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Computational Nanochemistry Report on the Oxicams—Conceptual DFT Indices and Chemical Reactivity

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ABSTRACT: A density functional theory study of eight oxicams was carried out in order to determine their global and local reactivities. These types of reactivities were measured by means of global and local reactivity descriptors coming from the conceptual density functional theory. Net electrophilicity as a global reactivity descriptor and local hypersoftness as a local reactivity descriptor were the used tools to distinguish reactivity and selectivity among these oxicams. Globally, isoxicam presents the highest electron donating capacity; meanwhile, the highest electron accepting capacity is exhibited by droxicam. Locally, two oxicams present neither nucleophilic nor electrophilic relevant reactivity in their peripheral pyridine ring, droxicam and tenoxicam, so that their more reactive zones are found on the respective fused rings. Oxicams have been divided into two subgroups in order to facilitate the local analysis of reactivity. One group is characterized because their most important condensed values for local hypersoftnes are well-separated: 4-meloxicam, lornoxicam, meloxicam, and normeloxicam. Meanwhile, the opposite situation is found in droxicam, isoxicam, piroxicam, and tenoxicam. As a whole, the nucleophilic characteristic noticeably predominates in these eight oxicams instead of an electrophilic behavior, thus meaning a greater tendency to donate electrons rather than withdrawing them; a consequence of this behavior implies a favorable interaction with a hypothetical receptor bearing one or more electron acceptor functional groups rather than electron donor functional groups; this would imply a maximization of this interaction from the covalent point of view.

1. INTRODUCTION

Oxicams belong to a class of non-steroidal anti-inflammatory drugs (NSAIDs) that bind closely to plasma proteins.[1] These are highly efficient drugs to be used in treatments of rheumatological diseases and to reduce the inflammatory effect after surgery. In consequence, there has been an increased interest in performing more investigations concerning this family of compounds. For instance, antioxidant activities of oxicams have been reported[2] and experiments of molecular modeling and docking have been carried out.[3] Interactions between NSAIDs and different models of membrane have been performed;[4] other studies have indicated that oxicams are able to modify membrane properties.[5]

Photophysical studies have revealed that piroxicam, meloxicam, and tenoxicam exhibit an extreme sensitivity to their microenvironment;[6] additionally, the mutagenic potential of piroxicam, meloxicam, and their precursors was evaluated, thus leading to the fact that these drugs are non-genotoxic.[7]

More attention has been paid on the spectra due to their molecular structures;[8,9] from the reactivity point of view and in order to go deep about the possible role of metal ions in the photosensitizing effect of piroxicam in biological systems, metal complexes of piroxicam have been prepared and characterized spectroscopically;[10] metal complexes based on meloxican and tenoxicam have been synthesized and analyzed through X-ray techniques.[11]

Since the polymorphism might have an impact on the quality and efficacy of pharmaceutical products, crystal modifications of piroxicam obtained by crystallization from several solvents using modern analytical techniques have also been characterized. As the reader can note, a lot of experimental research has been carried out and it is still being performed up to today.

In contrast, there are just a few theoretical studies associated with these kinds of compounds. One of them consists of predicting the pK_a of oxicams by means of quantum chemical calculations,[12] but the use of reactivity descriptors has not acquired a main role in the characterization of oxicams. The knowledge of reactivity on a molecule is an essential concept; it is of crucial interest because it allows one to understand interactions that are operating during a reaction mechanism. In particular, electrostatic interactions have been successfully explained by the use of the molecular electrostatic potential.[13,14] On the other hand, there is no unique tool to quantify and rationalize covalent interactions.

However, with the aim of evaluating the reactivity of sites for covalent interactions, since 2005, a descriptor of local reactivity whose name is simply dual descriptor[15,16] has allowed reaction mechanisms to be rationalized in terms of overlapping

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nucleophilic regions with electrophilic regions in order to get a maximum stabilization, thus leading to final products or intermediates; all those favorable nucleophilic−electrophilic interactions have been explained as a manifestation of the principle of maximum hardness;[17] in addition, chemical reactions have been understood in terms of the the hard and soft acids and bases principle,[15,18−20] a principle that has been used even with the aim of replacing the use of the molecular orbital theory to understand the whole chemistry.[21] In fact, the present work is a good chance to test the capability of the most recent reactivity descriptors coming from the conceptual DFT;[22−25] therefore, the framework of this conceptual theory will be presented in the next section.

2. THEORETICAL BACKGROUND

Within the conceptual framework of DFT,[24] the chemical potential μ, which measures the escaping tendency of electron from equilibrium, is defined as

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

where χ is the electronegativity.

The global hardness η[26−29] can be seen as the resistance to charge transfer, and its importance is based on the fact that it rules chemical reactions giving rise to the principle of maximum hardness.[29,30] Its mathematical definition is exposed as follows:

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

Along with the latter, a connection between the Fukui function and the chemical hardness has been entirely developed by Ayers and Parr, thus establishing variational principles for describing chemical reactions.[31] Proofs and applications of these principles have been published by Torrent-Sucarrat and co-workers.[32−34]

Using a finite difference approximation, eqs 1 and 2 are written in terms of the first vertical ionization potential, I, and the first vertical electron affinity, A; additionally with the use of the Koopmans' theorem,[35−38] the above expressions can be written in terms of ε_H and ε_L, meaning the energies of the highest occupied and lowest unoccupied molecular orbitals, HOMO and LUMO, respectively. However, in order to obtain a higher accuracy in our results, the use of the finite difference approximation has been employed, so that the Koopmans' theorem was not used at all in the present work, thus leading to computation of the global reactivity descriptors only in terms of I and A as follows:

$$\mu \approx -\frac{1}{2}(I + A) \tag{3}$$

$$\eta \approx (I - A) \tag{4}$$

At the beginning, the chemical hardness had been defined including a 1/2 factor, and written so, it has been used to estimate the electronic properties of simple solids.[39] Currently, according to the modern notation, such a coefficient is not more used without affecting the most essential conclusions like the elucidation of the hard/soft acid/base principle.[20] Since the global softness is defined as the reciprocal of chemical hardness,[24] its physical significance is immediate because it quantifies the ease to charge transfer of a system:

$$S = \left(\frac{\partial^2 E}{\partial N^2}\right)^{-1}_{v(\mathbf{r})} \tag{5}$$

The operational formula is directly deduced:

$$S \approx (I - A)^{-1} \tag{6}$$

Returning to the main two global reactivity descriptors of conceptual DFT, it is important to bear in mind that the chemical potential is not able to measure the electrophilicity by itself; furthermore, a criterion of electrophilicity should take into account the effect of both chemical potential and chemical hardness. With such a purpose, the electrophilicity index, ω, was proposed as cited in the respective literature.[40−43] It represents the stabilization energy of the system when it gets saturated by electrons coming from the surrounding:

$$\omega = \frac{\mu^2}{2\eta} \approx \frac{(I + A)^2}{8(I - A)} \tag{7}$$

This global reactivity descriptor must be understood as an intrinsic quantifier of electrophilicity that arises when the molecular system under analysis is put in contact with a reservoir of electrons having zero chemical potential and zero chemical hardness; hence, this descriptor measures the absolute electrophilicity.

