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Global and local reactivity descriptors based on quadratic and linear energy models for α,β-unsaturated organic compounds

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Global and local descriptors of chemical reactivity can be derived from conceptual density functional theory. Their explicit form, however, depends on how the energy is defined as a function of the number of electrons. Within the existing interpolation models, here, the quadratic and the linear energy model were used to derive global descriptors as the electrophilicity and nucleophilicity (defined as the negative of the ionization potential) and local descriptors employing either the corresponding condensed fukui function in the linear model or the local response of the global descriptor in the quadratic model. The ability of these descriptors to predict the reactivity of molecules with more than one reactive site was first studied on a set of α, β-unsaturated ketones, where experimental rate constants for the nucleophilic attack is known. With the validated descriptors the reactivity of α, β-unsaturated carboxylic compounds with different heteroatoms as α, β-unsaturated thioesters, esters and amides as alternative substrates for the enzymatic CO_2 fixation studied experimentally by Erb *et al.*[1] was addressed. The carbon dioxide fixation involves the reduction of the neutral α, β-unsaturated carboxylic compounds by a nucleophilic attack of a hydride anion from NADPH and the following electrophilic attack by carbon dioxide. It was

found that condensed values of the linear fukui function within the fragment of molecular response approximation describe best the reactivity of α, β-unsaturated ketones. For the two relevant processes involved in CO_2 fixation the amides present the largest reactivity in vacuum and in aqueous solution compared to the esters and thioesters and may, therefore, serve as alternative sustrates of carboxylases.

KEYWORDS
Reactivity descriptors , Fukui function, linear and quadratic energy models, α,β-unsaturated compounds

1 | INTRODUCTION AND BACKGROUND

There is a continuing interest in the rationalization of existing reactivity models and the development of new models to understand and predict chemical reactivity. This is the main objective of the so-called conceptual DFT [2, 3, 4, 5, 6, 7, 8, 9, 10], which gives rise to global and local indicators or descriptors. Among the global indicators one distinguishes the chemical potential[11], chemical hardness[12, 13, 14], electrophilicity[15, 16, 17] and nucleophilicity[18, 19]. On the other hand local descriptors as the fukui function[20, 21, 22] $f(r)$ are able to distinguish the most reactive region in a molecule.

In this study the ability of these descriptors to predict the nucleophilic attack on α, β - unsaturated thioester, ester and amides will be addressed. To our knowledge this is the first systematic study that focused on this group of molecules that present more than one nucleophilic site: the β-carbon atom and the carbon carbonyl atom. Therefore, for these molecules the regioselectivity described by the local descriptors have to go in hand with their global counterparts to describe the correct reactivity trends of these compounds.

In organic chemistry α, β - unsaturated thioesters, esters and amides have not obtain much attention, since it is known that they are much less reactive than their carbonyl analogues (aldehydes and ketones). In biology, however, α, β - unsaturated thioesters are involved in the fatty acid synthesis and play an important role in various processes. Recently, it has been shown that they also participate in the fixation of carbon dioxide in alternative carbon fixation cycles[1, 23, 24, 25]. In this cycle one of the important step is the reduction of the α, β - unsaturated thioester by the reduced form of nicotinamide adenosine dinucleotide phosphate (NADPH) to produce an enolate that binds CO_2 (see Figure 1).

This reaction is catalyzed by Crotonyl - CoA - carboxylase yielding enantiomeric products and has been widely studied by Erb *et al.* [1]. Recently, enzymes of the same family were shown to also catalyze various thioesters with different substitutions of the alkyl chain[26]. The possibility to use alternative substrates for the catalyzed reaction enables a possible application of these enzymes in industrial processes to create valuable organic compounds. However, to find these alternative substrates a rational and systematic approach is required that conserves or increases the reactivity of the substrate without altering the binding to the enzyme and therefore maintains the catalytic action of the enzyme. In this study, we start from the natural substrate, an α, β - unsaturated thioester, and change the hetero-atom on the carboxy group of crotonyl-type substrates (α, β - unsaturated thioesters, esters and amides). Maintaining the rest of the molecule intact will not change the binding affinity of the substrate to the enzyme but may impact the overall reactivity of the compound. If alternative substrates could be identified that are as reactive or even more reactive than

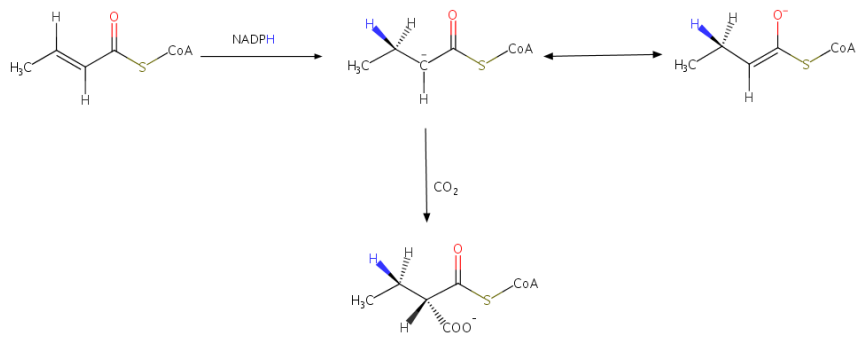

FIGURE 1 Reduction and subsequent carboxylation reaction of Crotonyl-CoA.

the natural substrates, a pool of alternative substrates would be provided, which may be used to produce catalytically valuable organic compounds with enzymes, prior to the validation with future experiments.

The change of the chemical reactivity of a molecule is addressed within Density Functional Theory (DFT) by reactivity indicators as responses of the system to changes in global parameters (number of electrons, N), and a local function (external potential, $v(r)$) that defines the system. Taking the energy of the system depending on the number of electrons and the external potential, and then deriving the same, two types of quantities are naturally obtained: the global descriptors such as the chemical potential μ and the hardness η and the local descriptors such as the Fukui function $f(r)$.

