Selectivity Descriptors for the Michael Addition Reaction as Obtained from Density Functional Based Approaches

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Density functional (DF) based numerical approaches for computing orbital and atomic reactivity indices were employed in the study of selectivity descriptors for the 1,4 Michael addition reaction. To this aim, atomic and orbital Fukui indices and atomic softnesses for 2-arylmethylene-1,4-butanolides and *N*,*N*-disubstituted phenylacetamides were computed. Further on, these local selectivity descriptors have been rationalized in terms of the Pearson's hard−soft-acid−base principle to explain the observed regioselectivity. It is shown that the methods employed for local (atomic and orbital) reactivity index computations are useful and reliable for prediction of the regioselectivity upon conjugate addition of ambident nucleophiles to 2,3-unsaturated carboxylic esters. All the results reveal similar degree of localization/hardness of the 1,4-butanolides **C4** and active α-carbon belonging to the *N*,*N*-dimethyl-phenylacetamide, while the soft α-carbon in $LiCH_2CN$ reacts with the soft **C2** 1,4-butanolide center.

I. Introduction

Knowledge about selectivity and reactivity is of primary importance in the study of various reaction mechanisms. Better quantitative description of these two key concepts is the basis for understanding many chemical processes in different application fields, such as catalysis, adsorption, materials science, biology, pharmacology, etc. Therefore, Pearson's hard−soft/acid−base (HSAB) principle,[1] reading "hard likes hard and soft likes soft", has been widely used in rationalizing and understanding seemingly very disparate phenomena in contemporary chemistry. Very recently, Woodward[2] has summarized the perspective of the HSAB applications on reactions in organic synthesis and selective catalysis in an exhaustive review. The interpretation of a huge number of reactions led to the conclusion that despite the usefulness of the HSAB principle (with its traditional understanding of qualifying the entire molecule as hard or soft), the accurate prediction of regio- and stereoselectivity requires knowledge about the energetics and the orbital HSAB matching at the assumed reaction sites.[2] The theoretical research efforts in this area in the past years[3−15] made it possible to go beyond the so-called global HSAB principle and to provide details about its local applications. Using condensed Fukui functions at various atomic sites of the molecule, Chattaraj[10] points out that the hard−hard interactions are charge controlled, whereas the Fukui function is the ideal descriptor for the frontier controlled soft−soft interactions. Although the chemical descriptors used separately can be regarded as promising tools, consideration of more than one indicator would lead to more reliable conclusions.

From a theoretical standpoint, the so-called reactivity indices have been introduced as descriptors of selectivity and reactivity. These indices include mainly the notions of global and local softness and hardness, and the Fukui functions. The theory that allowed the rigorous definition[16] of these chemical paradigms is the density functional theory[16,17] (DFT). Within the DFT framework, the chemical reactivity descriptors are defined as various energy derivatives with respect to the electron density. The need of quantification of the chemical descriptors has motivated the development and the implementation of various numerical algorithms[18−34] that approximate further these energy derivatives and yield numerical values of selectivity and reactivity at atomic or orbital scale.

This theoretical study of the selectivity descriptors within DFT was prompted by the experimentally observed[35] behavior of the conjugate addition of ambident nucleophiles to 2,3-unsaturated carboxylic esters, known as Michael reaction.[36] Some interesting results on the addition of lithium derivatives of acetonitrile and *N*,*N*-disubstituted phenylacetamides to a series of cyclic analogues of the 2,3-unsaturated carboxylic esters and the corresponding 2-arylmethylene-1,4-butanolides have been reported.[35] The latter compounds can be used as building blocks for the synthesis of a large variety of natural products containing γ-lactone rings, many of which are pharmacologically active.

As published by Murray and al.,[37] the reaction between $LiCH_2CN$ and 2-phenylmethylene-1,4-butanolide proceeds as 1,2-addition to form 2-cyanomethylene-3-methylenetetrahydrofurane. The reaction with the Reformatsky reagents preserves the same regioselectivity.[38] On the other hand, it was found[35] that the reaction of the lithium derivatives of some *N*,*N*-disubstituted phenylacetamides with 3-methylene- and 2-arylmethylene-1,4-butanolides (Figure 1) takes place as typical 1,4-addition.

The observed regioselectivity of the reaction under consideration cannot be explained in terms of electronic and substitution effects. Therefore, the HSAB principle was proposed as a possible alternative.