The electron donating (ω^-) and electron accepting (ω^+) powers have been defined as[44]

$$\omega^- = \frac{(3I + A)^2}{16(I - A)} \tag{8}$$

and

$$\omega^+ = \frac{(I + 3A)^2}{16(I - A)} \tag{9}$$

It follows that a larger ω^+ value corresponds to a better capability of accepting charge, whereas a smaller ω^- value of a system makes it a better electron donor. In order to compare ω^+ with $-\omega^-$, the following definition of net electrophilicity has been proposed:[45]

$$\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^- \tag{10}$$

that is, the electron accepting power relative to the electron donating power. This global reactivity descriptor measures the relative electrophilicity; that is why it is called the net electrophilicity.

After providing the physical meaning for global reactivity descriptors mathematically defined, local reactivity descriptors will be defined in more detail. Electronic density is the first local reactivity descriptor to be used when electrostatic interactions are predominant between molecules; within the framework of conceptual DFT,[29,46−51] it is defined as follows:

$$\rho(\mathbf{r}) = \left[\frac{\delta E}{\delta v(\mathbf{r})}\right]_N$$

However, when chemical reactions are governed by interactions mainly of covalent nature, in such a case, a second-order LRD called Fukui function[24,52−54] is used instead of electronic density. Fukui function is defined in terms of the derivative of $\rho(\mathbf{r})$ with respect to N; through a Maxwell relation, the same descriptor is interpreted as the variation of μ (the chemical potential) with respect to $v(\mathbf{r})$[24] (the external potential):

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$$f(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})} = \left[\frac{\delta \mu}{\delta v(\mathbf{r})}\right]_N \tag{11}$$

The function $f(\mathbf{r})$ reflects the ability of a molecular site to accept or donate electrons. High values of $f(\mathbf{r})$ are related to a high reactivity at point $\mathbf{r}$.[24]

Since the number of electrons N is a discrete variable,[55] right and left derivatives of $\rho(\mathbf{r})$ with respect to N have emerged. By applying a finite difference approximation to eq 11, two definitions of Fukui functions depending on total electronic densities are obtained:

$$f^+(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)^+_{v(\mathbf{r})} = \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r}) \tag{12}$$

$$f^-(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)^-_{v(\mathbf{r})} = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r}) \tag{13}$$

where $\rho_{N+1}(\mathbf{r})$, $\rho_N(\mathbf{r})$, and $\rho_{N-1}(\mathbf{r})$ are the electronic densities at point $\mathbf{r}$ for the system with $N + 1$, N, and $N - 1$ electrons, respectively. The first one, $f^+(\mathbf{r})$, has been associated to reactivity for a nucleophilic attack so that it measures the intramolecular reactivity at site $\mathbf{r}$ toward a nucleophilic reagent. The second one, $f^-(\mathbf{r})$, has been associated to reactivity for electrophilic attack so that this function measures the intramolecular reactivity at site $\mathbf{r}$ toward an electrophilic reagent.[56]

The densities of frontier molecular orbitals (FMOs), $\rho_L(\mathbf{r})$ (LUMO density) and $\rho_H(\mathbf{r})$ (HOMO density), come to the picture, since it has been shown[56,57] that when the frozen orbital approximation (FOA) is used there is a direct relation between $f^{\pm}(\mathbf{r})$ and the density of the appropriate FMO, thus avoiding calculations of the system with $N + 1$ and $N - 1$ electrons:

$$f^+(\mathbf{r}) \approx \rho_L(\mathbf{r}) \tag{14}$$

$$f^-(\mathbf{r}) \approx \rho_H(\mathbf{r}) \tag{15}$$

On the other hand, the use of eqs 14 and 15 (second level of approximation to the dual descriptor) instead of eqs 12 and 13 (first level of approximation to dual descriptor) allows one to prevent performing a calculation involving species with $N + 1$ and $N - 1$ electrons without losing the qualitative picture of the local reactivity. The first level of approximation based on total electronic densities will always be more accurate than the second level of approximation based on densities of FMOs.

Condensation to atoms is achieved through integration within the kth-atomic domain Ω_k:[58,59]

$$f_k^{+/-} = \int_{\Omega_k} f^{+/-}(\mathbf{r})\, d\mathbf{r} \tag{16}$$

$f_k^{\pm}$ is now an atomic index that is used to characterize the electrophilic/nucleophilic power of atom k.

Even much better, Morell et al.[15,16,21,60−63] have proposed a local reactivity descriptor (LRD) which is called the dual descriptor (DD) $f^{(2)}(\mathbf{r}) \equiv \Delta f(\mathbf{r})$. In spite of having been discovered several years ago, a solid physical interpretation was not provided in such a moment.[64] Morell and co-workers used the notation $\Delta f(\mathbf{r})$, but currently it has been replaced by the modern notation $f^{(2)}(\mathbf{r})$ in order to highlight the fact that this is a Fukui function of second order. Its physical meaning is to reveal nucleophilic and electrophilic sites on a molecular system at the same time. Mathematically, it is defined in terms of the derivative of the Fukui function, $f(\mathbf{r})$,[24] with respect to the number of electrons, N. Through a Maxwell relation, this LRD may be interpreted as the variation of η (the molecular hardness which measures the resistance to charge transfer[27]) with respect to $v(\mathbf{r})$, the external potential. The definition of $f^{(2)}(\mathbf{r})$ is shown as indicated by Morell et al.:[15,16]

$$f^{(2)}(\mathbf{r}) = \left(\frac{\partial f(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})} = \left[\frac{\delta \eta}{\delta v(\mathbf{r})}\right]_N \tag{17}$$

As mentioned above, DD allows one to obtain simultaneously the preferable sites for nucleophilic attacks ($f^{(2)}(\mathbf{r}) > 0$) and the preferable sites for electrophilic attacks ($f^{(2)}(\mathbf{r}) < 0$) into the system at point $\mathbf{r}$. The importance of this local reactivity descriptor has been demonstrated by means of a re-interpretation of Woodward−Hoffmann rules.[65] DD has also demonstrated to be a robust tool to predict specific sites of nucleophilic and electrophilic attacks in a much more efficient way than the Fukui function by itself because a dual descriptor is able to distinguish those sites of true nucleophilic and electrophilic behavior; in consequence, some works have been published with the aim of remarking the powerfulness of $f^{(2)}(\mathbf{r})$ and all those LRDs depending on DD.[15,16,21,60−63,66,67]

The general working equation to obtain DD is given by the arithmetic difference between nucleophilic and electrophilic Fukui functions.[21] A well-known first level of approximation, provided that the original system is electrically neutral and contains N electrons, implies the use of the finite difference method where the sum of electronic densities of the system with one more electron ($N + 1$ electrons, meaning an anion) and one less electron ($N - 1$ electrons, meaning a cation) is subtracted by the double of the total electronic density of the original system provided that there is no degeneracy in frontier molecular orbitals at least. Inasmuch as this level of approximation implies a risk in getting a proper convergence in anions under quantum chemical treatment, a second level of approximation has been used for some years ago, thus involving the use of densities of frontier molecular orbitals as follows:

$$f^{(2)}(\mathbf{r}) = f^+(\mathbf{r}) - f^-(\mathbf{r}) \approx \rho_L(\mathbf{r}) - \rho_H(\mathbf{r}) \tag{18}$$

where the densities of the LUMO and HOMO are represented by $\rho_L(\mathbf{r})$ and $\rho_H(\mathbf{r})$, respectively. Molecular symmetry can have an influence upon the local reactivity, and on the other hand, it has been demonstrated that the Fukui function must conserve the symmetry.[68] Observations that density and density derivatives must transform according to the totally symmetric representations were noticed by De Proft and co-workers,[69] and the mathematical foundations with the aim of facing possible degenerate states[70] were developed previously to this work; in consequence, all elements of analysis from the point of view of conceptual DFT are now available to broach different types of molecular systems. In addition, inasmuch as the degeneracy that may arise in frontier molecular orbitals is related with the molecular symmetry, within the framework of the second level of approximation, this phenomenon has been taken into account, thus providing a mathematical expression to be applied on closed-shell molecular systems, such an expression has been tested on highly symmetric molecules like Buckminster fullerene.[71,72]

Hence, when an interaction between two species is well described through the use of this LRD, it is said the reaction is controlled by frontier molecular orbitals (or frontier-

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controlled) under the assumption that remaining molecular orbitals do not participate during the reaction.