The explicit form of these descriptors depends on the function used to describe the dependence of the energy with the number of electrons N (e.g. quadratic, linear, etc) as proposed recently by Heidar-Zadeh *et al.* [27]. In this study we used different energy models to obtain global and local reactivity descriptors for α, β - unsaturated thioester, ester and amides able to provide alternative substrates for enzymatic CO_2 fixation. The capacity of these descriptors to describe the reactivity of these compounds was priorly validated with experimentally reported rate constants of α, β - unsaturated ketones with gluthatione in aqueous solution[28].

2 | THEORETICAL METHODS

2.1 | Global descriptors

The dependence of the energy of a molecular system on the number of electrons can be represented by different models: quadratic, exponential, rational, linear, etc. [27, 29, 30]. In this study we are going to consider the quadratic model:

$$E_{quad}(N; a_k) = a_0 + a_1 N + a_2 N^2 \tag{1}$$

and the linear model:

$$E_{linear}(N; a_k) = a_0 + a_1 N \tag{2}$$

Using the linear model we can strictly obtain only the chemical potential as a global descriptor of reactivity because the derivative of the energy is not continuous with respect to the number of electrons[31, 32]. The chemical potential is defined as the derivative from above and below of the energy with respect to the number of electrons at constant external potential,

$$\begin{aligned} \mu^{+} &= \left(\frac{\partial E}{\partial N}\right)^{+}_{v(\mathbf{r})} = -A \\ \mu^{-} &= \left(\frac{\partial E}{\partial N}\right)^{-}_{v(\mathbf{r})} = -I \end{aligned} \tag{3}$$

Neglecting orbital relaxation upon changes in the total number of electrons the electron affinity A could be approximated as the Lowest Unoccupied Molecular Orbital (LUMO) energy ε_{LUMO}. On other hand the ionization potential can also be approximated as the negative of the Highest Occupied Molecular Orbital (HOMO) energy ε_{HOMO} via the application of Koopmans' theorem[33] in the Hartree Fock method. Using Density Functional Theory the ionization potential is related to the energy of the HOMO only for the exact functional via Janak's theorem [34] and the electron affinity only relates to the energy of the LUMO under some specific circumstances[35]. But in this study we are not focused on the exact value of the ionization potential or the electron affinity but rather on the relative values between similar molecules using the same DFT functionals. Therefore, possible errors from the approximations discussed above would be similar in all molecules and the relative values of the orbital energies would reproduce the correct relative reactivity order of the molecules. This was confirmed in our results when the orbital energies were compared to the values of the ionization potential and the electron affinity calculated with the finite difference method, where the energy of the cation and anion are calculated with the same DFT method in vacuum.

According to Parr's definition[15], the electrophilicity ω of a molecule can be defined as the energy difference, $\Delta E(N) = E_{N_0} - E_{N_{max}}$, where E_{N_0} is the energy of the neutral molecule and $E_{N_{max}}$ is the energy of the molecule with the maximal fraction of an electron it can accept without increasing its energy. Based on the quadratic energy model ΔN_{max} is defined as:

$$\Delta N_{max} = -\frac{\mu}{\eta} \tag{4}$$

and the electrophilicity proposed by Parr[15] adopts the following form:

$$\omega = \frac{\mu^2}{2\eta} \tag{5}$$

In the linear model, the analogous definition for the electrophilicity would be $\Delta E(N) = E_{N_0} - E_{N_0+1}$ and in this case it equals the vertical electron affinity A, which can be approximated by the energy of the LUMO or calculated by the finite difference approach.

To describe the nucleophilicity N_{FD} of a molecule we adopted the method proposed by Contreras *et al.*[18], where $N_{FD} = E_{N_0} - E_{N_0-1}$. The nucleophilicity N_{FD} is given as $N_{FD} = -I$, where I corresponds to the vertical ionization potential.

2.2 | Local descriptors

The local response of the electron density of a molecule to the change in the number of electrons is given by the Fukui function,

$$f(r,N)=\left(\frac{\partial(\delta E/\delta v_{ext})_N}{\partial N}\right)_{v_{ext}}=\left(\frac{\partial\rho(r,N)}{\partial N}\right)_{v_{ext}} \tag{6}$$

,where E is the energy, N is the number of electrons, v_{ext} is the external potential and $\rho(r,N)$ the electron density of the molecule, which depends on the total number of electrons N in the molecule[20].

Based on the linear energy model (eq. 2) the Fukui function can be obtained as a derivative from above and below with respect to the number of electrons at constant external potential, because the derivative of $\rho(r,N)$ is discontinuous with respect to N.

$$\begin{aligned}\left(\frac{\partial\rho_N(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})}\Bigg|_{N=N_0^+}&=\rho_{N_0+1}(\mathbf{r})-\rho_{N_0}(\mathbf{r})=f_{N_0}^{+}(\mathbf{r})\\ \left(\frac{\partial\rho_N(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})}\Bigg|_{N=N_0^-}&=\rho_{N_0}(\mathbf{r})-\rho_{N_0-1}(\mathbf{r})=f_{N_0}^{-}(\mathbf{r})\end{aligned} \tag{7}$$

Neglecting orbital relaxation with a change in the total number of electrons, the frontier molecular orbital approach (FMO)[20, 21] approximates the Fukui function by the molecular density of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) as follows:

$$f_{N_0}^{+}(\mathbf{r})=\rho_{N_0+1}(\mathbf{r})-\rho_{N_0}(\mathbf{r})=\rho^{LUMO}(r) \tag{8}$$

$$f_{N_0}^{-}(\mathbf{r})=\rho_{N_0}(\mathbf{r})-\rho_{N_0-1}(\mathbf{r})=\rho^{HOMO}(r) \tag{9}$$

Based on the quadratic energy model Heidar-Zadeh *et al.*[36] proposed the use of a local response descriptor for electrophilicity as:

$$\begin{aligned}I_{\omega;N}(r)=\left(\frac{\partial\omega}{\partial v(r)}\right)_N&=\left(\frac{\partial\left[E(N_{max})-E(N_0)\right]}{\partial v(r)}\right)_N\\ &=\rho_{N_{max}}(r)-\rho_{N_0}(r)\end{aligned} \tag{10}$$

With the quadratic energy model for the electron density of the N-electron system one obtains the following working expression

$$I_{\omega;N}(r) = -\left(\frac{\mu}{\eta}\right) f(r) + \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2 f^2(r) \tag{11}$$

, where $f(r)$ is the quadratic Fukui function and f^2(r) is the dual descriptor[37, 38, 39, 40].

