.55939	0.06644	0.5047	–0.0536
5	CH_2=S	–0.35227	0.03559	0.3373	–0.0110
6	$(CH)_2$C=O	–0.39286	0.05850	0.3593	–0.0498
7	$(NH_2)_2$C=O	–0.41446	0.06333	0.3762	–0.1722
8	$(NH_2)_2$C=S	–0.31813	0.04853	0.2911	–0.0340
9	SiH_2=O	–0.44595	0.02247	0.4075	–0.0098
10	SiH_2=S	–0.36239	0.00849	0.3396	0.0079

[a] The values of I and A are calculated by eqs. 6, see details in the text.

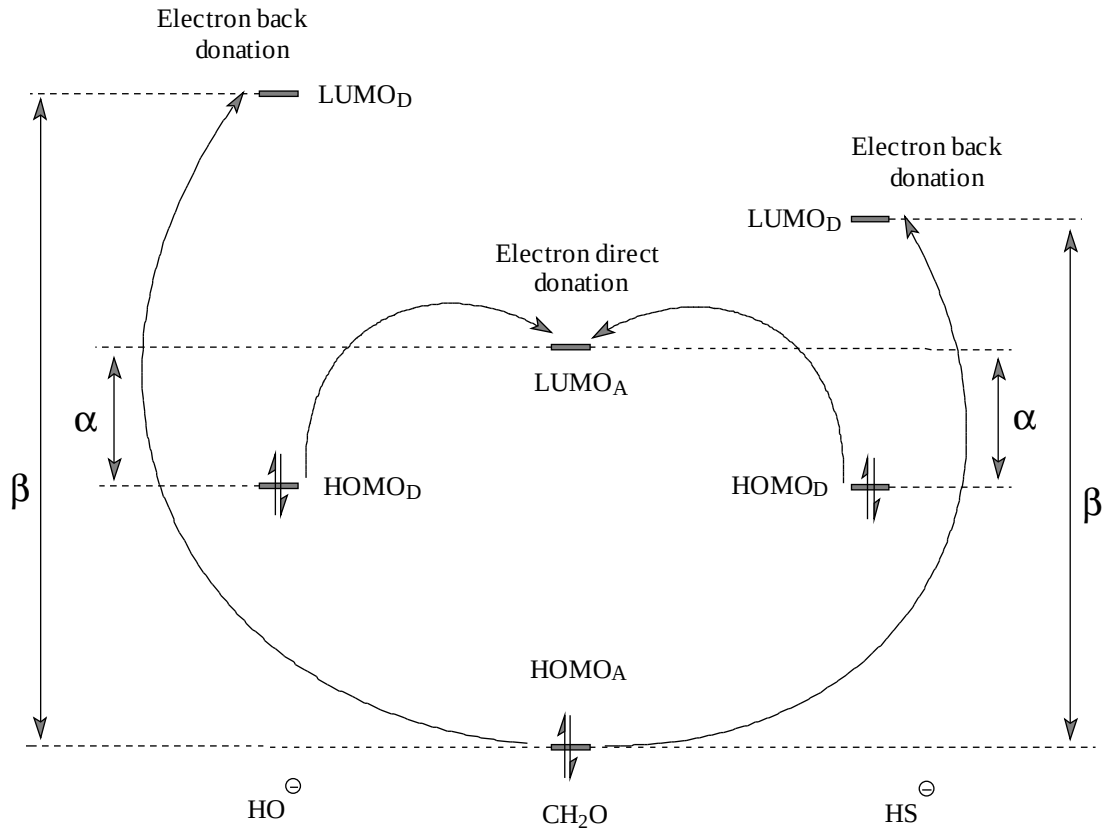

Figure 2. *A scheme describing the directions of charge transfer by the frontier orbitals of the reagents. Direct charge transfer occurs from the HOMO$_D$-nucleophile to LUMO$_A$-electrophile, some extent of charge transfer occurs in the opposite direction from the HOMO$_A$-electrophile to LUMO$_D$-nucleophile. The amount of electron back-donation is an important factor in determining the stability of the TC. The difference in orbital levels between SH$^-$ and OH$^-$ is reflected by the* a *and* b *parameters, and determines the value of the ΔE_{CT} affecting the TC stabilization.*

stability of combined system *D:A* (*TC*). By combining eqs. 2 and 3 with eq 5, we can obtain an expression for *DN* (eq 7).