Since chemists are more interested in atoms and not in locations in 3D space given by a vector position **r**, the dual descriptor can also be condensed through an appropriate integration within the *k*th atomic domain Ω_k:

$$\int_{\Omega_k} f^{(2)}(\mathbf{r})\, d\mathbf{r} = f_k^{(2)} \tag{19}$$

When $f_k^{(2)} > 0$, the process is driven by a nucleophilic attack on atom *k* and then that atom acts an electrophilic species; conversely, when $f_k^{(2)} < 0$, the process is driven by an electrophilic attack over atom *k* and therefore atom *k* acts as a nucleophilic species. The relevance in using these conceptual tools lies in the fact that they will allow one to rationalize possible reaction mechanisms by following the hard/soft acid/base (HSAB) principle,[73] thus providing a rigorous physical support to any possible specific interaction that might arise when each oxicam can be modeled to establish an interplay with enzymes or any other biological molecule. More detailed and updated information about the physical basis of the global and local HSAB principles and their link with polarizability, charge, and electronegativity has been rigorously developed and mathematically exposed by Ayers.[29]

However, DD is a subintensive property, thus meaning that its condensed values become insignificant as the size of the molecule increases. To overcome this intrinsic behavior of this local reactivity descriptor, another local reactivity descriptor has been defined so that it permits one to measure local reactivities according to the molecular size.[21,61] Such a descriptor is the local hypersoftness whose exact equation is exhibited as follows:[61−63,74,75]

$$s^{(2)}(\mathbf{r}) = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial \mu^2}\right)_{v(\mathbf{r})} = \frac{f^{(2)}(\mathbf{r})}{\eta^2} - \frac{f(\mathbf{r})}{\eta^3}\left\{\left(\frac{\partial \eta}{\partial N}\right)_{v(\mathbf{r})}\right\} \tag{20}$$

Since the term written inside braces is negligible,[61] the respective working equation is expressed as follows:

$$s^{(2)}(\mathbf{r}) \approx \frac{f^{(2)}(\mathbf{r})}{\eta^2} \equiv f^{(2)}(\mathbf{r})\cdot S^2 \tag{21}$$

where *S* stands for the global softness.[24,23,27]

Similarly, the local hypersoftness can also be condensed through an appropriate integration within the *k*th atomic domain Ω_k:

$$\int_{\Omega_k} s^{(2)}(\mathbf{r})\, d\mathbf{r} = s_k^{(2)} \tag{22}$$

Then, the use of local hypersoftness allows one to make sure that the measurement of local reactivity on a molecular system will be comparable with the local reactivity of other systems without considering differences in size.

3. COMPUTATIONAL METHODS

All computational studies were performed with the Gaussian 09[76] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of all molecules were determined by means of the gradient technique.[77,78] The force constants and vibrational frequencies were determined by computing analytical frequencies on the stationary points obtained after the optimization to check if there were true minima.

For the calculation of the molecular structure and properties of the studied systems, we have chosen the hybrid meta−GGA density functional M06,[79−83] which consistently provides satisfactory results for several structural and thermodynamic properties.[79,80,84] The basis sets used in this work were CBSB7 (which is equal to the 6-311G(2d,d,p)) for molecular structures and CBSB3 (which is equal to the 6-311++G(2df,2p) on H−Ne and to the 6-311++G(3d2f) on Na−Ar) basis sets[85,86] for the other electronic properties.

The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. As an approximation to eq 16, Yang and Mortier[87] proposed condensed functions are given by $f_k^+ = q_k(N+1) - q_k(N)$ (for nucleophilic attack), where q_k stands for the electronic population on atom *k* in the molecule; a similar expression was defined to obtain f_k^-. The main problem when using this approach lies in the fact that quantum chemical calculations on anions might not converge, thus preventing the computation of condensed Fukui functions by means of this mathematical procedure. More about condensation of Fukui functions can be found in refs 58, 59, and 88−90. Fortunately, it is possible to evaluate condensed Fukui functions with more accuracy from single-point calculations directly, without resorting to additional calculations involving the systems with $N - 1$ and $N + 1$ electrons:

$$f_k^+ = \sum_{a\in k}\left[c_{ai}^{\,2} + c_{ai}\sum_{b\neq a} c_{bi}S_{ab}\right] \qquad (\text{where } i = \text{LUMO}) \tag{23}$$

and

$$f_k^- = \sum_{a\in k}\left[c_{ai}^{\,2} + c_{ai}\sum_{b\neq a} c_{bi}S_{ab}\right] \qquad (\text{where } i = \text{HOMO}) \tag{24}$$

with c_{ai} being the LCAO coefficients and S_{ab} the overlap matrix. The condensed Fukui functions are normalized; thus, $\sum_k f_k = 1$.

Since this method has been derived from Mulliken population analysis, the use of a large and highly diffuse basis set is not recommended. Even so, since our main interest is oriented in obtaining some condensed values of the dual descriptor instead of electrophilic and nucleophilic Fukui functions by themselves, the use of eqs 23 and 24 is accepted owing to the mathematical design of the dual descriptor, as eq 18 indicates a cancellation or decrease of the intrinsic error contained on each Fukui function by an arithmetic subtraction as defined for computing the dual descriptor. The robustness of the dual descriptor has been demonstrated by means of providing qualitatively the same information even after changing the basis set.[72]

The condensed Fukui functions, according to eqs 23 and 24, have been calculated using the AOMix molecular analysis program[91,92] starting from single-point energy calculations. We have presented, discussed, and successfully applied the described procedure in our previous studies on different molecular systems.[93−96] The condensed dual descriptor has been defined as $f_k^{(2)} = f_k^+ - f_k^-$;[15,16] hence, local hypersoftness is simply computed as $s_k^{(2)} \simeq (f_k^{(+)} - f_k^-)\cdot(I - A)^{-2}$. On each oxicam, condensed local hypersoftness values were obtained by a multiplication between its respective squared global softness and the condensed-on-atom dual descriptor, thus giving origin to the condensed-on-atom local hypersoftness column as

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observed in Tables 3−10. The procedure is explained as follows: $f_k^{(2)}$ is expressed in atomic units. Meanwhile, S is measured in milli eV raised to the power of −1; however, before performing the multiplication, the milli factor is turned back into 10^{-3} and then S is raised to the power of 2. The resulting value uses the unit milli eV raised to the power of −2, meaning m(eV^{-2}); the parentheses is put in order to make clear that the prefix milli is not raised to the power of −2.

4. RESULTS AND DISCUSSION

The molecular structures of the eight oxicams—4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam—considered in this study are shown in Figures 1−8.