Following the same framework in this work a local response for nucleophilicity N_{FD} is proposed based on the linear energy model. Since the nucleophilicity N_{FD} is represented by $-I$, the negative of the ionization potential, the local response for nucleophilicity is defined as:

$$\begin{aligned} I_{N_{FD};N}(r) &= \left(\frac{\partial N}{\partial v(r)}\right)_N = \left(\frac{\partial\left[E(N_0) - E(N_0 - 1)\right]}{\partial v(r)}\right)_N \\ &= \rho_{N_0}(r) - \rho_{N_0-1}(r) \end{aligned} \tag{12}$$

Replacing the electron density for the quadratic energy model yields

$$I_{N_{FD};N}(r) = f(r) - \frac{1}{2} f^2(r) = f^-(r). \tag{13}$$

If the electron density of the linear energy model is used instead to replace the electron density above the same function $f^-(r)$ is obtained.

2.3 | Condensed Local descriptors

To compare the local descriptors between different molecules one might condense the quadratic and linear Fukui functions and the local responses to the atoms in the molecule using the Hirshfeld-I method[41] and the FMO approximation. In this method a weight function is used which is expressed as:

$$w_A^{H-I}(r, N) = \frac{\rho^0_{A,N_A}(r)}{\Sigma_{A=1}^{M} \rho^0_{A,N_A}(r)}. \tag{14}$$

where $\rho^0_{A,N_A}(r)$ is the proatomic electronic density of the atom A with N_A number of electrons and M the total number of atoms in the molecule.

The condensed Fukui function of atom A for the linear energy model using the fragment molecular response approach (FMR)[42, 43, 44, 45] is obtained as:

$$f_A^{\pm \mathrm{FMR}} = \int w_A(r, N) f^{\pm}(r) dr \tag{15}$$

and the condensed local descriptor of the quadratic energy model as:

$$I^{\mathrm{FMR}}_{A,\omega;N} = \int w_A(r,N) I_{\omega;N}(r) dr \tag{16}$$

The response of molecular fragment approach (RMF)[42] was also evaluated, where the electron density is condensed into atomic populations,

$$N_A = \int w_A(r)\,\rho(r)\,dr \tag{17}$$

,and the dependence of the weight function with the total number of electrons of the molecule is considered by the following expression

$$f_A^{+\mathrm{RMF}} = \int w_A(N+1,r)\,\rho(N+1,r) - w_A(N,r)\,\rho(N,r)\,dr \tag{18}$$

and,

$$f_A^{-\mathrm{RMF}} = \int w_A(N,r)\,\rho(N,r) - w_A(N-1,r)\,\rho(N-1,r)\,dr \tag{19}$$

Finally, for each of the atomic condensed values of the Fukui function (FMR and RMF) we alternatively also calculated the condensed, linear, local softness defined as[46, 47, 48]

$$s_A^{\pm} = S f_A^{\pm} = \frac{1}{\eta} f_A^{\pm}. \tag{20}$$

The condensed local softness can be interpreted as a scaled Fukui function, which when summed up over all atoms yields the global softness of the molecule in contrast to the Fukui function that is normalized to one. Accounting for the difference in the global softness between molecules, the local softness was proposed to be more suitable for the comparison of local reactivities between molecules with differ considerably in size[46, 47, 48].

3 | COMPUTATIONAL DETAILS

All geometries were optimized at the ωB97X-D3 / 6-311G(d,p) level of theory for neutral molecules and ωB97X-D3 / 6-311++G(d,p) level for anionic molecules. For the aqueous phase each electronic structure method was combined with the SMD solvent model[49] employing the ORCA package[50]. The descriptors were calculated using HORTON 2.0.0 [51] and ChemTools packages[52].

4 | RESULTS AND DISCUSSION

The reactivity of α, β-unsaturated thioesters, amides and esters was addressed with global and local reactivity descriptors based on Conceptual Density Functional Theory. Since no experimental data was available for these compounds appropriate reactivity descriptors were first validated on a set of α, β-unsaturated ketones with known experimental reaction rates.

4.1 | Validation of reactivity descriptors for α, β-unsaturated molecules

Recently, a validation of local descriptors in carbonyl systems with a single reactive site was reported by Heidar-Zadeh *et al.*[36]. Most of these compounds possess only one nucleophilic site, the carbonyl carbon atom. α, β unsaturated molecules, however, have more than one nucleophilic site and therefore the validation of the reactivity descriptors from this study was reconsidered.

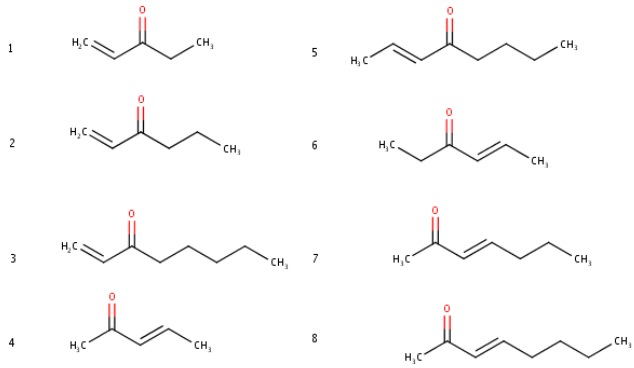

FIGURE 2 Electrophilic α,β-unsaturated ketones used to validate the local and global reactivity descriptors

As an initial step α, β-unsaturated ketones were selected for which experimental values of their reactivity towards a nucleophile were reported. The prediction of the reactivity in a set of α, β-unsaturated ketones becomes more complex due to the increase of the number of nucleophilic reactive sites, the β carbon and carbonyl carbon atom. Global and local descriptors (based on the linear and quadratic energy models) were evaluated in aqueous phase and then compared with the experimental rate constant reported by Schwobel *et al.* [28] to verify the performance of different reactivity descriptors for the chosen molecules. These rate constants correspond to the reaction between α,β-unsaturated ketones in Figure 2 and glutathione in an aqueous phase and will be used as an indicator of the reactivity of the molecules.