$$\Delta N_{CT} = (\beta - \alpha) / 2(\beta + \alpha) \quad (7)$$

The expression for ΔE_{CT} is directly derived from ΔN_{CT} in eq 8.

$$\Delta E_{CT} = -1/8\ (\beta - \alpha) \quad (8)$$

where $\alpha = (\varepsilon^A_{LUMO} - \varepsilon^D_{HOMO})$, $\beta = (\varepsilon^D_{LUMO} - \varepsilon^A_{HOMO})$; and ε^D_{LUMO}, ε^D_{HOMO} and ε^A_{LUMO}, ε^A_{HOMO} are the respective frontier orbital energies for the initial donor *D* and acceptor *A*.

The values for α and β are positive, and because $\beta > \alpha$, the calculated value of ΔE_{CT} in eq 8 is always negative. According to perturbational MO (PMO) theory, the stability of *D:A* is inversely proportional to the value of the energy gap $\varepsilon^A_{LUMO} - \varepsilon^D_{HOMO}$ (α in eqs 7 and 8) [19]. The same result is obtained by DFT, where the stability of *D:A* increases as the value of *a* decreases (see eq. 8 and Fig. 2).

Equation 8, in contrast to the well known nonlinear Eq. 3, has a very simple mathematical form – it demonstrates the linear dependence of the value of ΔE_{CT} on the gaps between energy levels of reagents' frontier MOs – α and β. This is a big advantage for practical applications. It is important to emphasize that eq 8 provides a new interpretation of frontier orbital control of the *D:A* stability because it takes into consideration the simultaneous charge transfer in the opposite direction (LUMO$_D$ ⇐ HOMO$_A$ from the acceptor's HOMO to the donor's LUMO) as well. Such "back-donation" of electrons decreases the stability of the *TC*. Therefore, the stability of the *TC* becomes higher as the energy gap $\varepsilon^D_{LUMO} - \varepsilon^A_{HOMO}$ (β) increases because of the back-electron transfer from the acceptor to the donor (D ⇐ A) is smaller. Thus, the result that emerges from the mathematical development described above (Eq. 7-8), is that electron back donation from the HOMO$_A$ of the carbonyl group to the LUMO$_D$ of the nucleophile is not a negligible component according to DFT, and because of this it has a role in destabilizing the products. This conclusion has a general implication because, to the best of our knowledge, prior interpretations [20] of donor-acceptor interactions in terms of frontier orbitals have considered only the direct charge transfer (HOMO$_D$ ⇒ LUMO$_A$). The validity of this development is shown by checking the

linear correlation between the energy gaps of the frontier MO's - values of α and β discussed above, and the E_{react} for the stable *TC*'s calculated by *ab initio* (eq. 9).

$$E_{react} = 1702.46\,\alpha - 333.91\,\beta - 35.17, \quad (9)$$

R = 0.937, F = 35.8, Standard Error = ± 14.9 kcal/mol, observations = 13. The E_{react} values are presented in kcal/mol and α and β – in the a.u.

The signs of the coefficients reflect the trend that would indicate in which direction α and β influence the value of E_{react} . The signs of the coefficients for E_{react} turn out to be the same as the signs for the α and β parameters established for ΔE_{CT} in eq 8. Consequently, the *ab initio* calculated *TC* stability (E_{react}) and the donor-acceptor charge transfer energies (ΔE_{CT}), determined from the simple qualitative model based on DFT, are governed by the same electronic factors. The conclusion is that the charge transfer process (ΔE_{CT}) is the main energy component that reflects the different abilities of SH^- and OH^- to stabilize the anionic *TC* species. Figure 3 presents a graphical comparison of the E_{react} values calculated by *ab initio* and estimated in Eq. 9.

