Substituent Effects

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Received: October 13, 2004; In Final Form: April 8, 2005

Inductive and resonance effects of different substituents (CH_3, Cl, NH_3, CN, NO_2) on the reactivity of the nitrogen and oxygen centers of several saturated and unsaturated hydroxylamine derivates toward hard and soft electrophiles are analyzed in terms of various conceptual DFT based descriptors calculated using B3LYP/6-311G** method. In most cases, the $\pm I$ and $\pm M$ effects are correctly described by these descriptors. The way the substituent effect dies down as the distance between the substituent and the active center increases is also analyzed. It is observed that more than one effect is to be considered to properly understand the effect of a substituent on reactivity.

1. Introduction

The substituent effect lies in the heart of the analysis of structure−activity relationships. Several factors such as inductive ("through bond" and "through space" (field)), resonance (mesomeric), and polarization effects augmented by steric and solvent (field) effects contribute toward the substituent effects on chemical reactivity.[1] Both the "through bond" and "through space" type inductive effects decrease rapidly as the distance from the substituent increases. Various linear free energy relationships have been proposed in gaining insight into the chemical properties (mainly equilibrium and rate constants) in terms of substituent constant originally put forward by Hammett.[2]

In recent years, attempts have been made to correlate substituent constants with density functional theory (DFT) based reactivity descriptors. For a review, see Geerlings et al.,[3] who have presented the intramolecular reactivity sequences under the heads of electrophilic reactions, ambident nucleophiles, nucleophilic additions, radical reactions, concerted reactions, and medicinal chemistry whereas the intermolecular reactivity sequences are put as general considerations, substitutions, additions, eliminations, acidity and basicity.

The electron-releasing and electron-withdrawing characteristics of substituent groups are generally classified[1a,b] as $+I$ and $-I$, respectively, in terms of their inductive effects and $+M$ and $-M$, respectively, for their resonance effects. For example: CH_3 ($+M$, $+I$); NH_2, Cl ($+M$, $-I$); CN, NO_2 ($-M$, $-I$), etc. It may be noted that in ref 1c a different convention is used, viz., electron donor groups exhibit $-I$, $-M$ effects whereas electron acceptor substituents exhibit $+I$, $+M$ effects. In this paper, we follow the convention of refs 1a and 1b.

Conceptual DFT has been quite successful in providing theoretical foundations of popular qualitative chemical concepts.[3,4] For an N-electron system with total energy, E, electronegativity, χ,[5,6] and hardness, η,[7−9] are defined as

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \tag{1}$$

and

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{2}$$

where μ and $v(\vec{r})$ are chemical and external potentials, respectively. The global softness[5] is the inverse of hardness,

$$S = \frac{1}{\eta} \tag{3}$$

To understand the site selectivity in a molecule, local descriptors[3] like the Fukui function,[10] $f(\vec{r})$, and the local softness,[11] $s(\vec{r})$, have been introduced. They are defined as follows:

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\partial \mu}{\partial v(\vec{r})}\right)_N \tag{4}$$

and

$$s(\vec{r}) = f(\vec{r})S \tag{5}$$

In the present work, we try to analyze the effect of substituents on the reactivity at the N- and O-sites of different saturated and unsaturated hydroxylamine derivates in terms of conceptual DFT based reactivity descriptors. Section 2 presents the nature of the problem, and the computational details are given in section 3. Results are discussed in section 4, and finally section 5 contains some concluding remarks.

2. Nature of the Problem

The main effect of the substituent in case of saturated hydroxylamine derivatives (see Scheme 1) is assumed to be inductive in nature and hence for X = CH_3, it is $+I$, and for X = Cl, NH_2, CN, and NO_2, it is $-I$, in nature. For an increase in m by 1, we move to the next homologue by adding a $-CH_2$ group.