Table 1 displays the global descriptors for all molecules in Figure 2 together with the logarithm of the experimental rate constant. The electrophilicity of α, β– unsaturated ketones is described within the quadratic energy model by the electrophilicity index ω from Parr. Comparing the values of the electrophilicity ω with experimental values one concludes that the electrophilicity only discriminates between families of compounds but not in one family as e.g. the three molecules with the double bond in the aliphatic chain on the right side of the molecule (molecules 4, 7 and 8). The energy of the LUMO, which can be approximated as the electron affinity and may be used as an alternative electrophilicity descriptor, shows the same trend in which the most reactive compounds are separated from the less

TABLE 1 Global descriptors for molecules in the validation set of Figure 2 using the quadratic energy model and the ωB97X-D3 / 6-311G(d,p) level of theory in aqueous solution (SMD solvation model). Log(k) represents the log values of the experimental rate constants in $M^{-1}min^{-1}$, ω is the electrophilicity (eV), ΔN_{max} is the fractional amount of an elementary charge the system has to obtain to reach N_{max} electrons, and ε_{LUMO} is the energy of Lowest Unoccupied Molecular Orbital in eV.

N^o	Name	log(k)	ΔN_{max}	ω	ε_{LUMO}
1	1-penten-3-one	3.10	0.4385	0.9925	0.6336
2	1-hexen-3-one	3.07	0.4392	0.9925	0.6251
3	1-octen-3-one	3.03	0.4388	0.9895	0.6281
4	3-penten-2-one	1.43	0.4292	0.9559	0.7335
5	2-octen-4-one	1.42	0.4230	0.9274	0.7979
6	4-hexen-3-one	1.38	0.4227	0.9282	0.8023
7	3-hepten-2-one	1.10	0.4286	0.9522	0.7402
8	3-octen-2-one	1.06	0.4285	0.9521	0.7414

reactive but no discrimination between the less reactive compounds is achieved.

Global descriptors describe the reactivity of the molecule as a whole and are not able to discriminate between two reactive sites. Therefore, one does not know if they describe the reactivity on the β or the carbonyl carbon atom in the molecule. Local descriptors, however, do assign reactivity to specific sites when they are condensed to atoms and might be more suitable for α,β-unsaturated molecules.

As described in the methods section local reactivity descriptors might be calculated employing different approximations. They depend on the energy model used to express the dependence of the energy on the total number of electrons and are usually condensed to atoms with an Atom-In-Molecule approach to be able to compare them between different molecules. Here, one also distinguishes between the Fragment of Molecular Response (FMR), where the condensation to atoms does not depend on the total number of electrons of the system, and the Response of Molecular Fragment (RMF) where the weight function used to condense the local descriptor to atoms also depend on the number of electrons (see Methods section).

In Table 2 the local descriptors from the quadratic energy model $I_{\omega;N}(r)$ and the linear energy model $f^+(r)$ were condensed to atoms for each molecule in Figure 2 using the RMF and the FMR approach and the Hirshfeld-I partitioning method to verify how these approximations alter the different descriptors. Using the RMF approach both descriptors identify the most reactive site as the β carbon atom in all molecules as known from the experimental data. In the FMR approximation $I_{\omega;N}(r)$ assigns the most reactive site to the oxygen atom but the condensed value of $f^+(r)$ is largest on the β carbon atom as expected.

Since the molecules have similar sizes and functional groups that differ only in their position, the experimental reactivity order described by the rate constant for the compounds (second column of Table 2) should be also reproduced by the local descriptors. The RMF approach, however, is not able to assign differences in the reactivities between the compounds for either of the two local descriptors. In the FMR approach the local descriptor $I_{\omega;N}(r)$ does not reproduce the most reactive site (it assigns it to the oxygen atom) and $f^+(r)$ obtained from the linear energy model identifies correctly the β carbon atom as the most reactive site and additionally also reproduces the experimental reactivity order given by the experimental rate constant. This correct reactivity order holds for all the molecules with just one

TABLE 2 Condensed local descriptors for molecules in the validation set using the quadratic and linear energy models at the ωB97X-D3 / 6-311G(d,p) level of theory using frontier molecular orbital approach(FMO) in aqueous solution (SMD solvation model) and the log values of the experimental rate constants k ($M^{-1}min^{-1}$). $I_{\omega;N}$ is the condensed local response of the electrophilicity ω, f^+ is the condensed linear Fukui function and s^+ is the condensed linear, local softness (in E_h) for the different atoms in each molecule.

