SUBSTITUENT EFFECTS IN FRONTIER ORBITALS OF CYCLIC HYDROXAMIC ACIDS

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Abstract- AM1 full geometry optimization of seven substituted cyclic hydroxamic acids (Hx) was performed. A qualitative correlation between E_{lumo} vs Hammett's σ_p was observed. The reactivity of these 7-substituted Hx with hard nucleophiles seems to follow basic principles of frontier orbitals theory. Experimental support was obtained from the reaction of six Hx with 2-methoxyethylamine.

Cyclic hydroxamic acids (Hx), present in cereal extracts, show a number of different biological activities.[1] The main Hx component in maize and wheat is 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA), while in rye it is the demethoxylated analog (DIBOA) (Figure 1).[2] Little is known about the molecular mechanism of action of these compounds, however their biological activity has been associated with their strong electrophilic character.[2] It has been suggested that this activity is related to electrophile-nucleophile interactions, that should arise from nucleophilic centers such as amine or thiol groups from amino acid residues, present in enzymes involved in fundamental processes.[3-5] The chemical reactivity of these natural products and their derivatives has been studied in some detail.[2,6-9] Structure-reactivity relationships have shown that the pseudo-first order rate constants for the decomposition in solution, as well as the ionization constants and antimicrobial activity, depends on the electron-donor-acceptor characteristics of the substituent on position 7 of the aromatic ring.[10,11]

Electronic effects of the substituent on the electrophilic character of the hydroxamic acid functionality, might be understood in terms of the stabilization of a charged resonant structure (Figure 1), where the unshared electrons of the nitrogen atom are delocalized to the carbonyl fragment, and to a lesser extent to the aromatic ring.[12]

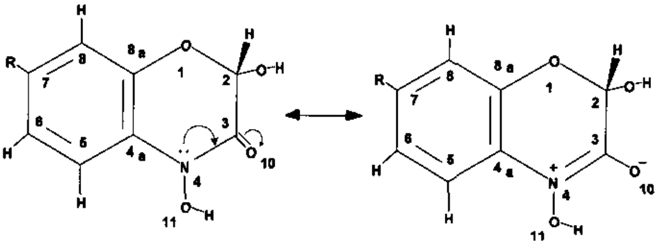


Figure 1

($R = NH_2$, OCH_3, CH_3, H, Cl, CN, NO_2)

This structure has been postulated as the reactive species against different nucleophiles[12,13] as well as in the antimicrobial activity.[11] These results strongly suggest that the frontier orbitals should have significant aromatic character, partially delocalized over the heterocyclic ring.

In this work we have examined the effect that substitution in position 7 of the aromatic ring has on the frontier orbitals energy of a series of cyclic hydroxamic acids. The orbital energies were obtained from fully optimized AM1 structures,[14] and the probability function of the frontier orbitals of two representative members of the series were calculated using the CNDO/2 approximation,[15] and plotted. Experimental data was obtained from the reaction of the Hx with 2-methoxyethylamine, in non-aqueous solution.

DIMBOA and DIBOA were isolated from ethereal extracts of maize (Zea mays L.) c.v.T.-128 and rye (Secale cereale L.) c.v. Tetra respectively, using a process described before.[3] The other members of the series were prepared following previously reported synthetic routes.[10,16] Second order rate constants for the reaction of six Hx with 2-methoxyethylamine were obtained by measuring the dissapearence of the uv absorption band, characteristic of these molecules, as a function of time, in anhydrous dioxane. The concentrations were 6 x 10^{-5} M the hydroxamic acid and 12 x 10^{-5} M the amine. Unimolecular decomposition controls were performed in parallel and no measurable disappearance of the Hx was observed. Standard errors on the measured rate constants were smaller than 5%.

The AM1 molecular orbital calculations were performed using the program MOPAC v. 6.0[17] running on an APOLLO DN-10000 computer. The CNDO/2 calculations were performed with a modified version of Pople's original program,[15] and the probability functions of the frontier orbitals were calculated and plotted using a program previously written for that purpose.[18]

Table 1 shows selected geometrical parameters of the minimum energy calculated structures. Apparently the substituent at position seven has no effect on the conformation of the heterocyclic ring.

Table 1. Selected torsional angles of the Hx, calculated using the AM1 method.

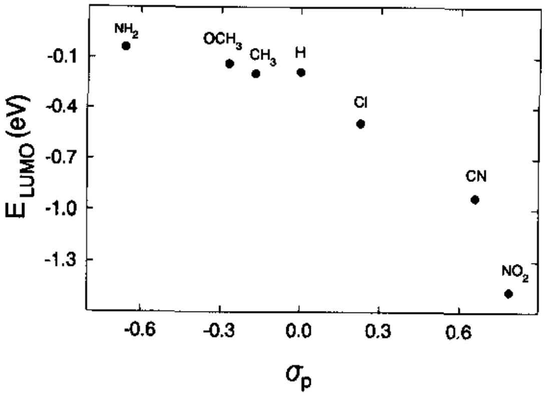
TORSION (degrees) R:	NH_2	OCH_3	CH_3	H	Cl	CN	NO_2
$C_5C_4N_3O_{11}$	-164	-164	-164	165	-164	-165	-167
$O_1C_2C_3N_4$	42	42	41	42	41	41	41
$C_3C_2O_1C_{8a}$	- 33	- 34	- 33	- 34	- 33	- 33	- 34
$C_2O_1C_{8a}C_{4a}$	18	18	18	18	19	18	19
$O_{10}C_3N_4O_{11}$	23	23	22	21	22	21	20

Table 2 shows the AM1 total energy and the frontier orbitals energy of the fully optimized geometries of the 7-substituted Hx. The negative values of the LUMO energies shows the strong electrophilic character of these molecules. The electronic effect of these substituents on the LUMO energies is compared with the Hammett's σ_p constants[19] and a qualitative correlation is observed (Figure 2). The electrophilic characteristics of these Hx could be associated to the nature of the LUMO orbitals.