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10.1021/jp045319a CCC: $30.25

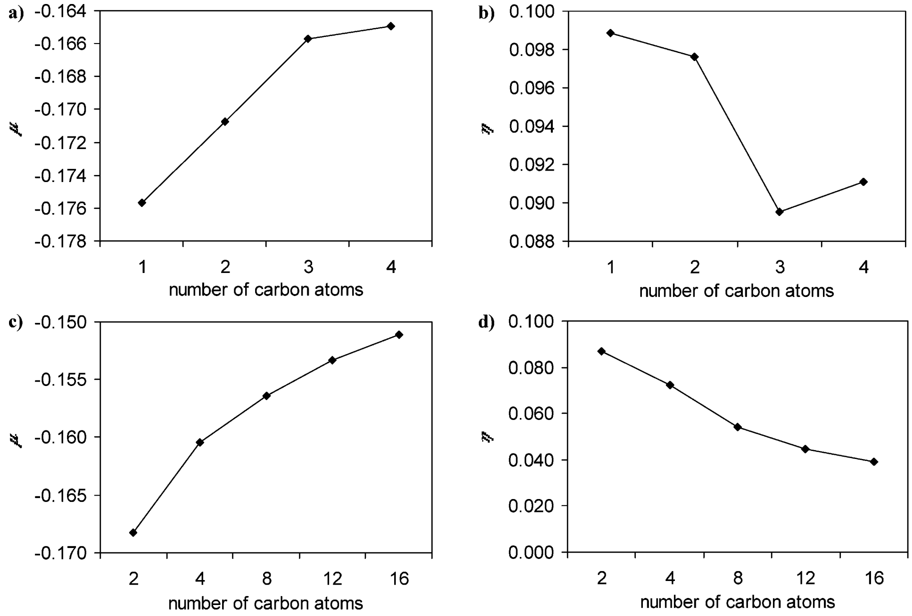
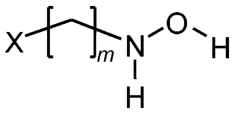
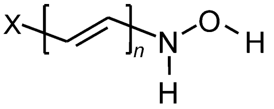


Figure 1. Global properties for the NO_2−substituted systems: (a) chemical potential and (b) hardness of the saturated systems, and (c) chemical potential and (d) hardness of the unsaturated systems. The values are in au.

SCHEME 1: Saturated Systems Employed in This Work, *m* = 1, 2, 3, or 4



SCHEME 2: Unsaturated Systems Employed in This Work, *n* = 1, 2, 4, 6, or 8



On the other hand, the resonance effect is considered to be the major substituent effect because of the conjugation present in the unsaturated hydroxylamine derivatives (see Scheme 2), and hence for X = CH_3, NH_2, Cl, it is +*M*, and for CN and NO_2, it is −*M*, in nature.

Note that an increase in *n* by 1 refers to the addition of a −CH=CH unit, so it introduces two additional C-centers. The N- and O-sites are favorable for electrophilic attacks. For hard electrophiles the charges in those centers, and for soft electrophiles the local softnesses in those centers, are supposed to provide[12] information of relative reactivity toward electrophilic attack when the substituents and/or the chain length vary. Note that this is a nonlocal reactivity problem.

A finite difference approximation together with Koopmans' approximation provides[13]

$$\mu = \frac{\epsilon_H + \epsilon_L}{2} \qquad (6)$$

and

$$\eta = \frac{\epsilon_L - \epsilon_H}{2} \qquad (7)$$

The condensed to atom *k* local softness is given by

$$s_k^{\alpha} = f_k^{\alpha} S \qquad (8)$$

where α = +, -, and 0 refer to nucleophilic, electrophilic, and radical reactions, respectively. In the present work, we consider only s_N^- and s_O^- to analyze the potential of electrophilic attack therein. The necessary Fukui functions are calculated by using a frozen core approximation[14] as

$$f_k^{\alpha} = \sum_{m\in k} f_m^{\alpha} = [|C_{m\alpha}|^2 + C_{m\alpha}\sum_{n\neq m} C_{n\alpha}S_{mn}] \qquad (9)$$

as well as by a finite difference approximation,[15]

$$f_k^- = q_k(N) - q_k(N-1) \qquad (10)$$

where $q_k(N)$ is the Mulliken population (gross charge) on the atom *k* of the *N*-electron molecule.

3. Computational Details

Geometries for all of the molecules are optimized at the B3LYP/6-311G** level of theory. Global quantities are calculated using eqs 3, 6, and 7 and local quantities, by eqs 8−10. For comparison, an additional calculation is performed for the NO_2-substituted saturated hydroxylamine derivative with the aug-cc-pVDZ basis set.