The orbital energies of the $HOMO_D$ orbitals of SH^- and OH^-, which reflect the value of the direct charge transfer, are very close (see Table 3). The energy of the SH^- $HOMO_D$ is even slightly higher (by 0. 011 a.u.) than that of OH^-. Because the difference is negligible, however, the stability of the *TC*s formed by HO^- and HS^- are expected to be similar. On the other hand, the orbital energy difference between the $LUMO_D$ orbitals of SH^- and OH^- is very large: the SH^- $LUMO_D$ is 0. 16 a.u. lower (6-31+G*) than that of OH^-. The contribution of the $LUMO_D \Leftarrow HOMO_A$ back donation significantly increases as the energy gap between the relevant orbitals decreases (see eqs. 8 and 9). Because the energy gap is much smaller for the sulfur nucleophile (see Table 3), the main reason for destabilization of the *TC* by SH^- is the increased amount of back donation involved in this type of attack. Stable *TC*s will be obtained when the electrophilic group has a low-lying $HOMO_A$ orbital (as in CF_2O).

In the present work we have analyzed only the energy levels of the interacting reagent's MOs, because we were interested exclusively in the process of charge transfer between nucleophile and electrophile during the formation of a *TC*. We demonstrated that the significance of this phenomena for the stabilization of a tetrahedral product emerges only if one takes into consideration mutual directions of the charge transfer: donor-acceptor and acceptor-donor. In such a case the general trend in product stability for the relevant reaction can be well predicted in a simple linear correlation equation. Nevertheless, we would like to stress that for a better understanding of the full picture and to improve quantitative estimations of the E_{react} values in any linear correlation like Eq.9, one must consider also the overlap interactions between AOs of reactive centers of reagents creating the covalent bond in a *TC* product (or/and electron populations on these atoms). The carbonyl like bond A=Y of a reagent due to the more electronegative atom Y is polarized. As a result, the orbital lobe on the atom A in the doubly occupied π_A MO decreases. This causes the reduction of the value of overlap integrals between the relevant AOs of the reactive centers and the formation of a weaker covalent bond, which is the reason of the general elongation of this bond in *TC*s observed here in comparison with the equivalent ordinary covalent bonds (see Table 1). According to the Hard and Soft Acids and Bases (HSAB) principle, overlap interactions play a much more significant role for the soft base HS^- than for the hard HO^- [16]. Our *ab initio* calculated values of E_{react} confirm this statement. Table 2 demonstrates that HS^- stabilizes the anionic *TC* much better for the soft substrate H_2CS (-22.2 kcal/mol) with a weakly polarized bond C=S, than for the hard F_2CO (-9.8 kcal/mol), where the central carbonyl carbon is surrounded by three extremely electronegative substituents

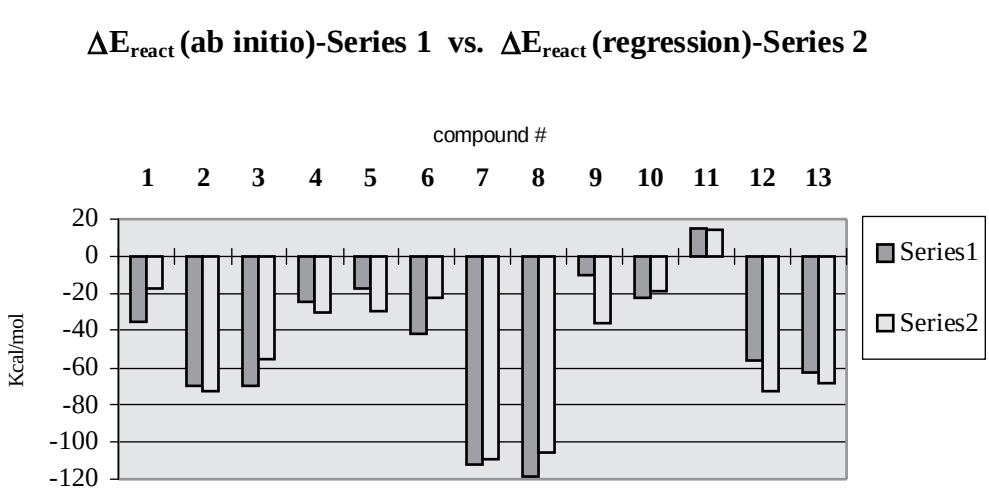

Figure 3. *Graphical comparison of the E_{react} values calculated by ab initio and estimated in Eq. 9.*

– F and O. In contrast, the relevant values of E_{react} are indistinguishable for the hard base HO^-, where the charge transfer due to the interaction of frontier reagent's MOs dominates (see Eqs. 7 and 8, and Table 1 for the values of ΔN_{CT} calculated by Eq. 2). The values are -69.6 kcal/mol for H_2CS, and -69.8 kcal/mol for F_2CO. Thus, the general tendency observed here– much more stable *TC*s are formed for the HO^- series – is regulated by the charge transfer process.