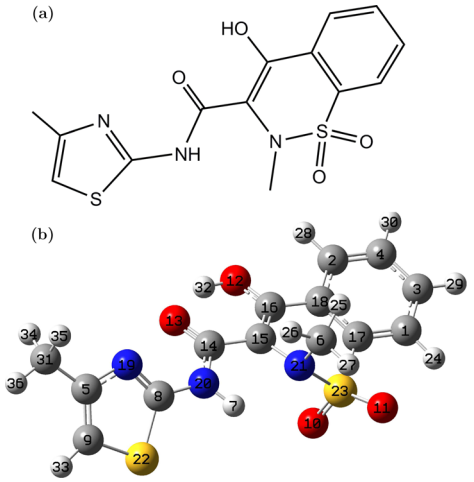

Figure 1. (a) 4-Meloxicam structural formula. (b) Optimized molecular structure of the 4-meloxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

The results for the calculation of the first vertical ionization potentials I and the first vertical electron affinities A, global electronegativity χ, total hardness η, global electrophilicity ω, and global softness S of the 4-meloxican, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam molecules with the M06 density functional and the CBSB3 basis set are presented in Table 1.

Table 1. Ionization Potential I, Electron Affinities A, Electronegativity χ, Total Hardness η, Global Electrophilicity ω, and Global Softness S of the 4-Meloxican, Droxicam, Isoxicam, Lornoxicam, Meloxicam, Normeloxicam, Piroxicam, and Tenoxicam Molecules Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

oxicam	I	A	$\chi = -\mu$	η	ω	S
4-meloxicam	7.962	0.957	4.460	7.005	1.419	142.8
droxicam	8.679	1.813	5.246	6.866	2.004	145.6
isoxicam	8.021	0.738	4.380	7.283	1.317	137.3
lornoxicam	8.012	1.274	4.643	6.738	1.600	148.4
meloxicam	7.988	0.926	4.457	7.062	1.406	141.6
normeloxicam	8.155	0.964	4.560	7.191	1.445	139.1
piroxicam	7.988	0.926	4.457	7.062	1.406	141.6
tenoxicam	7.838	0.857	4.348	6.981	1.354	143.2

[a]All values are expressed in eV units, except for S which is expressed in m(eV)$^{-1}$ units.

The results for the calculation of the electron donating ω^- and electron accepting ω^+ powers and the net electrophilicity $\Delta\omega^\pm$ of the 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam molecules with the M06 density functional and the CBSB3 basis set are presented in Table 2.

Table 2. Electron Donating (ω^-) and Electron Accepting (ω^+) Powers, along with the Net Electrophilicity $\Delta\omega^\pm$ of the 4-Meloxicam, Droxicam, Isoxicam, Lornoxicam, Meloxicam, Normeloxicam, Piroxicam, and Tenoxicam Molecules with the M06 Density Functional and the CBSB3 Basis Set[a]

oxicam	ω^-	ω^+	$\Delta\omega^\pm$
4-meloxicam	5.507	1.047	6.554
droxicam	7.060	1.814	8.875
isoxicam	5.279	0.899	6.177
lornoxicam	5.942	1.299	7.241
meloxicam	5.483	1.026	6.509
normeloxicam	5.620	1.061	6.681
piroxicam	5.483	1.026	6.509
tenoxicam	5.318	0.970	6.288

[a]All values are expressed in eV units.

The results for the calculation of the condensed electrophilic Fukui function $f^-(\mathbf{r})$, nucleophilic Fukui function $f^+(\mathbf{r})$, and dual descriptor $f^{(2)}(\mathbf{r})$ along with the local hypersoftness $s^{(2)}(\mathbf{r})$ over the atoms (with the exception of hydrogen atoms) of the 4-meloxicam, droxicam, isoxicam, lornoxicam, meloxicam, normeloxicam, piroxicam, and tenoxicam molecules with the M06 density functional and the CBSB3 basis set are presented in Tables 3−10, respectively.

From Table 1, it is immediately clear that the order relationship for the chemical potential μ is given as follows:

$$\text{droxicam} < \text{lornoxicam} < \text{normeloxicam} < \text{4-meloxicam} < \text{meloxicam} = \text{piroxicam} < \text{isoxicam} < \text{tenoxicam}$$

In the case of the chemical hardness η, we note that

$$\text{lornoxicam} < \text{droxicam} < \text{tenoxicam} < \text{4-meloxicam} < \text{meloxicam} = \text{piroxicam} < \text{normeloxicam} < \text{isoxicam}$$

From conceptual DFT, it is understood that a reagent with high chemical potential is a good electron donor, whereas a reagent with a small chemical potential is a good electron acceptor. Besides, there is a correspondence between chemical hardness and the stability of the respective reagent so that the molecular system becomes more stable when its chemical hardness increases.

According to this information, it is inferred that droxicam presents the lowest value of chemical potential. Meanwhile, the highest value is exhibited by tenoxicam, meaning that electrons from tenoxicam are willing to leave the system; obviously this is a trend and not a real situation. Thus, along with the trend to leave the system, the difficulty of electrons to leave the system is measured through the use of chemical hardness. As just mentioned in the preceding paragraphs, the chemical hardness complements the analysis; this global reactivity descriptor indicates that lornoxicam presents the lowest resistance to charge transfer; in consequence, some covalent interactions are more favored in this molecule in comparison with possible covalent interactions that would be happening in the remaining

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Table 3. Electrophilic $f^-(\mathbf{r})$ and Nucleophilic $f^+(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the 4-Meloxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00200	0.00620	0.00420	0.08559
C2	0.00650	0.06430	0.05780	**1.17791**
C3	0.00730	0.14410	0.13680	**2.78785**
C4	0.00020	0.04290	0.04270	0.87019
C5	0.17800	0.00050	−0.17750	**−3.61728**
C6	0.00260	0.00230	−0.00030	−0.00611
C8	0.12870	0.00980	−0.11890	**−2.42307**
C9	0.24580	0.00940	−0.23640	**−4.81761**
O10	0.00090	0.00790	0.00700	0.14265
O11	0.00070	0.00650	0.00580	0.11820
O12	0.02260	0.04150	0.01890	0.38516
O13	0.00910	0.04890	0.03980	0.81109
C14	0.00650	0.06920	0.06270	**1.27777**
C15	0.05130	0.09220	0.04090	0.83350
C16	0.02490	0.15360	0.12870	**2.62278**
C17	0.00410	0.10510	0.10100	**2.05828**
C18	0.00200	0.11990	0.11790	**2.40269**
N19	0.01910	0.01180	−0.00730	−0.14877
N20	0.10380	0.01550	−0.08830	**−1.79947**
N21	0.01050	0.01020	−0.00030	−0.00611
S22	0.12690	0.01010	−0.11680	**−2.38027**
S23	0.00230	0.01920	0.01690	0.34441
C31	0.00930	0.00010	−0.00920	−0.18749

[a]All those values that satisfy the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for the condensed local hypersoftness values which are expressed in $m(eV)^{-2}$ units. Hydrogen atoms are not shown.

oxicam-type molecules. On the contrary, isoxicam would prefer interactions with less soft species (or harder species) rather than soft species.

As the reader can notice, the use of more global reactivity descriptors is needed to acquire a more complete insight on the reactivity for each system. For instance, returning to isoxicam, this molecule presents a high chemical potential and a high chemical hardness as well; therefore, the combined effect of both global reactivity descriptors must be observed as a whole; to achieve such a purpose, the electrophilicity is the third global reactivity descriptor in use.