To recover the behavior in which the effect of the substituent on the reactive centers (N and O) for a large chain length should by minimal, several frontier orbitals (5 for saturated and 10 for unsaturated hydroxylamine derivatives) are considered. This implies that eq 9 is used to calculate f_k^{α} for several α's and these quantities are summed with equal weight keeping the total number of electron transferred to be unity. All calculations have been carried out with the GAUSSIAN98 program.[16]

4. Results and Discussion

Figure 1 presents the variation of global reactivity descriptors, chemical potential and hardness, for the saturated and unsaturated NO_2-substituted hydroxylamine derivatives. In general, the chemical potential increases and the hardness decreases with an increase in the chain length for both the saturated (but for *m* = 4) and unsaturated compounds.

TABLE 1: Global and Local (Condensed) Softness Values (au) for Different Saturated Hydroxylamine Derivatives[a]

	m^b											
	1			2			3			4		
substituent	S	s_O^-	s_N^-	S	s_O^-	s_N^-	S	s_O^-	s_N^-	S	s_O^-	s_N^-
CH_3	7.0333	1.6976	1.2499	7.2103	1.4746	1.1304	7.0867	1.4319	1.0829	7.0499	1.3910	1.0621
H	6.9974	2.3688	1.5822	7.0985	1.8657	1.2179	7.0356	1.5208	1.1394	7.0629	1.4335	1.0819
Cl	7.4663	1.6634	1.2447	7.5838	1.5964	1.1532	7.7190	1.6389	1.1521	7.7800	1.5015	1.1525
NH_2	7.2351	2.0621	1.3789	7.5304	1.5983	1.1913	7.3814	1.4711	1.1229	7.1824	1.3820	1.0692
CN	7.2873	1.4918	1.1369	7.3782	1.4641	1.3858	7.5366	1.4868	1.2301	7.3719	1.4448	0.9417
NO_2	10.1153	2.1204	1.1300	10.2422	1.9419	1.0852	11.1694	1.9052	1.1118	10.9788	1.4291	1.0980

[a] Fukui functions are calculated using frozen core approximation with 5 frontier orbitals except for NO_2- substituted systems for which 10 frontier orbitals are used. [b] For *m*, see the text.

TABLE 2: Global and Local (Condensed) Softness Values (au) for Different Unsaturated Hydroxylamine Derivatives[a]

	n^b														
	1			2			4			6			8		
substituent	S	s_O^-	s_N^-	S	s_O^-	s_N^-	S	s_O^-	s_N^-	S	s_O^-	s_N^-	S	s_O^-	s_N^-
CH_3	7.6526	1.6888	1.1424	11.3282	1.9106	1.2041	15.6556	1.7777	1.0804	19.3237	2.1803	1.3023	22.4391	2.4171	1.4613
NH_2	9.1500	2.0011	1.5174	11.8814	2.1122	1.3909	16.2774	1.8320	1.1540	19.9880	2.2514	1.3690	23.1428	2.5102	1.5409
Cl	8.8125	2.0523	1.3416	11.6618	1.9701	1.2353	16.0128	1.8169	1.0789	19.6889	2.2244	1.3146	22.8154	2.4537	1.4705
H	8.5973	2.0070	1.6831	11.2366	1.2143	1.4143	15.5945	1.7791	1.0857	19.2883	2.1801	1.2959	22.4266	2.3962	1.4487
CN	10.0155	1.8894	1.3432	12.7722	1.8489	1.1767	17.3400	1.9720	1.1367	21.1372	2.2599	1.3387	24.3576	2.5302	1.5166
NO_2	11.5214	2.0548	1.2202	13.7960	1.8371	1.1296	18.4077	2.0983	1.1904	22.2941	2.4373	1.4131	25.6148	2.5363	1.4946

[a] Fukui functions are calculated using frozen core approximation with 10 frontier orbitals. [b] For *n*, see the text.