An open question remains, however. As emerges from the qualitative approach of DFT, the values of ΔE_{CT} and ΔN_{CT} are proportional (eqs. 2 and 3). Consequently, because they are more stable for OH^- than for SH^-, *TC*s derived from a hydroxy nucleophile attack are expected to have a larger charge transfer value than those derived by an SH^- attack. Equation 2 indeed confirmed this conclusion for all the calculated series (see Table 1). The charge transfer values derived from *ab-initio* calculations, on the other hand, show the opposite trend: Table 1 shows that in all calculated structures, the charge transfer values, as extracted from the Mulliken population analysis [21] and the Natural Atomic Orbitals (NAO) population analysis [22] (both of which are implemented in the GAUSSIAN-92), are higher for the less-stabilized sulfur nucleophile. Thus, a discrepancy occurs between the accurate MO *ab-initio* and the simplified model of donor-acceptor interactions [15,16] based on DFT used here.

Participation of inner orbitals in the interaction.

To explain this discrepancy we should examine the orbital picture of D-A interactions. To derive eqs. 7 and 8, we used Koopman's theorem, which provides a way to estimate of electronegativity and hardness through the energies of frontier orbitals. The frontier-orbital approach characterizes mainly the *global* intermolecular donor-acceptor charge transfer process, related to the reacting molecules as a whole. On the other hand, as shown by Parr et al. [23], all molecular orbitals of the reagents, including their inner shells, should be involved in the process of interatomic charge transfer between the reactive centers and their orbital electronegativities should be equalized. Therefore, the frontier-orbital approach only partially reflects the picture of electron-density redistribution in a *TC*. To obtain a more complete picture, the doubly occupied, valence-shell orbitals should also be taken into account. We must take into consideration the *local* electron redistribution between the nucleophilic and electrophilic centers in the *TC*, where the major role belongs to the reagents' inner occupied orbitals. Summarizing the process of electronegativty equalization between all MO's of reagents that combine into the product, we can identify two channels for electron density redistribution between reagents: *global* – originating in the reagent's frontier MOs interactions, and *local*, caused mainly by the electronegativity equalization between AOs of reactive centers. Several electronegativity equalization formulations have been proposed for calculating the partial charges of atoms in molecules [24]. For our qualitative picture, however, we shall use only the basic idea that the electron flow on a polar bond is directed from the atom with low χ to the atom with high χ and that the value of the charge transfer is proportional to the difference in their electronegativities. Yet, such a scheme is convenient for a qualitative systematization of the dominant factors influencing the process of charge transfer. The *local* channel of electron-density redistribution can be characterized by the absolute atomic electronegativities [25] of the reactive centers. Thus, the value of the total charge transfer ΔN_{CT} may be expressed through its components ΔN_{global} and ΔN_{local} in symbolic form as shown in eq 10.

$$\Delta N_{CT} = \Delta N_{global} + sign[\chi_{at}(A) - \chi_{at}(D)]\ \Delta N_{local} \qquad (10)$$

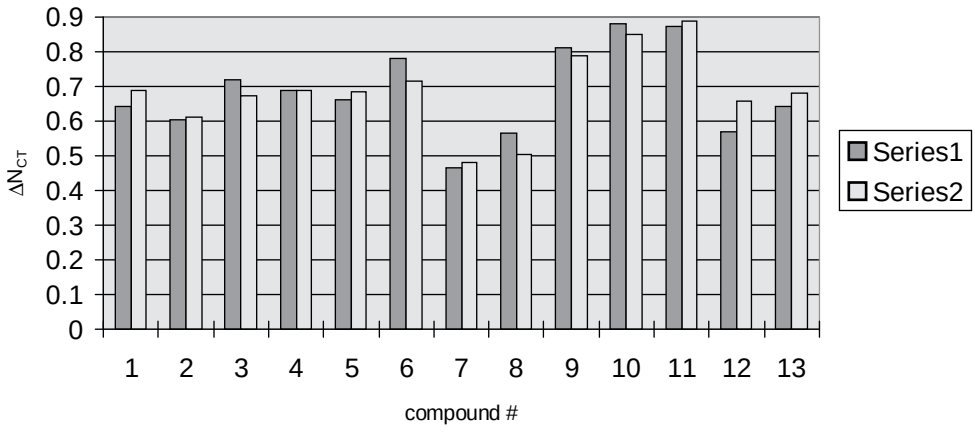

Figure 4. *Graphical comparison of the values ΔN_{CT} (ab initio) derived from the Mulliken population analysis with linear regression estimation by eq. 11.*