		Response of molecular fragment			Fragment of molecular response		
Molecule	log(k)	$I_{\omega;N}$	f^+	s^+	$I_{\omega/sy;N}$	f^+	s^+
1-Penten-3-one	3.10						
C_β		0.1661	0.5580	1.4715	0.0898	0.2768	0.7299
$C_{C=O}$		0.1145	0.4308	1.1360	0.0799	0.2129	0.5614
O		0.1294	0.1178	0.3106	0.1263	0.1805	0.4759
1-hexen-3-one	3.07						
C_β		0.1661	0.5571	1.4734	0.0898	0.2762	0.7304
$C_{C=O}$		0.1156	0.4319	1.1422	0.0796	0.2119	0.5604
O		0.1277	0.1173	0.3102	0.1253	0.1805	0.4773
1-octen-3-one	3.03						
C_β		0.1662	0.5572	1.4756	0.0897	0.2761	0.7311
$C_{C=O}$		0.1166	0.4323	1.1448	0.0796	0.2120	0.5614
O		0.1247	0.1168	0.3093	0.1231	0.1802	0.4772
3-Penten-2-one	1.43						
C_β		0.1681	0.5687	1.4918	0.0768	0.2433	0.6382
$C_{C=O}$		0.1121	0.4393	1.1523	0.0736	0.2028	0.5319
O		0.1303	0.1109	0.2909	0.1273	0.1772	0.4648
2-octen-4-one	1.42						
C_β		0.1593	0.5517	1.4483	0.0729	0.2357	0.6187
$C_{C=O}$		0.1180	0.4591	1.2052	0.0767	0.2141	0.5620
O		0.1232	0.1131	0.2969	0.1213	0.1802	0.4730
4-hexen-3-one	1.38						
C_β		0.1592	0.5521	1.4463	0.0730	0.2363	0.6190
$C_{C=O}$		0.1162	0.4561	1.1948	0.0769	0.2146	0.5622
O		0.1260	0.1146	0.3002	0.1232	0.1807	0.4733
3-hepten-2-one	1.10						
C_β		0.1667	0.5671	1.4884	0.0745	0.2359	0.6191
$C_{C=O}$		0.1165	0.4506	1.1826	0.0755	0.2089	0.5482
O		0.1282	0.1136	0.2981	0.1266	0.1820	0.4776
3-octen-2-one	1.06						
C_β		0.1666	0.5657	1.4843	0.0747	0.2356	0.6181
$C_{C=O}$		0.1167	0.4508	1.1828	0.0755	0.2093	0.5491
O		0.1270	0.1140	0.2991	0.1257	0.1823	0.4783

exception: 2-octen-4-one (5). For this molecule the condensed value of $f^+(r)$ on the β carbon atom decreases much faster than the experimental rate constant when compared to the preceding 3-penten-2-one (4). But, since the Fukui function is normalized to one for all molecules, when the number of atoms in 2-octen-4-one increases with respect to 3-penten-2-one the Fukui function would be also distributed over more atoms. This distribution over more atoms could decrease the $f^+(r)$ value for the β carbon atom. These two molecules differ in 3 carbon atoms and 6 hydrogen atoms, which condensed $f^+(r)$ values sum 0.006. This difference between the two molecules could explain the deviation of the reactivity trend given experimentally.

Previously, it has been shown that when molecule differ in molecular size the local softness might be more appropriate to compare the local reactivities between the molecules since it takes the difference in the softness or polarizability of the molecules into account (see Methods section)[47, 48]. However, for the α,β-unsaturated ketones studied here the condensed values of the local softness do not reproduce the correct experimental reactivity trend and the difference between 2-octen-4-one (5) and 3-penten-2-one (4) persists. This might indicate that the comparison of the values of condensed Fukui functions or local softness might be more appropriate in molecular systems which share a similar number of atoms and functional groups.

Interestingly, the order of the condensed values of $I_{\omega;N}(r)$ on the β carbon under the FMR approach reproduces the same trend observed in the global descriptor ω for all molecules of the validation set. Considering that ω and $I_{\omega;N}(r)$ are the global and local reactivity descriptors derived from the same quadratic energy model the reactivity order of the local and global descriptors is consistent within the energy model but does not reproduce the experimental reactivity of the compound.

Taking all these observation into accounts the FMR approach in combination with the condensed Fukui function $f^+[C_\beta]$ reproduces the reactivity order given by the experimental values of the rate constants best and was therefore used to study the reactivity of α, β-unsaturated esters, thioesters and amides.

4.2 | Reactivity descriptors in α, β-unsaturated esters, thioesters and amides

The reactivity of α, β-unsaturated esters, thioesters and amides to form the reactive enolate after hydride transfer and the subsequent carbon dioxide fixation by the enolate was addressed in two different processes. For the hydride transfer reaction the electrophilicity and therefore the nucleophilic attack on the neutral α, β-unsaturated esters, thioesters and amides was considered. For the carbon dioxide fixation reaction the nucleophilicity of the enolate intermediate was studied. For the two processes the values of global and local descriptors have been calculated for the respective neutral and anionic molecules in vacuum and in aqueous solution. Solvent effects on reactivity were estimated using the implicit SMD solvation model[49].

The studied molecules differ in the substituent R1 on the β carbon atom, the heteroatom X (oxygen, nitrogen or sulfur), and the group covalently bound to the heteroatom R2 (hydrogen, methyl, or dimethyl). To identify the different molecules the following syntax was adopted : R1-X-R2, e.g. H-S-Me, Me-S-Me, H-O-Me, Me-O-Me, H-N-H_2, Me-N-H_2, H-N-Me_2 or Me-N-Me_2

4.2.1 | Nucleophilic attack of the hydride anion on the α, β-unsaturated thioesters, esters and amides

In the nucleophilic attack of the hydride anion on the α, β - unsaturated esters, thioesters and amides (see Figure 3) the molecules are electrophiles and therefore global descriptors as the electrophilicity ω and the electron affinity were calculated. For the electron affinity the finite difference (FD) approach was compared to the energy of the LUMO. The

global descriptors are shown in Table 3.

TABLE 3 Global descriptors for the electrophilicity (in eV) of neutral α,β-unsaturated thioesters, esters and amides at ωB97X-D3 / 6-311G(d,p) level of theory in vacuum and aqueous solution.