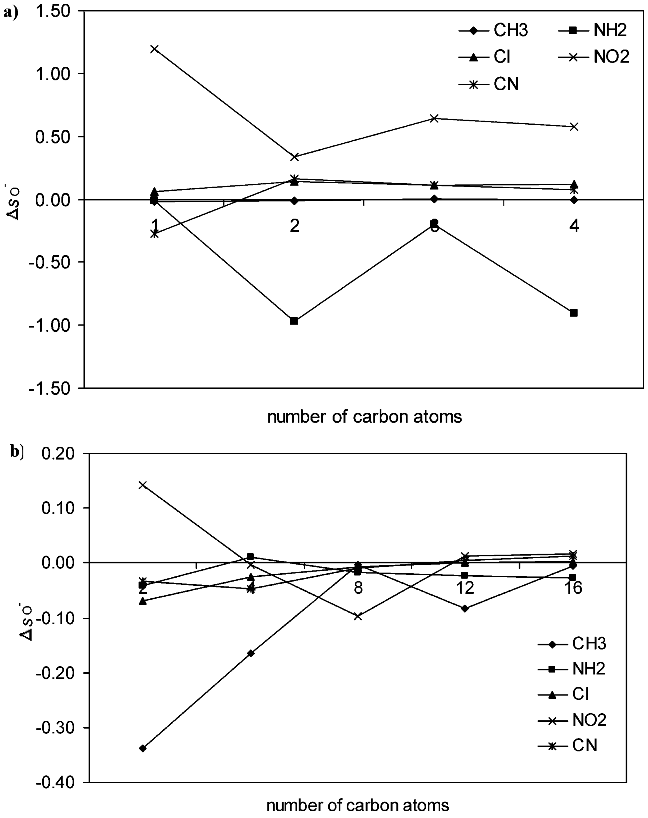


Figure 2. Variation of relative condensed softness, $\Delta s_O^-(X) = s_O^-(X) - s_O^-(H)$, at the O-site for (a) saturated and (b) unsaturated hydroxylamine derivatives as the chain length increases. Fukui functions are calculated using one frontier orbital.

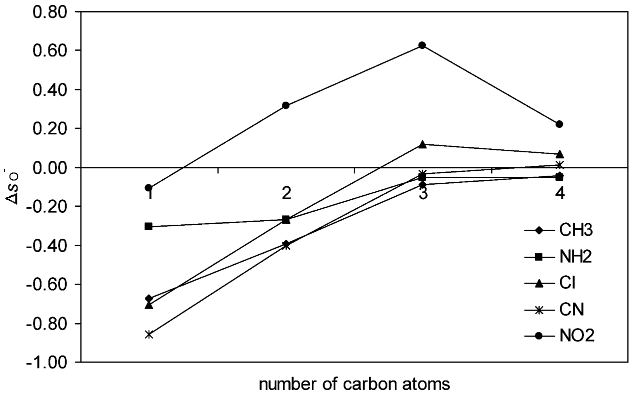


Figure 3. Variation of relative condensed softness, $\Delta s_O^-(X) = s_O^-(X) - s_O^-(H)$, at the O-site for saturated hydroxylamine derivatives as the chain length increases. Fukui functions are calculated using five frontier orbitals except for NO_2-containing systems for which 10 orbitals are used.

Figure 2 is mainly provided to show that the substituent effect changes with an increase in the chain length and ultimately dies down. To recover this fact arising out of chemical intuition, sometimes more than one frontier orbital is necessary to approximate the Fukui function. For a reasonably good result, 5 frontier orbitals for the saturated systems (NO_2-substituted compounds need 10 orbitals) and 10 frontier orbitals for the unsaturated systems suffice. It may, however, be noted that the number of frontier orbitals is chosen in an ad hoc manner.

Global and local (condensed to N- and O-centers) softnesses for the saturated and unsaturated compounds are respectively presented in Tables 1 and 2. In general, the substituted systems (both saturated and unsaturated) are softer than the corresponding unsubstituted ones.

Considering the $+I$ and $-I$ nature of the substituents, for the saturated hydroxylamine derivatives, one would expect that $s_O^-(CH_3)$ and $s_N^-(CH_3)$ would be larger than $s_O^-(H)$ and $s_N^-(H)$, respectively, and $s_O^-(X{\equiv}Cl,NH_2,CN,NO_2)$ and $s_N^-(X{\equiv}Cl,NH_2,CN,NO_2)$ would be smaller than $s_O^-(H)$ and $s_N^-(H)$, respectively, because the CH_3 group will facilitate and Cl, NH_2, CN, and NO_2 groups will hinder electrophilic attacks at N- and O-sites of the $-NHOH$ group due to their electron releasing and electron withdrawing properties, respectively.[1] In more than 50% of the cases, we observe the expected trends (Table 1). Similarly, the resonance effects ($+M$ and $-M$) would dictate that for the unsaturated systems $s_{O,N}^-(CH_3,NH_2,Cl) > s_{O,N}^-(H) > s_{O,N}^-(CN,NO_2)$. In slightly less than 50% of the cases (Table