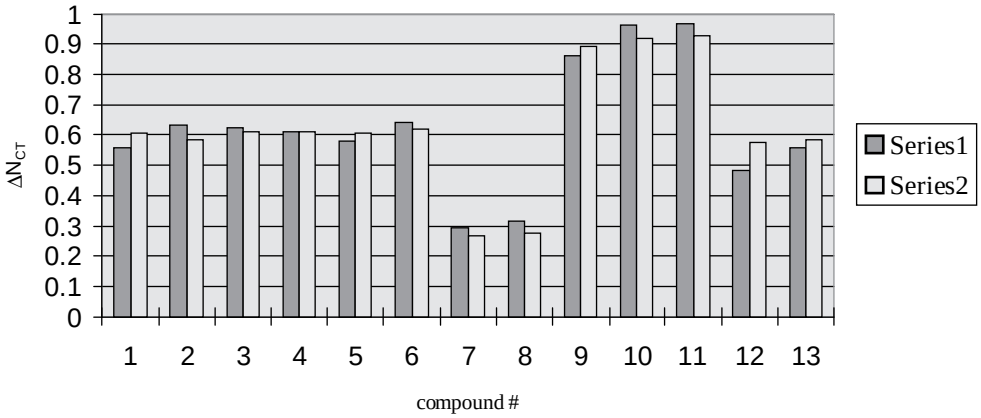

Figure 5. *Graphical comparison of the values ΔN_{CT} (ab initio) derived from the NAO population analysis with linear regression estimation by eq. 12.*

where $\chi_{at}(A)$ and $\chi_{at}(D)$ are the respective absolute atomic electronegativities [25] of the D and A reactive centers. To check the validity of eq 10, we performed a multiple regression analysis that correlates calculated *ab initio* values of ΔN_{CT} with the values of α and β characterizing the frontier orbital control on the global charge transfer (ΔN_{global}) and the difference in absolute atomic electronegativities of reaction centers – $[\chi_A - \chi_D]$, which depends mainly on the features of occupied inner and valence MOs and characterizes the local charge transfer – ΔN_{local}. We used two sets of *ab initio* calculated charge transfer values ΔN_{CT} derived from Mulliken (eq. 11) and NAO (Eq.12) population analysis (see Table 1).

ΔN_{CT} (*ab initio*) =

$$1.661\ \alpha - 0.548\ \beta + 0.080\ [\chi_A - \chi_D] + 0.966 \qquad (11)$$

Multiple R = 0. 931; F=19.4; Standard Error = ±0.053; Number of observations = 13.

ΔN_{CT} (*ab initio*) =

$$0.206\ \alpha - 0.148\ \beta + 0.218\ [\chi_A - \chi_D] + 0.973 \qquad (12)$$

Multiple R = 0.979; F= 68.3; Standard Error = ± 0.050; Number of observations = 13.

Eqs. 11 and 12 show good correlations between ΔN_{CT} (*ab initio*) and the reagents' electronic structure parameters characterizing ΔN_{global} and the ΔN_{local}. Thus, we may conclude that our idea, expressed in eq. 10, about the two operating channels for the electronic density redistribution between combining reagents looks reasonable. This resolves the discrepancy posed above.

At the end of this discussion we would like to stress that the NAO variant of population analysis demonstrates much better applicability (compare the regression quality in Eqs. 11 and 12) for the description of the donor-acceptor charge transfer processes in comparison with the traditional Mulliken approach. The graphical comparison of the values ΔN_{CT} (*ab initio*) derived from the Mulliken and NAO population analysis with linear regression estimations by eqs. 11 and 12 are presented in Figures 4 and 5, respectively.