Table 2. Frontier orbitals and total energies for the 7-substituted Hx calculated using the AM1 method.

R	$E_{tot.}$(eV)	E_{homo}(eV)	E_{lumo}(eV)
NH_2	- 2828.089	- 8.524	- 0.038
OCH_3	- 3083.077	- 8.845	- 0.135
CH_3	- 2763.092	- 9.015	- 0.195
H	- 2607.222	- 9.169	- 0.185
Cl	- 2967.297	- 9.228	- 0.492
CN	- 2927.682	- 9.485	- 0.930
NO_2	- 3437.997	- 9.867	- 1.479

Figure 2. Correlation between the energy of the LUMO and the σ_p Hammett parameters of the Hx.



The LUMO energies were obtained from a AM1 closed shell single-determinant calculation. To obtain more information about the nature of the frontier orbitals, a CNDO/2 calculation and plot of the probability functions were performed on two representative members of the series, the nitro and methoxy derivatives. There were no particular reasons to choose CNDO/2 instead of AM1 for the representation of the frontier orbitals, except that the program was already available.[18] Even more, the CNDO/2 coefficients in the expansions of the orbitals are very similar to those obtained using the AM1 approximation. The CNDO/2 calculations were performed on the AM1 minimium energy structures. The plot is shown in *Figure 3 and* can be observed that the effect of substitution at position 7 affects mainly the LUMO orbital. The LUMO shows an important charge displacement from the nitrogen over the carbonyl group, particularly *with electron-donor substituents, in agreement* with the postulated resonant structures.

Around the hydroxamic acid group the LUMO of DIMBOA is able to accomodate higher electron density than the LUMO of the nitro derivative. Even more, this seems to indicate that the effect of the substituent in the electrophilic character of these molecules is principally related to the hydroxamic acid group. These results support the hypothesis that the reactivity of these molecules against nucleophiles should be related to the electrophilic character of the LUMO. According to frontier orbitals theory,[20] the molecule with higher energy LUMO will be a harder electrophile, and consequently should react faster with a hard nucleophile. Similarly, molecules with lower energy LUMO will not be as hard, and should react comparatively slower.

To test this prediction, we have measured second order rate constants *for the decomposition of six of the Hx* with 2-methoxyethylamine, a hard nucleophile, in anhydrous dioxane. As observed from Figure 4, the logarithm of the second order rate constant, correlates qualitatively with the energy of the LUMO orbital. Therefore, the reactivity of these hydroxamic acids against nucleophiles can be understood in terms of electronic effects of the substituent on the reactive molecular orbital. For instance, the stability of the resonant charged species that has been postulated in the reactivity of the Hx (Figure 1), must be strongly influenced by the electronic properties of substituents at position 7.

Figure 3. Electron density plots of the HOMO and LUMO ortbitals of DIMBOA and the 7-Nitro derivative. Contours are x 10^{-3} electrons and calculated 0.1Å above the aromatic ring plane.

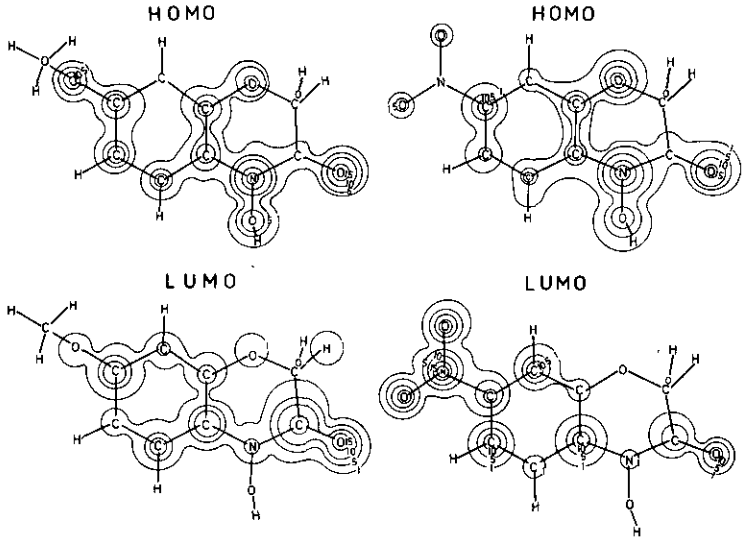
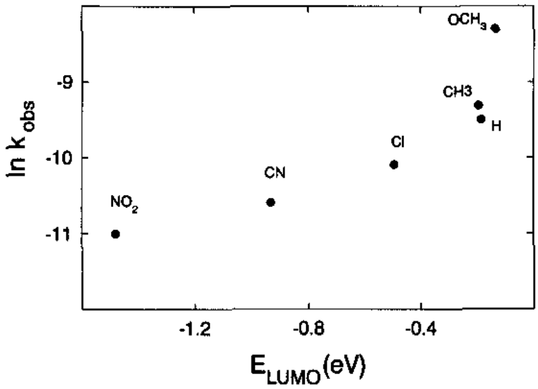


Figure 4. Plot of the logarithm of the second order rate constants versus the energy of the LUMO orbital.



From this work we conclude that substitution at position 7 of these structures does not seems to modify the minimum energy conformation of the heterocycle. Instead, it affects the nature of the frontier orbitals, particularly the LUMO, influencing the reactivity against nucleophiles.

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