TABLE 3: Condensed Softness Values Calculated Using a Finite Difference Approximation (au) and Mulliken Charges for Saturated Hydroxylamine Derivatives

	m^a															
	1				2				3				4			
substituent	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N
CH_3	1.1918	1.9431	−0.3648	−0.2518	1.0358	1.7524	−0.3618	−0.2469	1.1681	1.9450	−0.3639	−0.2625	1.0877	1.7733	−0.3639	−0.2641
H	1.2623	2.0077	−0.3682	−0.2565	1.1604	1.9134	−0.3651	−0.2483	1.1846	1.9367	−0.3643	−0.2601	1.1346	1.7919	−0.3639	−0.2616
Cl	1.0975	1.6626	−0.3597	−0.2384	0.9048	1.5002	−0.3495	−0.2419	1.0441	1.5436	−0.3595	−0.2631	0.9726	1.5421	−0.3611	−0.2601
NH_2	0.9647	1.2117	−0.3685	−0.2630	0.3689	0.9987	−0.3735	−0.2454	0.7570	1.2234	−0.3650	−0.2635	0.6705	0.9715	−0.3638	−0.2634
CN	1.2859	2.5691	−0.3570	−0.2548	1.0513	1.6437	−0.3548	−0.2329	1.1832	1.7900	−0.3573	−0.2645	1.1001	1.7496	−0.3604	−0.2614
NO_2	1.6426	1.9394	−0.3560	−0.2268	1.1791	2.0715	−0.3611	−0.2421	1.5583	2.4528	−0.3573	−0.2670	1.3379	2.0931	−0.3600	−0.2607

[a] For *m*, see the text.

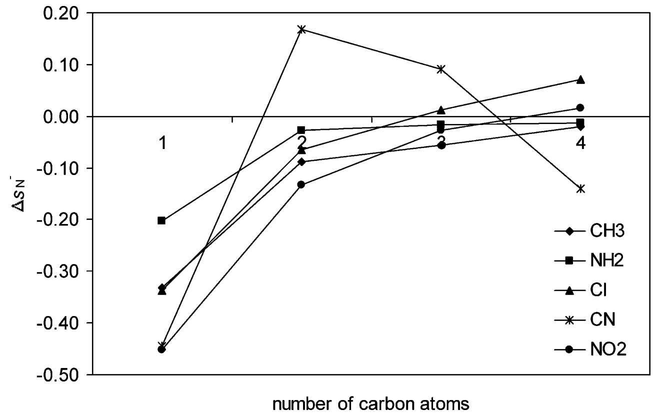


Figure 4. Variation of relative condensed softness, $\Delta s_N^-(X) = s_N^-(X) - s_N^-(H)$, at the N-site for saturated hydroxylamine derivatives as the chain length increases. Fukui functions are calculated using five frontier orbitals except for NO_2− containing systems for which 10 orbitals are used.

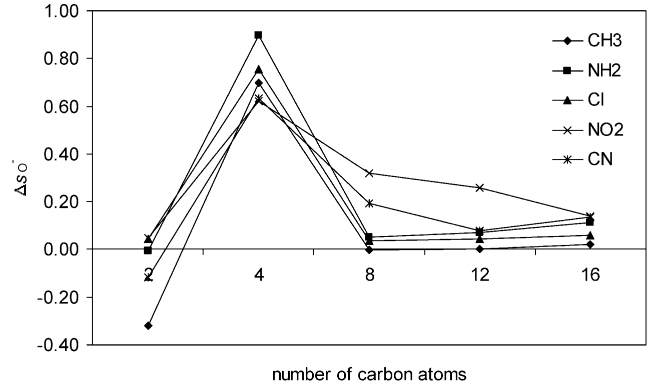


Figure 5. Variation of relative condensed softness, $\Delta s_O^-(X) = s_O^-(X) - s_O^-(H)$, at the O-site for unsaturated hydroxylamine derivatives as the chain length increases. Fukui functions are calculated using 10 frontier orbitals.