The order relationship for the electrophilicity ω is

$$\text{isoxicam} < \text{tenoxicam} < \text{meloxicam} = \text{piroxicam} < 4$$

$$\text{-meloxicam} < \text{normeloxicam} < \text{lornoxicam} < \text{droxicam}$$

As observed, it is possible to point out that the major energy stabilization due to a maximum electron flow from a donor environment is presented by droxicam, meaning this compound would be favored energetically from a nucleophilic attack. Meanwhile, isoxicam, our example in the former paragraph, exhibits the lowest value of electrophilicity whose interpretation is that it would be less stabilized by a nucleophilic attack in comparison with remaining oxicams.

However, as electrophilicity measures a stabilization energy with respect to an electron bath, in order to obtain a more representative value of electrophilicity for each oxicam, the net electrophilicity $\Delta\omega^{\pm}$ is used, thus revealing a behavior in terms of electron donating ω^- and electron accepting ω^+ powers.

To achieve this goal, I and A values coming from Table 1 are used as inputs to obtain values of Table 2, but note that concepts such as μ^+, μ^- and $\eta = \mu^+ - \mu^-$ lead to exactly the same results according to Gázquez and co-workers.[44] On the basis of these results, it is possible to identify that droxicam exhibits the lowest electron donating power, ω^-, and the highest electron accepting power, ω^+. Nevertheless, isoxicam presents the highest electron donating power and the lowest electron accepting power. Thus, in terms of global reactivity, isoxicam possesses the highest electron donating capacity and droxicam has the highest electron accepting capacity. Only at this point of our analysis, we infer that the use of the net electrophilicity $\Delta\omega^{\pm}$ does not change the analysis performed by means of the electrophilicity ω at all because the order relationship is conserved as follows:

$$\text{isoxicam} < \text{tenoxicam} < \text{meloxicam} = \text{piroxicam} < 4$$

$$\text{-meloxicam} < \text{normeloxicam} < \text{lornoxicam} < \text{droxicam}$$

The molecular structural resemblance among these eight ixocams has shown as a result that order relationships established whether by ω or by $\Delta\omega^{\pm}$ are the same. This information has allowed us to find the most reactive of these eight oxicams from the global point of view.

There is no doubt the information given above would help to facilitate other computational procedures like quantitative structure−activity relationships (QSAR) and quantitative structure−property relationships (QSPR). Nevertheless, conceptual DFT provides local reactivity descriptors to measure specific possible interactions between a candidate for a drug and a specific position on a biomolecule.

Unlike using more than one global reactivity descriptor, our attention has been paid to only one local reactivity descriptor due to its novelty and because its use has not been spread routinely for measuring selectivities in molecules of biological interest as oxicams.

Provided that covalent interactions are a focus of interest in this work, local hypersoftness has been suggested as a suitable tool to distinguish the reactivity on different sites of a molecule in consistency with the molecular size; thus, the obtained information is associated with the selectivity, leading to covalent interactions more or less favorable depending on condensed-on-atom high or low values, respectively. In order to explore and identify all molecular sites that would be susceptible to take part in covalent interactions, the dual descriptor has been used as a first-stage tool because it is suitable, provided nucleophilic and electrophilic Fukui functions have been computed, to quantify the local reactivity (or site selectivity) mainly of covalent nature but without taking into account the molecular size so that its immediate value prevents direct comparisons with other molecules; that is why it must be multiplied by the global softness raised to the square.

For all of oxicams, the condensed Fukui functions, dual descriptor, and local hypersoftness are shown in Tables 3−10. Owing to reasons exposed in the Theoretical Background section, the analysis is focused on local hypersoftness only. In particular, the analysis has been centered on the most important values which were selected by means of an arbitrary criterion which consists of highlighting all of those condensed values of $s_k^{(2)}$ that are equal or greater than 1.0 and equal or less than −1.0. This is summarized as $|s_k^{(2)}| \geq 1.0$. Hydrogen atoms have been excluded from this analysis exposed hereafter.

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When on an oxicam molecule, it is possible to group all of those condensed hypersoftness values equal or greater than 1.0 apart from all of the local hypersoftness values equal or smaller than −1.0; we will say that the local hypersoftness presents well-separated phases. In agreement with this criterion of distinction, two kinds of oxicams have been found: On the one hand, 4-meloxicam, lornoxicam, meloxicam, and normeloxicam show condensed local hypersoftness values given in well-separated phases; on the other hand, phases of local hypersoftness values are not well-separated in the following oxicams: droxicam, isoxicam, piroxicam, and tenoxicam.

As observed from Table 3, in 4-meloxicam, the likelihood to undergo electrophilic attacks is the highest on atoms of methylthiazole ring, with the carbon atom 9 being the most reactive to this type of attack. Meanwhile, any possible nucleophilic attack should be oriented preferentially toward the fused rings (benzothiazinedioxide) where the carbon atom 3 is the most reactive.

Note that atoms C9 and C3 are very far from each other. Taking into account all of those values written in boldface, from smallest to largest, the found order relationship in condensed local hypersoftness values is the following:

$$\begin{aligned} &C9 < C5 < C8 < S22 < N20 < C31 < N19 < C6 \\ &< N21 < C1 < O11 < O10 < S23 < O12 < C13 \\ &< C15 < C4 < C2 < C14 < C17 < C18 < C16 \\ &< C3 \end{aligned}$$

This information is of crucial interest because, before performing a docking procedure and under the assumption that interactions are predominantly of covalent nature, the electrophilic groups of a hypothetical receptor will react preferably with the methylthiazole ring because it bears the main negative phase of the local hypersoftness and nucleophilic groups of the same receptor will interact mainly with the fused rings because they are surrounded by the positive phase of the dual descriptor, thus facilitating the insertion of the 4-meloxicam inside an enzyme's cavity.

From Table 4, belonging to droxicam, evidently C15 is more likely to undergo a nucleophilic attack, whereas electrophilic attacks will take place preferentially on atom N20 followed by C21 atom; these centers of maximum reactivity are located in the three fused rings. The reader can note that the peripheral pyridine presents no preferential reactivity to be attacked neither by nucleophilic nor electrophilic reagents, so that it should not be involved in covalent interactions, although it might be important in electrostatic interactions; however, this was not a matter of analysis in the present work. The order relationship according to information revealed by local hypersoftness is the following:

$$\begin{aligned} &N20 < C21 < O14 < C2 < O19 < C9 < S25 < C16 \\ &< O13 < N24 < C6 < C4 < C7 < C8 < O12 < C10 \\ &< C1 < N23 < C3 < O11 < C22 < C17 < C5 \\ &< C18 < C15 \end{aligned}$$

As the reader can note, C20 and C15 are the most reactive atoms for receiving electrophilic and nucleophilic attacks, respectively. They are pretty close to each other in the middle of the molecule, so that the most intense covalent interactions will be concentrated on the three fused rings. This basic principle of chemical reactivity can be applied on the remaining oxicams under the assumption that covalent interactions are of our main interest during the oxicam−enzyme interaction. In such a case, we observe the following: In droxicam (Figure 2 and Table 4), it is possible to note that N20 is the most available atom (Table 11) to be attacked by an electrophilic reagent, and in general, this behavior is focused on the ring of the middle of the molecule showing a nucleophilic behavior.