The analysis of the computational results for the charge distribution on the reactive centers for different electrophiles reacted with SH^- and OH^- is described below. The results illustrate the validity of eq. 10. For the calculated series of *TC*s formed by an OH^- nucleophile, we observe that the ΔN_{local} charge transfer on the newly formed bond is always directed

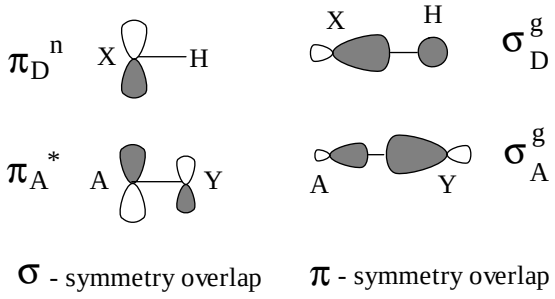

Figure 6. *Examples of the lobal structure of the MOs of the reagents participating in the overlap interactions between the reactive centers – nucleophilic X and electrophilic A. The overlap has two symmetry types:*
σ (for the $HOMO_D$ and $LUMO_A$) and π (for the doubly occupied σ_D^g and σ_A^g MOs of the reagents' valence shells) in the local coordinates of the newly forming bond X–A in the TC.

Table 4. *Values of* χ, η *[*a*] calculated for the reagents.*

no.	Comp.	$\chi = 1/2(I + A)$	$\chi = -(\varepsilon_{HOMO} + \varepsilon_{LUMO})/2$	$\eta = 1/2(I - A)$	$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$
1	HO^-	–0.1657	–0.1573	0.2246	0.2606
2	HS^-	–0.0892	–0.0834	0.1552	0.1776
3	CH_2=O	0.1735	0.1836	0.2312	0.2595
4	CF_2=O	0.2256	0.2465	0.2792	0.3129
5	CH_2=S	0.1632	0.1584	0.1742	0.1940
6	$(CH)_2$C=O	0.1548	0.1672	0.2046	0.2257
7	$(NH_2)_2$C=O	0.1020	0.1756	0.2742	0.2389
8	$(NH_2)_2$C=S	0.1286	0.1348	0.1626	0.1833
9	SiH_2=O	0.1989	0.2118	0.2087	0.2343
10	SiH_2=S	0.1738	0.1770	0.1659	0.1855

[a] All values of χ *and* η *(in a.u.) are calculated with the molecular geometries optimized at 6–31+G* level.*

from the electrophilic center to the attacking, highly electronegative oxygen atom (absolute atomic electronegativity = 7. 54 [25]). For the parallel set of *TC*s formed by HS^-, the local interatomic charge transfer ΔN_{local} should be either absent or directed in the opposite direction – from sulfur to carbon, depending on the valent surrounding of the electrophilic center. The reason is that sulfur has an absolute atomic electronegativity that is slightly lower than that of carbon [6. 22 (S) vs. 6. 27 (C)] [25]. During the formation of a *TC* with carbon electrophiles, the total *ab-initio* calculated charge transfer ΔN_{CT} is expected to be considerably larger for HS^- than for HO^-. It is found that for the carbon electrophile reactions, the charge on the nucleophilic atom on the *TC* (oxygen or sulfur) is always more negative on the oxygen derivative than on the sulfur derivative (see values of the NAO analysis in Table 1). The charge on oxygen in compound **2** is -0.8623 compared with -0.2492 on sulfur in compound **9**. In principle, in the case of the low electronegative silicon atom (4. 77) [25] as the electrophile center, the charge transfer picture should differ from carbon. Indeed, the observed values of the negative charge for both oxygen and sulfur nucleophiles in *TC*s is significantly smaller for carbon electrophiles than for silicon electrophiles (Table 1) (see compounds **10** and **13** for sulfur and compounds **1** and **7** for oxygen).

It is interesting to speculate about the "geometrical" aspect of the electron charge transfer between reagents. Because of a local symmetry, at least two orthogonal types of overlap interactions, σ and π, occur in a new bond forming between the orbitals of the reactive centers. Thus, the global and local redistribution of electrons between the donor and the acceptor should be expressed through two parallel channels of orbital interactions, with a different local symmetry type that depends on the bond between the reactive centers. One channel (global), shown in eq 2, is characterized by the total electronegativity and hardness of the reagents, which are the global parameters of interacting molecules. Eq. 7 demonstrates that the electron flow occurs through the interaction of the HOMO and LUMO pairs of the donor and acceptor. Because of the geometrical features of *TC* products (see Fig. 1), where the donor fragment X-H makes a frontal attack on the bond of the acceptor A-Y, the direct donor-acceptor charge transfer channel occurring through the overlap interaction of $HOMO_D$ (π_D^n) and $LUMO_A$ (π_A^*) is of σ-symmetry in the local coordinates of the bond between *D* and *A*. The schematic lobal diagram is presented in Fig. 6.