R1-X-R2	ε_{LUMO}	A_{FD}	ω	ΔN_{max}	ε_{LUMO}	A_{FD}	ω	ΔN_{max}
		Vacuum				Solvent		
H-S-Me	0.4053	-0.3591	1.0259	0.4584	0.4902	2.0244	0.9958	0.4501
H-O-Me	0.8852	-0.9659	0.9833	0.4204	0.9122	1.6489	0.9835	0.4186
H-N-H_2	1.1989	-1.3224	0.8143	0.3887	1.2200	1.3632	0.8581	0.3912
H-N-Me_2	1.1711	-1.1020	0.7472	0.3842	1.1166	1.4067	0.7664	0.3894
Me-S-Me	0.6291	-0.4979	0.9327	0.4359	0.6442	1.8258	0.9330	0.4347
Me-O-Me	1.1252	-1.1020	0.8651	0.3973	1.0836	1.4095	0.8733	0.4004
Me-N-H_2	1.4390	-1.4530	0.7341	0.3675	1.4001	1.1129	0.7696	0.3732
Me-N-Me_2	1.3857	-1.2734	0.6785	0.3643	1.2943	1.1700	0.7115	0.3732

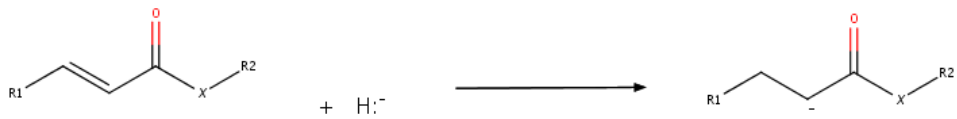

FIGURE 3 Nucleophilic attack of hydride anion on α,β-unsaturated carboxylic molecules

The electrophilicity ω defined by Parr identifies α,β-unsaturated thioesters as the most reactive molecules followed by esters and the amides. Changing the R1 group from hydrogen to a methyl group decreases the reactivity. The effect of the aqueous solvent represented by the implicit solvent model in the electronic structure calculations decreases slightly the reactivity with respect to the values in vacuum.

The electron affinity might also be used as a global descriptor for the electrophilicity. The electron affinity of the molecular systems is evaluated under the finite difference approach, which involves the calculation of the unstable anion or using the energy of the LUMO neglecting the relaxation of the molecular orbitals upon electron addition. At the ωB97X-D3 / 6-311G(d,p) level of theory the energies of the LUMO are positive and the electron affinity negative and close to each other in absolute value in vacuum calculations. This implies that in vacuum the anion is less stable than the neutral molecular system. The reactivity order obtained from the electron affinity, however, agrees with the one predicted by ω. When the solvent is added, the electron affinity from the finite difference approach differs considerably from the energy of the LUMO, since the implicit solvent makes the anion more stable than the neutral molecular system. This results in positive electron affinities A_{FD}, which again show the same reactivity order as the electrophilicity ω defined by Parr. As will be shown below the electron affinity as global descriptor presents a common reactivity order with the condensed value of $f^{+}(r)$ on the carbon carbonyl atom and not on the β carbon atom.

From the analysis of the global descriptors α,β-unsaturated thioesters would be the most reactive molecules followed by esters and amides and the methyl group and the addition of the solvent lead both to a decrease in their

reactivity. However, as noted in the validation of the descriptors described above, one has to take into account that global descriptors only describe the molecule as a whole and not the reactivity of one specific site. In the case of the ketones described above the global descriptors were shown to not reproduce the reactivity order of the β carbon atom, which is the most reactive one as evidenced from the experimental study.

TABLE 4 Local descriptors for the electrophilicity of neutral α,β-unsaturated thioesters, esters and amides (linear and quadratic energy models under FMR approach) using frontier molecular orbital(FMO) approximation (ωB97X-D3 / 6-311G(d,p)) in vacuum and aqueous solution.

		Vacuum		Solvent	
R1-X-R2	atom	$I_{\omega;N}$	f^+	$I_{\omega;N}$	f^+
H-S-Me	C_β	0.0975	0.2823	0.0935	0.2706
	$C_{C=O}$	0.0708	0.1974	0.0755	0.2173
H-O-Me	C_β	0.0975	0.3214	0.1389	0.3127
	$C_{C=O}$	0.0538	0.1522	0.0531	0.1686
H-N-H_2	C_β	0.0924	0.3362	0.0903	0.3243
	$C_{C=O}$	0.0416	0.1245	0.0461	0.1389
H-N-Me_2	C_β	0.0861	0.3226	0.0870	0.3148
	$C_{C=O}$	0.0416	0.1329	0.0464	0.1465
Me-S-Me	C_β	0.0803	0.2420	0.0806	0.2318
	$C_{C=O}$	0.0664	0.1983	0.0723	0.2191
Me-O-Me	C_β	0.1094	0.2746	0.1065	0.2674
	$C_{C=O}$	0.0457	0.1529	0.0508	0.1703
Me-N-H_2	C_β	0.0733	0.2863	0.1015	0.2760
	$C_{C=O}$	0.0393	0.1257	0.0391	0.1421
Me-N-Me_2	C_β	0.0687	0.2748	0.0717	0.2680
	$C_{C=O}$	0.0391	0.1333	0.0443	0.1487

Therefore, local descriptors were calculated for the α,β-unsaturated thioesters, esters and amides employing the linear and quadratic energy model under the FMR approximation (the RMF approximation was discarded since it did not reproduce the correct reactivity order in ketones). The Fukui functions $f^+(r)$ (linear energy model) and $I_{\omega;N}(r)$ (quadratic energy model) in combination with the FMO approach [42] were condensed to atoms with the Hirshfeld-I partition method [41] (the finite difference approach was not considered due to the unstable anions in vacuum). The condensed values for the reactive β and carbonyl carbon atoms are shown in Table 4. Also here the influence of the solvent on the local reactivity descriptor was considered.

The condensed values of the fukui functions $f^+(r)$ (linear energy model) show their largest value on the β carbon atom as expected. This is rationalized from the distribution of the fukui function $f^+(r)$ with a large contribution on this atom shown for the system Me-S-Me as representative of all molecules in Figure 4. The carbonyl carbon atom present smaller condensed values for $f^+(r)$. Also the condensed values of $I_{\omega;N}(r)$ (quadratic energy model) display their

maximum to the β carbon atom.