Table 4. Electrophilic $f^{-}(\mathbf{r})$ and Nucleophilic $f^{+}(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the Droxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.06680	0.07310	0.00630	0.13364
C2	0.03970	0.00750	−0.03220	−0.68304
C3	0.00170	0.02770	0.02600	0.55153
C4	0.00200	0.00190	−0.00010	−0.00212
C5	0.07450	0.13670	0.06220	**1.31942**
C6	0.00090	0.00060	−0.00030	−0.00636
C7	0.00030	0.00020	−0.00010	−0.00212
C8	0.00180	0.00200	0.00020	0.00424
C9	0.01750	0.00370	−0.01380	−0.29273
C10	0.00160	0.00560	0.00400	0.08485
O11	0.03510	0.06350	0.02840	0.60244
O12	0.00720	0.00890	0.00170	0.03606
O13	0.00510	0.00380	−0.00130	−0.02758
O14	0.03500	0.00060	−0.03440	−0.72971
C15	0.01210	0.08590	0.07380	**1.56548**
C16	0.00410	0.00270	−0.00140	−0.02970
C17	0.03320	0.09360	0.06040	**1.28124**
C18	0.02310	0.09430	0.07120	**1.51033**
O19	0.04730	0.02230	−0.02500	−0.53031
N20	0.19320	0.02130	−0.17190	**-3.64643**
C21	0.20400	0.13340	−0.07060	**-1.49760**
C22	0.12640	0.16470	0.03830	0.81244
N23	0.01380	0.02400	0.01020	0.21637
N24	0.00240	0.00140	−0.00100	−0.02121
S25	0.02210	0.01150	−0.01060	−0.22485

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units with the exception of condensed local hypersoftness values which are expressed in $m(eV)^{-2}$ units. Hydrogen atoms are not shown.

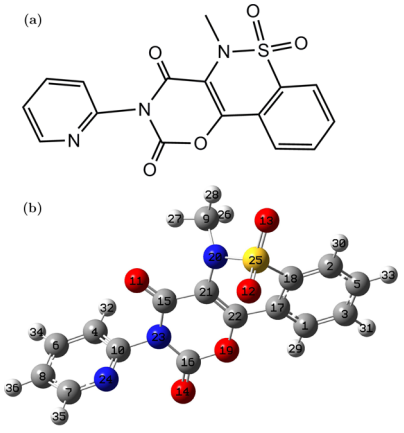

Figure 2. (a) Droxicam structural formula. (b) Optimized molecular structure of the droxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

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On the contrary, the di-ceto ring exhibits an electrophilic behavior, thus meaning it is available to be attacked by a nucleophilic reagent; in particular, the C15 atom shows the most positive value of condensed local hypersoftness not far from atom N20. Hence, the nucleophilic and electrophilic behavior zones in droxicam are not far away one from each other.

This same analysis of order relationships can be done oxicam by oxicam, but it is not necessary for our purposes so that in order to make the lecture easier, hereafter the reader can observe Table 11 where minima and maxima of condensed values of local hypersoftness for each oxicam are exhibited.

Like 4-meloxicam, a similar analysis is applied on lornoxicam, meloxicam, and normeloxicam. First, let us see the case of lornoxicam (Figure 4 and Table 6). Just like it was found for 4-

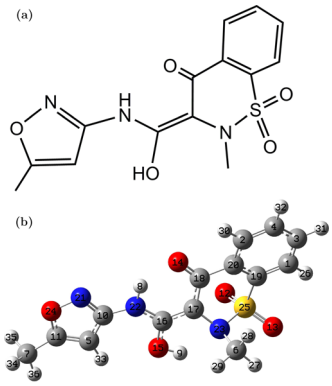

Figure 3. (a) Isoxicam structural formula. (b) Optimized molecular structure of the isoxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

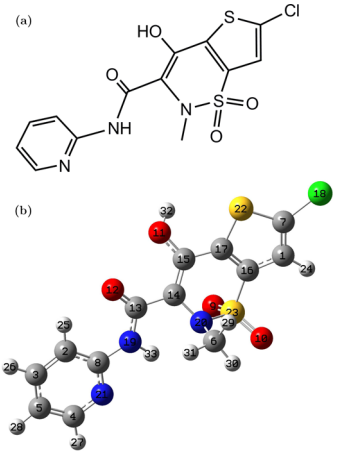

Figure 4. (a) Lornoxicam structural formula. (b) Optimized molecular structure of the lornoxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

meloxicam, it is revealed that both phases of local hypersoftness are well-separated; thus, the pyridine ring is defined as a nucleophilic substructure. Meanwhile, the fused rings have a noticeably electrophilic behavior; in consequence, electrophilic functional groups of enzymes or any other receptor will preferably react toward the pyridine ring and nucleophilic groups of enzyme will react with the fused rings of lornoxicam. The S22 atom is the most electrophilic in this molecule, and the C5 is the most nucleophilic atom (Table 11). In meloxicam

Table 5. Electrophilic $f^{-}(\mathbf{r})$ and Nucleophilic $f^{+}(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the Isoxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00110	0.00600	0.00490	0.09238
C2	0.00590	0.06150	0.05560	**1.04822**
C3	0.00700	0.13920	0.13220	**2.49236**
C4	0.00080	0.04340	0.04260	0.80314
C5	0.01080	0.00250	−0.00830	−0.15468
C6	0.01470	0.00130	−0.01340	−0.25263
C7	0.00060	0.00010	−0.00050	−0.00943
C10	0.02320	0.00870	−0.01450	−0.27337
C11	0.00570	0.00190	−0.00380	−0.07164
O12	0.00920	0.00550	−0.00370	−0.06976
O13	0.01160	0.00450	−0.00710	−0.13386
O14	0.11130	0.11760	0.00630	0.11887
O15	0.01640	0.02170	0.00530	0.09992
C16	0.03190	0.10220	0.07030	**1.32536**
C17	0.39260	0.01250	−0.38010	**−7.16601**
C18	0.02280	0.16150	0.13870	**2.61490**
C19	0.00410	0.10090	0.09680	**1.82497**
C20	0.00490	0.12950	0.12460	**2.34908**
N21	0.09670	0.02290	−0.07380	**−1.39135**
N22	0.15380	0.02460	−0.12920	**−2.43580**
N23	0.02040	0.00420	−0.01620	−0.30542
O24	0.03440	0.00560	−0.02880	−0.54297
S25	0.00980	0.01790	0.00810	0.15271

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in m(eV)$^{-2}$ units. Hydrogen atoms are not shown.

(Figure 5 and Table 7), it has been found that the C3 atom exhibits the most electrophilic behavior and the C10 atom presents the most nucleophilic tendency. As mentioned above, meloxicam has almost the same structure as 4-meloxicam. The phases' distribution of the local hypersoftness is the same so that, again, it is possible to infer that nucleophilic groups of a receptor like an enzyme are going to interact with the fused rings and electrophilic groups are going to react oriented toward the methylthiazole ring of meloxicam. Normeloxicam (Figure 6 and Table 8) and piroxicam (Figure 7 and Table 9) also present a common fused-two-ring and different peripheral rings which are available for electrophilic attacks, mainly on double bond atoms similarly to the reactivity of the methylthiazole ring of 4-meloxicam and meloxicam; nucleophilic attacks should occur preferably on fused rings. To end, it is noted from Table 11 that lornoxicam is the only molecule presenting a sulfur atom that assumes the role of the most electrophilic atom.