Fig. 6 also demonstrates an example of the π-symmetry overlap interaction between the occupied σ_D^g and σ_A^g MOs of the reagents that are responsible for the covalent bonds in the donor X-H and the acceptor A=Y fragments, respectively. If the frontier orbitals operate through a σ channel ΔN_s, then logically, the alternative channel of the local electron density redistribution (ΔN_{local}) between reactive centers should be of local π-symmetry. This channel belongs to the inner orbitals of the reagents. The separation of the frontier-MO and inner-MO interactions of the reagents into different symmetrical types is an oversimplification used here only for the transparency of a qualitative model.

Summary

A simplified model of donor-acceptor charge transfer processes based on the DFT was applied to the explanation of the *ab initio* calculations. The sulfhydryl anion has a significantly lower potential to stabilize *TC* products than the hydroxide anion because of the larger extent of electron back donation from the $HOMO_A$ to the $LUMO_D$ of the sulfhydryl anion.

The importance of the electron back-donation effect is a new result, derived by straightforward manipulations with DFT equations. Carbonyl derivatives, which less back-donation are predicted to form fairly stable *TC*s, even with sulfur. For example, fluorine substituted derivatives (e.g. compound **9**, table 2) are calculated to give a stable tetrahedral anionic species.

We can identify two channels for the electron density redistribution between reagents: *global* – originated from the reagent's frontier MOs interactions, and *local*, caused mainly by the electronegativity equalization between AOs of reactive centers. The direction of the *local* flow depends on the differences between the atomic electronegativities of the reaction centers in the *TC* species. If the atomic electronegativities of the reactive centers are close, as in the case of the HS^- nucleophile that attacks carbon electrophiles, the charge transfer through the *local* channel is practically absent. If the effective atomic electronegativity of an electrophilic center is lower in comparison with a nucleophilic center, the directions of electron flows through the *global* and *local* channels are opposite. For example, the values of the donor-acceptor charge transfer are reduced for all *TC*s in the HO^- series in comparison with the HS^- series. The charge-transfer through the *global* channel is strongly dominated over the *local* channel, so in all stable *TC*s one can always observe the net charge transfer from a donor to an acceptor.

The knowledge of the rules governing the stability of *TC* has a direct application for the design of inhibitors for serine and cysteine proteases. In perspective, the back donation phenomenon discussed here, may be applied to the study of electron transfer processes involving oxidation- reduction enzymes.