The validation study showed that local descriptors may be used for molecules which share a common number of atoms and atom types. Therefore also here the values of local descriptors were compared between the different molecules to establish a reactivity order. When the local descriptor from the quadratic energy model $I_{\omega;N}(r)$ on the carbonyl carbon atom is considered, the thioesters are the most reactive molecules followed by the ester and the amides. This agrees with the same order of the global descriptors as the electrophilicity. However, in the validation set discussed above $I_{w;N}(r)$ was shown to not identify the most reactive site (β carbon atom) in the molecule under the FMR approach and to not describe the reactivity trend correctly.

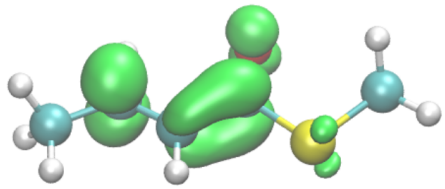

FIGURE 4 Fukui function $f^{+}(r)$ of the neutral Me-S-Me molecule in vacuum.

The other local descriptor $f^{+}(r)$ from the linear energy model, however, did reproduce the reactivity of the validation set reported in the experiment correctly. For the α,β-unsaturated thioesters, esters and amides the condensed values of $f^{+}(r)$ on the β carbon atom assigns the amides as the most reactive molecules followed by the esters and the thioesters. The presence of a methyl group in R1 diminishes their reactivity as the presence of the solvent or two methyl groups instead of hydrogen atoms bonded to the nitrogen atom. Interestingly, $f^{+}(r)$ on the carbonyl carbon also shows the same reactivity order of the electron affinity (A) for the thioester, ester and amides. From this comparison one might conclude that the global descriptors of α,β-unsaturated compounds are more associated with the reactivity on the carbonyl carbon atom and each local and global descriptor is consistent within its energy model.

The validation of local and global descriptors in ketones discussed above identified the condensed values of $f^{+}(r)$ as the most appropriate descriptor to predict reactivity in this type of molecules. Therefore, one can conclude that amides represent the most reactive molecules for the hydride transfer followed by the esters and the thioesters.

4.2.2 | Electrophilic attack of anionic α,β - unsaturated enolates by CO_2

After the hydride anion is transferred and the enolate is built the second step involved in the enzymatic CO_2 fixation is the electrophilic attack of the carbon dioxide molecule on the enolate (see Figure 5). For this step different reactivities of the enolate may also affect the overall enzymatic CO_2 fixation reaction mechanism. To assess the reactivity of the enolate as nucleophile towards CO_2, nucleophilic global and local reactivity descriptors were calculated for each enolate built from the molecules R1-X-R2 discussed above.

Table 5 displays for the anions the nucleophilicity index N_{FD} defined by Contreras[18] as the negative of the ionization potential and the energy of the HOMO ϵ_{HOMO}. The difference between the two is that N_{FD} accounts for the orbital relaxation after the removal of an electron from the anion. The negative value of the HOMO energy for all studied systems implies that the anions are stable and that the ionization potential is positive, as evidenced from a negative value of N_{FD}. In vacuum the two values are close to each other and show the same trend between the different molecules: The most nucleophilic enolate is the one formed from R1-N-H_2 followed by R1-N-Me_2, the ester and the

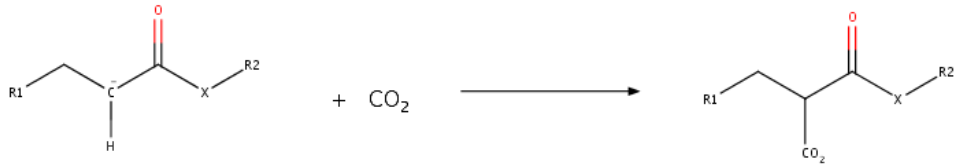

FIGURE 5 Carboxylation reaction of the enolate built through hydride addition.

thioester. There is a very small increase in nucleophilicity when the methyl group in R1 is replaced by a hydrogen atom.

Since the enolate presents a negative charge the aqueous solvent would stabilize the anion considerably resulting in an increase in the ionization potential and also in the energy of the HOMO. As evidenced in Table 5 both global nucleophilic indicators increase (absolute values) with the solvent and also present a larger difference between them. The difference arises because the orbital relaxation is expected to play a major role when the solvent is present, which might polarize the anion but to a lesser extend the neutral molecule. When the nucleophilic global indicators are compared to vacuum one observes that the solvent makes the difference between each molecule R1-X-R2 smaller but the overall reactivity order is maintained with only some minor changes in the order of the amides and the ester.

From these results one concludes that to describe the nucleophilicity of negatively charged species the ionization potential and the derived nucleophilicity is more appropriate to describe the reactivity of the molecular systems in the aqueous phase and that the methylated followed by the not methylated amides present the most reactive enolates from the molecules studied in aqueous solution.

TABLE 5 Global descriptors (in eV) for anionic α,β-unsaturated thioester, ester and amide enolates (ωB97X-D3 / 6-311++G(d,p)) in vacuum and aqueous solution.

R1-X-R2	ε_{HOMO}	N_{FD}	ε_{HOMO}	N_{FD}
	Vacuum		Solvent	
H-S-Me	-2.2699	-2.0734	-6.9612	-4.3482
H-O-Me	-1.6798	-1.5782	-6.7380	-4.0652
H-N-H_2	-1.5816	-1.4829	-6.6918	-3.9890
H-N-Me_2	-1.7587	-1.5319	-6.6299	-3.9700
Me-S-Me	-2.3836	-2.1224	-6.9336	-4.3537
Me-O-Me	-1.8306	-1.6435	-6.7185	-4.0707
Me-N-H_2	-1.7244	-1.5510	-6.6366	-3.9809
Me-N-Me_2	-1.8836	-1.5918	-6.5751	-3.9482

The nucleophilic global indicator (N_{FD}) for the enolates was contrasted with the local reactivity descriptor, which for both energy models is the fukui function $f^{-}(r)$ (see Methods section). The nucleophilic fukui function $f^{-}(r)$ was condensed to atoms for each enolate R1-X-R2 with the Hirshfeld-I method and the values for the α carbon atom, the carbonyl carbon atom and oxygen atom are shown in Table 6 for the molecules in vacuum and in aqueous solution represented by the SMD solvation model.