5. CONCLUDING REMARKS

The main idea of the present work is to provide qualitative information obtained by the use of reactivity descriptors coming from the conceptual DFT to rationalize the reactivity of eight oxicams. These global and local reactivity descriptors have allowed us to define a framework of reactivity among the selected oxicams. From the global point of view, the net electrophilicity index has revealed that droxicam shows the highest electron accepting capacity; meanwhile, isoxicam

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Table 6. Electrophilic $f^{-}(\mathbf{r})$ and Nucleophilic $f^{+}(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the Lornoxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00830	0.01320	0.00490	0.10793
C2	0.15520	0.00450	−0.15070	**−3.31934**
C3	0.00520	0.00180	−0.00340	−0.07489
C4	0.08280	0.00030	−0.08250	**−1.81715**
C5	0.19460	0.00790	−0.18670	**−4.11228**
C6	0.00300	0.00250	−0.00050	−0.01101
C7	0.01950	0.13280	0.11330	**2.49556**
C8	0.10620	0.00370	−0.10250	**−2.25768**
O9	0.00070	0.01150	0.01080	0.23788
O10	0.00150	0.00150	0.00000	0.00000
O11	0.01790	0.01790	0.00000	0.00000
O12	0.02910	0.03580	0.00670	0.14757
C13	0.00990	0.03700	0.02710	0.59691
C14	0.05300	0.13340	0.08040	**1.77090**
C15	0.03360	0.09910	0.06550	**1.44271**
C16	0.01510	0.13600	0.12090	**2.66296**
C17	0.00940	0.13490	0.12550	**2.76428**
Cl18	0.00950	0.02460	0.01510	0.33259
N19	0.18920	0.01310	−0.17610	**−3.87880**
N20	0.00500	0.01740	0.01240	0.27312
N21	0.03730	0.00560	−0.03170	−0.69823
S22	0.00370	0.12950	0.12580	**2.77089**
S23	0.00290	0.02270	0.01980	0.43612

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in $\mathrm{m(eV)}^{-2}$ units. Hydrogen atoms are not shown.

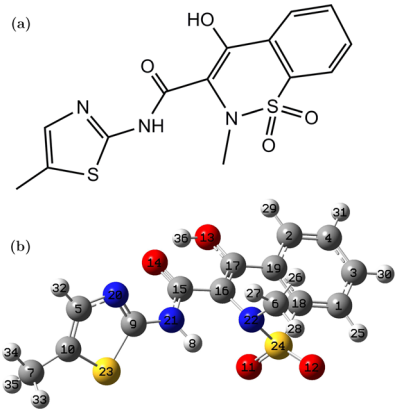

Figure 5. (a) Meloxicam structural formula. (b) Optimized molecular structure of the meloxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

Table 7. Electrophilic $f^{-}(\mathbf{r})$ and Nucleophilic $f^{+}(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the Meloxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00280	0.00630	0.00350	0.07018
C2	0.00850	0.06440	0.05590	**1.12087**
C3	0.00950	0.14590	0.13640	**2.73501**
C4	0.00030	0.04400	0.04370	0.87625
C5	0.18980	0.00060	−0.18920	**−3.79372**
C6	0.00340	0.00240	−0.00100	−0.02005
C7	0.00910	0.00020	−0.00890	−0.17846
C9	0.14330	0.00900	−0.13430	**−2.69290**
C10	0.21380	0.00830	−0.20550	**−4.12056**
O11	0.00130	0.00800	0.00670	0.13434
O12	0.00100	0.00660	0.00560	0.11229
O13	0.02860	0.04100	0.01240	0.24864
O14	0.00680	0.04690	0.04010	0.80406
C15	0.00660	0.00640	−0.00020	−0.00401
C16	0.06860	0.09400	0.02540	0.50931
C17	0.03080	0.15210	0.12130	**2.43223**
C18	0.00520	0.10630	0.10110	**2.0720**
C19	0.00290	0.12250	0.11960	**2.39815**
N20	0.03930	0.01050	−0.02880	−0.57748
N21	0.10740	0.01630	−0.09110	**−1.82668**
N22	0.01550	0.01030	−0.00520	−0.10427
S23	0.06560	0.00880	−0.05680	**−1.13892**
S24	0.00310	0.01950	0.01640	0.32884

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in $\mathrm{m(eV)}^{-2}$ units. Hydrogen atoms are not shown.

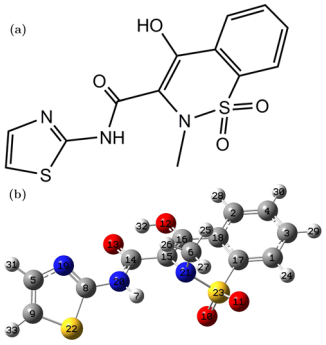

Figure 6. (a) Normeloxicam structural formula. (b) Optimized molecular structure of the normeloxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

presents the highest electron donating capacity. From the local point of view, the local hypersoftness has allowed us to identify the most reactive sites for nucleophilic and electrophilic attacks and to split this group of oxicams into two types of subgroups to make the analysis of local reactivity easier.

On the one hand, there are oxicams presenting well-separated phases in their local hypersoftness descriptor—4-meloxicam, meloxicam, lornoxicam, and normeloxicam—so that any possible electrophilic attack by a reagent coming from the environment will be oriented to the peripheral ring in comparison with nucleophilic attacks which should be centered on the respective fused rings on each oxicam of this category.

On the other hand, droxicam, isoxicam, piroxicam, and tenoxicam exhibit no well-separated phases of local hypersoftness; in fact, the most nucleophilic and electrophilic atoms are located very close to each other in the respective fused rings or near them, meaning the majority of local reactivity is centered on the fused rings. In fact, the pyridine ring in droxicam and tenoxicam has no relevant reactivity to possible nucleophilic or electrophilic attacks. Hence, the more reactive local zone on these two molecules is found on the fused rings only.

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Table 8. Electrophilic $f^-(r)$ and Nucleophilic $f^+(r)$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(r)$, and Condensed Local Hypersoftness $s^{(2)}(r)$ over the Atoms of the Normeloxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00480	0.00610	0.00130	0.02514
C2	0.01400	0.06450	0.05050	0.97659
C3	0.0162	0.14400	0.12780	**2.47145**
C4	0.00050	0.04280	0.04230	0.81802
C5	0.14530	0.00060	−0.14470	**−2.79827**
C6	0.00570	0.00230	−0.00340	−0.06575
C8	0.11530	0.01020	−0.10510	**−2.03427**
C9	0.18630	0.00990	−0.17640	**−3.41130**
O10	0.00220	0.00790	0.00570	0.11023
O11	0.00190	0.00650	0.00460	0.08896
O12	0.04420	0.04150	−0.00270	−0.05221
O13	0.00390	0.04840	0.04450	0.86056
C14	0.00590	0.06860	0.06270	**1.21252**
C15	0.11700	0.09250	−0.02450	−0.47379
C16	0.04590	0.15390	0.10800	**2.08855**
C17	0.00800	0.10510	0.09710	**1.87776**
C18	0.00590	0.11990	0.11400	**2.20458**
N19	0.03140	0.01110	−0.02030	−0.39257
N20	0.11860	0.01570	−0.10290	**−1.98993**
N21	0.02350	0.01010	−0.01340	−0.25914
S22	0.08930	0.01040	−0.07890	**−1.52580**
S23	0.00470	0.01930	0.01460	0.28234

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in $m(eV)^{-2}$ units. Hydrogen atoms are not shown.