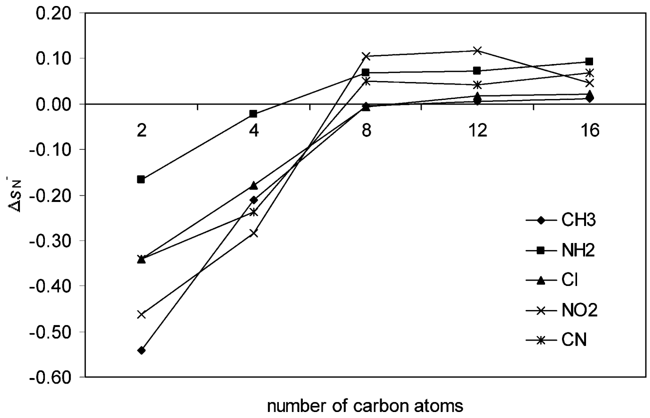


Figure 6. Variation of relative condensed softness, $\Delta s_N^-(X) = s_N^-(X) - s_N^-(H)$, at the N-site for unsaturated hydroxylamine derivatives as the chain length increases. Fukui functions are calculated using 10 frontier orbitals.

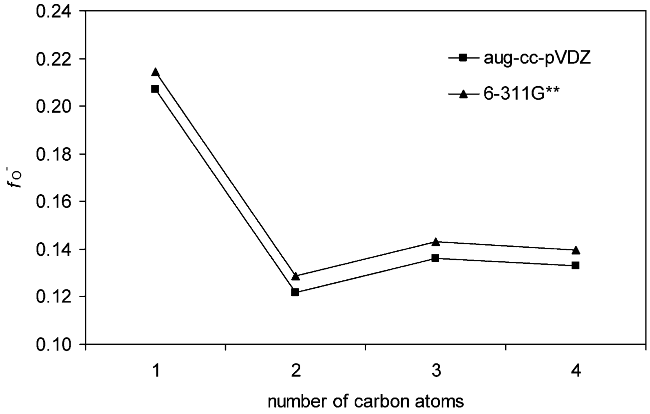


Figure 7. Variation of f_O^- for saturated hydroxylamine derivatives as the chain length increases for two different basis sets. This analysis was done just for the NO_2-substituted systems.

2), this happens to be true. It points out that there are other effects (including resonance effect for the saturated systems and inductive effect for the unsaturated systems), in addition to those considered above. Figures 3−6 depict these aspects. In almost all cases, the substituent effect becomes negligible for a large chain length when the substituent is far away from the active center although it does not go to zero monotonically.

Figure 7 delineates the adequacy of the 6-311G** basis set as it gives identical trends as with aug-cc-pVDZ basis set.

Table 3 reports the Mulliken charges and condensed softnesses (calculated using a finite difference approximation, eq 10) at the N- and O-sites of the saturated hydroxylamine derivatives. In more than 60% of the cases, the result is as expected. The charges properly reflect the reactivity toward hard electrophiles whereas the condensed softnesses adequately take care of the reactivity toward soft electrophiles.

Mulliken charges and condensed softnesses (using eq 10) at the N- and O-centers of the unsaturated hydroxylamine derivatives are presented in Table 4. The reactivity toward hard electrophiles is taken care of well by Mulliken charges (nearly 70% of the cases). The Cl-substituted compounds give consistently bad results. Unfortunately, the condensed softnesses cannot properly describe the reactivity toward the soft electrophiles. Note that a much better picture emerges in case the charges are taken with the negative sign (not the population/gross charge).

The new results obtained in the present work vis-à-vis what is expected from classical organic chemistry may be summarized as follows:

TABLE 4: Condensed Softness Values Calculated Using a Finite Difference Approximation (au) and Mulliken Charges for Unsaturated Hydroxylamine Derivatives