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References

1. Lowry, T. H.; Richardson, K. S. *Mechanisms and Theory in Organic Chemistry*; Harper and Row: New York, **1976**, 402 - 461.
2. March, J. *Advanced Organic Chemistry;* Wiley & Sons: New York, **1992**, 378 - 383.
3. Guthrie, J. P. *J. Am. Chem. Soc*. **1973**, *95*, 6999 - 7003.
4. Jencks, W. P. *Accounts Chem. Res.* **1980**, *13*, 161- 169.
5. Jencks, W. P. *Acc. Chem. Res*. **1976**, *9*, 425 - 432.
6. (a) Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman and Company: New York, **1988**, 405 - 426. (b) Polgar, L.; Halasz, P. *Biochem. J*. **1982**, *207*, 1 - 10. (c) McMurray, J. S.; Dyckes, D. F. *Biochemistry* **1986**, *25*, 2298 - 2301. (d) Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760 - 3767. (e) Brady, K.; Wei, A.; Ringe, D.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7600 - 7607. (f) Weiner, S. J.; Seibel, G. L.; Kollman, P. A. *Proc. Natl. Acad. Sci.* **1986**, *83*, 649 -653. (g) Stamato, F. M. L. G.; Longo, E.; Ferreira, R.; Tapia, O. *J. Theor. Biol.* **1986**, *118*, 45 - 59. (h) Warshel, A.; Russell, S. *J. Am. Chem. Soc*. **1986**, *108*, 6569 - 6579. (i) Warshel, A.; Naray-szabo, G.; Sussman, F. , Hwang, J. -K. *Biochemistry*, **1989**, *28*, 3629 - 3637. (j) Schroder, S.; Daggett, V.; Kollman, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 8922 - 8925. (k) Duncan, G. D.; Huber, C. P.; Welsh, W. J. *J. Am. Chem. Soc*. **1992**, *114*, 5784 - 5794.
7. Howard, A. E.; Kollman, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 7195 - 7200.
8. (a) Arad, D.; Langridge, R.; Kollman, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 491 - 502. (b) Arad, D.; Kreisberg, R.; Shokhen, M. *J. Chem. Inf. Comput. Sci.* **1992**, *33*, 345 - 349.
9. Cardy, H.; Loudet, M.; Policard, J.; Olliver, J.; Poquet, E. *Chem. Phys.* **1989**, *131*, 227- 243.
10. Heilbronner, E.; Schmelzer, A. *Helv. Chim. Acta* **1975**, *58*, 936 - 967.
11. (a) Hoffmann, R.; Radom, L.; Pople, J.; Schleyer, P. R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc*. **1972**, *94*, 6221- 6223. (b) David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc*. **1973**, *95*, 3806 - 3807. (c) Schleyer, P. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141-1150. (d) Apeloig, Y.; Karni, M. *J. Chem. Soc. Perkin Trans. II* **1988**, 625 - 636.
12. (a) Dewar, M. J. S. Hyperconjugation; Ronald Press: New York, **1962.** (b) de la Mare, P. B. D. *Pure Appl. Chem.* **1984**, *56*, 1755 - 1766.
13. Frish, M. J.; Head-Gordon, M.; Trucks,G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Pople, J. A. *Gaussian 92, Revision A,* Gaussian, Inc. , Pittsburgh PA, 1992.
14. *CRC Handbook of Chemistry and Physics*; ed. by Lide, D. R.; CRC Press: Boca Raton, **1993**, 9-15 – 9-41.
15. Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules;* Oxford University Press: New York, 1989.
16. Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512-7516.
17. Koopmans, T. C. *Physica*. **1934**, *1*, 104-106.
18. (a) Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250-255. (b) Zhou, Z; Parr, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5720-5724.
19. Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, **1969**.
20. (a) Fuigimoto, H. : Fukui, K. *Intermolecular Interactions and Chemical Reactivity; in Chemical Reactivity and Reactions Paths*, Klopman, G. (Ed.); Wiley: New York, **1974**; 23 - 54. (b) Klopman, G. *ibid* 57 - 166. (c) Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3692 - 3701.

(d) Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 197. (e) Pross A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99 - 196.
21. (a) Mulliken, R. S. *J. Chem. Phys*. **1955**, *23*, 1833. (b) Mulliken, R. S. *J. Chem. Phys*. **1962**, *36*, 3428.
22. Reed, A.E.; Curtiss, L.A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
23. (a) Parr, R. G.; Donnelly, R. A.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801- 3807. (b) Donnelly, R. A.; Parr, R. G. *J. Chem. Phys.* **1978**, *69*, 4431- 4439. (c) Liu, G. -H.; Parr, R. G. *J. Am. Chem. Soc*. **1995**, *117*, 3179 - 3188.
24. (a) Sanderson, R. T. *Chemical Bonds and Bond Energy,* 2nd edn.; Academic Press: New York, **1976**. (b) Ray, N. K.; Samuels, L.; Parr, R. G. *J. Chem. Phys.* **1979**, *70*, 3680 - 3684. (c) Politzer, P.; Weinstein, H. *J. Chem. Phys.* **1979**, *71*, 4218 -4220. (d) Gasteiger, J.; Marsili, M. *Tetrahedron*, **1980**, 36, pp 3219 - 3228. (e) Parr, R. G.; Bartolotti, L. J. *J. Am. Chem. Soc.* **1982**, *104*, 3801 - 3803. (f) Nalewajski, R. F.; Koninski, M. *J. Phys. Chem.* **1984**, *88*, 6234 - 6240.
25. Pearson, R. G. *Inorg Chem.* **1988**, 27, pp 734 - 740.