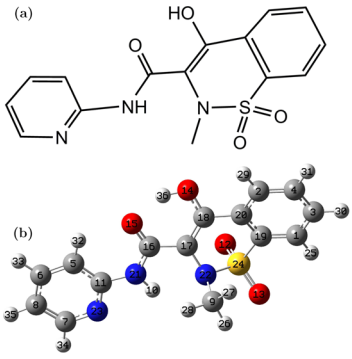

Figure 7. (a) Piroxicam structural formula. (b) Optimized molecular structure of the piroxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

Returning to the global reactivity analysis, among all of the oxicams, the lowest net electrophilicity values are found in isoxicam (Figure 3 and Table 5) and tenoxicam (Figure 8 and Table 10), thus revealing that the highest electron donating powers are localized in these two oxicams. To support this idea, local hypersoftnes has been used in order to reveal the most reactive atoms for electrophilic attacks. Indeed, the most negative condensed values of local hypersoftness were found in isoxicam and tenoxicam (C17 in isoxicam; C16 in tenoxicam), thus making them the best electron donating atoms of all the eight oxicams studied in this work. In spite of having essential differences in their respective structures, isoxicam and tenoxicam have very similar values of this local descriptor. In

Table 9. Electrophilic $f^-(r)$ and Nucleophilic $f^+(r)$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(r)$, and Condensed Local Hypersoftness $s^{(2)}(r)$ over the Atoms of the Piroxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00600	0.00640	0.00040	0.00802
C2	0.02050	0.06540	0.04490	0.90031
C3	0.02590	0.14110	0.11520	**2.30992**
C4	0.00130	0.03910	0.03780	0.75794
C5	0.11070	0.00790	−0.10280	**−2.06128**
C6	0.00360	0.00440	0.00080	0.01604
C7	0.05760	0.00050	−0.05710	**−1.14493**
C8	0.13860	0.01630	−0.12230	**−2.45229**
C9	0.00800	0.00230	−0.00570	−0.11429
C11	0.07310	0.01020	−0.06290	**−1.26123**
O12	0.00320	0.00740	0.00420	0.80422
O13	0.00370	0.00610	0.00240	0.04812
O14	0.06390	0.04190	−0.02200	−0.44113
O15	0.00100	0.04910	0.04810	0.96447
C16	0.00540	0.07570	0.07030	**1.40961**
C17	0.18050	0.08990	−0.09060	**−1.81666**
C18	0.06710	0.15710	0.09000	**1.80463**
C19	0.01300	0.10110	0.08810	**1.76653**
C20	0.01110	0.01450	0.00340	0.06817
N21	0.14570	0.01770	−0.12800	**−2.56658**
N22	0.01870	0.01030	−0.00840	−0.16843
N23	0.02800	0.01070	−0.01730	−0.34689
S24	0.00550	0.01760	0.01210	0.24262

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in $m(eV)^{-2}$ units. Hydrogen atoms are not shown.

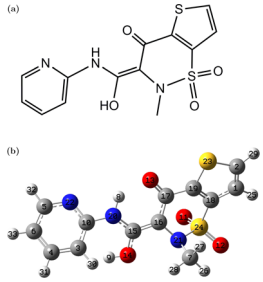

Figure 8. (a) Tenoxicam structural formula. (b) Optimized molecular structure of the tenoxicam molecule calculated with the M06 density functional and the CBSB7 basis set.

fact, determining reactivity should be a priority after obtaining geometrical optimizations. All that is needed is to use suitable and accurate enough concepts which are suspected to be related with an experimental property. For each oxicam, the electron accepting power is lower than the electron donating power, so that net electrophilicity is mainly driven by an electron donor tendency. According to the condensed values quoted in Table 11, it can be established that the nucleophilic character predominates in all analyzed oxicams; in consequence, interactions between any oxicam and a hypothetical receptor might be favored preferably when the receptor bears functional groups of the electron-withdrawing type.

After this complete analysis, it is possible to infer that a simple structural resemblance among two or more molecules

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Table 10. Electrophilic $f^-(\mathbf{r})$ and Nucleophilic $f^+(\mathbf{r})$ Condensed Fukui Functions, Condensed Dual Descriptor $f^{(2)}(\mathbf{r})$, and Condensed Local Hypersoftness $s^{(2)}(\mathbf{r})$ over the Atoms of the Tenoxicam Molecule Calculated with the M06 Density Functional and the CBSB3 Basis Set[a]

kth atom	f_k^-	f_k^+	$f_k^{(2)}$	$s_k^{(2)}$
C1	0.00810	0.00550	−0.00260	−0.05335
C2	0.01780	0.10410	0.08630	**1.77082**
C3	0.04180	0.01760	−0.02420	−0.49657
C4	0.00180	0.01090	0.00910	0.18673
C5	0.00770	0.00330	−0.00440	−0.09029
C6	0.04650	0.04090	−0.00560	−0.11491
C7	0.01700	0.00030	−0.01670	−0.34267
C10	0.00790	0.04160	0.03370	0.69150
O11	0.00770	0.00600	−0.00170	−0.03488
O12	0.00920	0.00360	−0.00560	−0.11491
O13	0.08940	0.11050	0.02110	0.43296
O14	0.02050	0.02300	0.00250	0.05130
C15	0.05320	0.12940	0.07620	**1.56358**
C16	0.36720	0.00830	−0.35890	**−7.36441**
C17	0.02400	0.15330	0.12930	**2.65316**
C18	0.00950	0.11060	0.10110	**2.07451**
C19	0.00810	0.07840	0.07030	**1.44251**
N20	0.13800	0.01660	−0.12140	**−2.49106**
N21	0.06860	0.00250	−0.06610	**−1.35633**
N22	0.02170	0.02210	0.00040	0.00821
S23	0.00480	0.09330	0.08850	**1.81597**
S24	0.01350	0.01320	−0.00030	−0.00616

[a]All values satisfying the arbitrary condition $|s_k^{(2)}| \geq 1.0$ are shown in boldface and expressed in atomic units except for condensed local hypersoftness values which are expressed in $m(eV)^{-2}$ units. Hydrogen atoms are not shown.

Table 11. Maxima and Minima Values of Condensed Local Hypersoftness Descriptor on Atoms in 4-Meloxicam, Droxicam, Isoxicam, Lornoxicam, Meloxicam, Normeloxicam, Piroxicam, and Tenoxicam Molecules with the M06 Density Functional and the CBSB3 Basis Set

oxicam	max $\{s_k^{(2)}\}$	kth atom	min $\{s_k^{(2)}\}$	kth atom
4-meloxicam	2.78785	C3	−4.81761	C9
droxicam	1.56548	C15	−3.64643	N20
isoxicam	2.61490	C18	−7.16601	C17
lornoxicam	2.77089	S22	−4.11228	C5
meloxicam	2.73501	C3	−4.12056	C10
normeloxicam	2.47145	C3	−3.41130	C9
piroxicam	2.30992	C3	−2.56658	N21
tenoxicam	2.65316	C17	−7.36441	C16

should not be enough and a unique criterion to estimate or predict results concerning the reactivity in front of other reagents but also electronic structure is relevant.

It is expected this information permits us to convince the scientific community to foster the use of the local hypersoftness as a local reactivity descriptor to predict covalent interactions, thus facilitating the analysis of interactions that could be playing a key role in chemical reactions of medicinal relevance.

We believe that the results exposed here are useful not only in the sense of pure knowledge related with these molecules of medical use but also in the guidance for other computational techniques by means of reliable and rational models of reactivity such as local hypersoftness which has been able to reveal most favorable sites to establish covalent interactions, thus preventing the use of intuition when modeling interactions with enzymes or other kinds of receptors. In particular, this study should help to optimize docking techniques and QSAR/QSPR studies because nucleophilic and electrophilic sites that were revealed would allow one to maximize interactions around those atoms presenting these highest reactivities, turning to these kinds of techniques in a more efficient procedure for doing chemistry.

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Notes

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