	n^a																			
	1				2				4				6				8			
substituent	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N	s_O^-	s_N^-	q_O	q_N
CH_3	0.7933	0.1268	−0.3332	−0.1918	0.8793	1.0918	−0.3306	−0.1900	0.7976	0.8709	−0.3268	−0.1879	0.7361	0.7366	−0.3253	−0.1871	0.6814	0.6375	−0.3245	−0.1868
NH_2	0.9122	0.1971	−0.3522	−0.2371	0.8773	0.9167	−0.3395	−0.1922	0.7743	0.7491	−0.3328	−0.1889	0.7025	0.6466	−0.3295	−0.1877	0.6397	0.5804	−0.3276	−0.1872
Cl	0.9561	1.1338	−0.3386	−0.2331	0.8634	1.1163	−0.3228	−0.1890	0.8113	0.9097	−0.3222	−0.1873	0.7572	0.7854	−0.3222	−0.1867	0.7045	0.6981	−0.3223	−0.1865
H	1.0863	1.3231	−0.3472	−0.2326	0.9182	1.1924	−0.3271	−0.1892	0.8322	0.9258	−0.3247	−0.1876	0.7620	0.7861	−0.3238	−0.1870	0.7037	0.6806	−0.3234	−0.1867
CN	1.0675	1.2549	−0.3238	−0.2276	0.9017	1.2040	−0.3107	−0.1903	0.8688	1.0087	−0.3149	−0.1876	0.8132	0.8992	−0.3173	−0.1866	0.7675	0.7714	−0.3189	−0.1862
NO_2	1.2689	1.5857	−0.3120	−0.2036	1.0137	1.4105	−0.3039	−0.1977	0.9410	1.1235	−0.3115	−0.1883	0.8963	0.9577	−0.3150	−0.1871	0.8192	0.8648	−0.3171	−0.1867

[a] For n, see the text.

1. Substituent effects for the saturated hydroxylamine derivatives are mainly inductive in nature, e.g., electron donating CH_3 ($+I$) and electron withdrawing NH_2, Cl, CN, NO_2 ($-I$), which is shown to be true in the majority of the cases, and for the cases which are exceptions, the other effects (e.g., resonance, steric effect, solvent effect, and other effects originating from weak interactions) are considered to contribute significantly. The discrepancies may also be due to the inadequacy of the conceptual DFT based reactivity descriptors and/or their method of calculation.

2. For the unsaturated hydroxylamine derivatives, the major substituent effect is mesomeric in nature, e.g., electron releasing NH_2, Cl ($+M$), CH_3 (hyperconjugation) and electron withdrawing CN, NO_2, ($-M$). This trend is observed in many cases where resonance may be assumed to be the major guiding factor.

3. The substituent effect dies down as we move away from it. This is shown to be true albeit not in a monotonic way.

4. To check the direction of the electron flow, a comparison between substituents of $+I$ and $-I$ and/or $+M$ and $-M$ categories is made and it is heartening to note that the expected trend is reproduced in the majority of cases. It may, however, be noted that the way the substituent effect decreases with chain length is different for different substituents.

5. Several factors are to be considered simultaneously even for simple systems such as those studied here and even in the absence of any solvent or external field, to adequately explain the effect of a substituent.

6. Hard−hard interactions are mostly electrostatic in nature and hence charge controlled but soft−soft interactions are mainly covalent in nature and hence frontier-controlled. Propensity of attack by hard electrophiles to the N- and O-centers of saturated and unsaturated hydroxylamine derivatives in the presence of different substituents ($\pm I$, $\pm M$) and different chain lengths is much better delineated by the Mulliken charges than the corresponding attack by soft electrophiles analyzed in terms of the associated local softnesses. It also highlights the fact that the nature of the electrophile in addition to that of the substituent is more important in the case of a soft−soft interaction when compared to that of a hard−hard interaction.

7. More than one frontier orbital is to be taken into account to have a consistent reactivity pattern.

5. Conclusions

Effects of substituents, including their positions relative to those of the active centers are analyzed for several saturated and unsaturated hydroxylamine derivatives by using different conceptual DFT based reactivity descriptors. In most cases, the inductive and resonance effects are properly taken care of. This study highlights the importance of considering several effects together. A single effect (inductive or resonance) may not be always adequate in delineating the overall effect of the substituent. The amount of chemical perturbation caused by a substituent eventually goes to zero when it is far away from the reactive centers. However, the decrease in the substituent effect with an increase in the chain length is not monotonic, even in a simple situation such as the one used in this work.

Acknowledgment. This work received financial support from CONACYT (México) under Contract No. 36482-E. We thank the Laboratorio de Visualización y Cómputo Paralelo at UAM-Iztapalapa for access to its computer facilities. N.G.-R. and M.H.M. thank CONACYT for Ph.D. scholarships. Valuable comments from Professor Andrés Cedillo are gratefully acknowledged. We thank the referee for constructive criticism, Professor Amit Basak for helpful discussion, and Mr. Utpal Sarkar for his help in the manuscript preparation.

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