Independent of the environment the largest value of the condensed nucleophilic reactivity descriptor derived from

TABLE 6 Condensed Fukui function f^- of different atoms (in square brackets) in anionic α,β-unsaturated thioester, ester and amide enolates (ωB97X-D3 / 6-311++G(d,p), FMR approach) in vacuum and aqueous solution.

R1-X-R2	$f^-[C_\alpha]$	$f^-[C(C=O)]$	$f^-[O(C=O)]$	$f^-[C_\alpha]$	$f^-[C(C=O)]$	$f^-[O(C=O)]$
	Vacuum			Solvent		
H-S-Me	0.4327	0.1104	0.1926	0.4029	0.1186	0.1669
H-O-Me	0.4826	0.0971	0.1968	0.4651	0.1063	0.1758
H-N-H_2	0.4785	0.0909	0.2005	0.4636	0.1060	0.1672
H-N-Me_2	0.4621	0.0934	0.2060	0.4450	0.1010	0.1463
Me-S-Me	0.4355	0.1068	0.1862	0.4081	0.1164	0.1639
Me-O-Me	0.4847	0.0936	0.1907	0.4691	0.1034	0.1713
Me-N-H_2	0.4779	0.0876	0.1957	0.4643	0.1039	0.1640
Me-N-Me_2	0.4688	0.0897	0.1916	0.4531	0.0968	0.1394

$f^-(r)$ is observed on the α carbon atom as one would expect. This agrees with the distribution of the fukui function $f^-(r)$ shown for the enolate in Figure 6. The second most reactive site in the molecules R1-X-R2 is located on the oxygen atom, since the negative charge is partially delocalized between the α carbon atom and this atom. Also here the presence of the solvent decreases the values of the condensed value of $f^-(r)$ on the α carbon atom and the oxygen carbonyl atom indicating a smaller reactivity as the global descriptors.

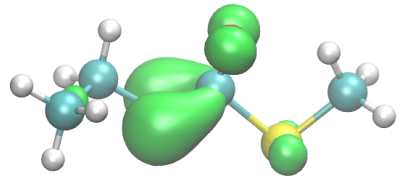

FIGURE 6 Fukui function $f^-(r)$ of anionic Me-S-Me molecule in vacuum.

Comparing the values of the condensed local nucleophilicity descriptor $f^-(r)$ on the most reactive α carbon atoms one identifies the largest values on the esters followed by the amides, which values become very similar after addition of the solvent. The thioesters and the methylated amides present significantly smaller values. For the enolates in the aqueous phase, therefore, the global nucleophilic descriptor and the associated local one $f^-(r)$ identified the amides and the esters as the most reactive α,β-unsaturated molecules towards the addition of an electrophile as CO_2 and the effect of adding a methyl group on R1 is only marginally.

5 | CONCLUSIONS

From the results presented above one concludes that for the nuleophilic attack on α,β-unsaturated compounds local reactivity descriptors are more appropriate to describe the reactivity of the most reactive site in the molecule, if the molecules share the same number of atoms and atom types. In the validation set, the condensed Fukui function $f^{+}(r)$ identified correctly the C_{β} atom under the FMR approach as the most reactive site and the value on this atom assigned the experimental reactivity order correctly to α,β-unsaturated ketones.

Additionally, it was established that local and global reactivity descriptor are consistent in the reactivity order of the molecules using the same energy model, as observed for the electrophilicity from Parr ω and the local, condensed, electrophilicity descriptor $I_{\omega,N}(r)$ on carbonyl carbon atoms for the quadratic model for α,β-unsaturated molecules.

For α,β-unsaturated thioesters, esters and amides, which are alternative substrates for CO_2 fixation by Crotonyl-CoA-carboxylases, the condensed value of the Fukui function $f^{+}(r)$ locates correctly the most reactive site on the β carbon atom for all studied R1-X-R2 systems and identified the amides as the molecules most prone to nucleophilic attack by the hydride anion. The thioesters, which are the natural substrates, present the smallest reactivity independent of the presence of a solvent. These results are encouraging as they propose amides as alternative more reactive substrates for CO_2 fixation assuming equal binding kinetics to the enzyme as the one of thioesters.

After the formation of the enolate species by the hydride anion an electrophilic attack by the carbon dioxide molecule has to take place to form the products. This step depends on the nucleophlicity of the enolates and was addressed with global and local nucleophilic reactivity descriptors. Here, it was found that global descriptors and the condensed value of $f^{-}(r)$ on the α carbon atom identified the esters and the amides as the most reactive ones followed by the methylated amides and the thioesters in the aqueous phase.

Altogether, the reactivity study on α,β-unsaturated compounds has evidenced that for molecules with more than one reactive site, global reactivity descriptors do not necessarily represent the reactivity on the most reactive site and therefore the experimentally observed reactivity trend. From the local descriptors that can be used to assign the reactivity to the studied molecules with similar chemical structure the condensed fukui function under the FMR approach reproduces the experimental values better than the condensed local descriptor $I_{\omega,N}(r)$ derived from the quadratic energy model.

With respect to the reactivity of α,β-unsaturated compounds as alternative substrates for enzymes to fix CO_2, amides seem to be the best candidates due to their larger affinity for the hydride transfer and their larger nucleophilicity for CO_2 after enolate formation. To confirm this result the reaction kinetics of the enzyme with these substrates could be studied experimentally (assuming the same binding kinetics). It should be noted, however, that the influence of the enzyme on the substrate reactivity or possible conformational changes of the substrate was not accounted for in this study and may lead to differences in the proposed reactivity order. These conformational effects and the influence of the enzymatic environment will be addressed in future work.

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