To check this hypothesis, we have computed the atomically and orbitally resolved reactivity indices of the reactants. For this purpose, we have employed three different DFT based

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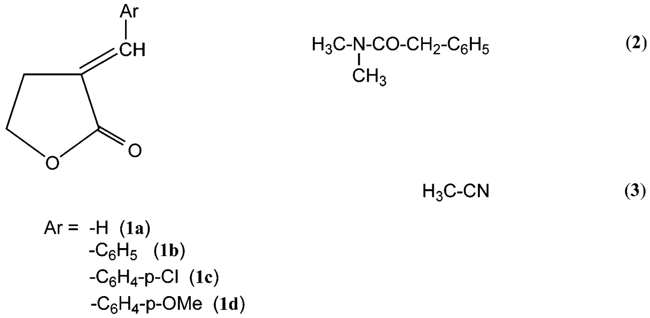

Figure 1. Chemical structures of the investigated 2-arylmethylene-1,4-butanolides **1a**−**d**, *N*,*N*-dimethyl-phenylacetamide **2**, and acetonitrile **3**.

computational schemes, which comprise computation of (1) orbital Fukui indices (OFI)[39] from the orbitally resolved hardness tensor;[23,26] (2) Fukui indices of each atom in the molecule (AFI) from the atomically resolved hardness tensor,[23,39] and the atom-in-molecule (AIM) softnesses,[39,40] expressed in mixed LCAO representation of second quantization as functions of Mayer atomic valences.[41] In the orbital approach, the hardness tensor is constructed from the Kohn−Sham orbitals using the fractional occupation number concept and Janak's extension[42] of the density functional theory.

II. Theoretical Background

Within the DFT formalism, the chemical potential μ and the total hardness η can be written as first and second derivative of the KS-energy with respect to the number of particles at constant external potential v

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v, \quad \eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_v = \left(\frac{\partial \mu}{\partial N}\right)_v \tag{1}$$

Several approximations (of varying accuracy) to the global hardness and softness have been proposed. One of the most widely applied formulas[27] to compute these quantities use the three-point finite difference and express μ and η through the electron affinity A and the ionization potential I

$$\begin{aligned} \mu &= -(I + A)/2 \\ \eta &= (I - A)/2 \end{aligned} \tag{2}$$

Further simplification of (2) is to account only for the HOMO−LUMO energy difference: $\mu = (\epsilon_{HOMO} + \epsilon_{LUMO})/2$ and $\eta = (\epsilon_{LUMO} - \epsilon_{HOMO})/2$.

Although μ is a global characteristic of a quantum system, hardness and softness are functions of the position and characterize the local response at a given point inside a molecular region. The reactivity-oriented description of the molecules requires knowledge about the local reactivity indices, since the electron density distribution is fundamental for the understanding of chemical reactivity. The reactivity−softness relationship postulated in HSAB is rationalized in terms of the local response properties of a system. On the other hand, the local hardness of a system in global equilibrium state may be arbitrarily set equal to the global hardness η and can be taken to be the average of orbital contributions.[43] Therefore, it is difficult to gain local information about the system from molecular electronegativity and hardness.[43,44] Local hardness and local softness were derived by Parr and Yang[45]

$$\eta(\mathbf{r}) = \frac{1}{N}\int \frac{\delta^2 F[\rho]}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')}\rho(\mathbf{r})\,d\mathbf{r}' \tag{3}$$

$$s(\mathbf{r}) = \left[\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right]_{v(\mathbf{r})} = \frac{1}{\eta}\left[\frac{\partial \rho(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})} \tag{4}$$

where $F[\rho]$ is the Hohenberg−Kohn universal functional.[16] These expressions are obtained through integration of the hardness and softness kernels

$$\eta(\mathbf{r},\mathbf{r}') = \frac{\delta^2 F[\rho]}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')} \tag{5}$$

$$s(\mathbf{r},\mathbf{r}') = \left[\frac{\partial \rho(\mathbf{r})}{\partial u(\mathbf{r}')}\right]_{v(\mathbf{r})} = -\frac{1}{\eta}\left[\frac{\partial \rho(\mathbf{r}')}{\partial u(\mathbf{r})}\right]_{v(\mathbf{r})} \tag{6}$$

where $u(\mathbf{r})$ is the modified potential[45]

$$u(\mathbf{r}) = v(\mathbf{r}) - \mu = -\frac{\delta F[\rho]}{\delta \rho(\mathbf{r})}$$

Another local characteristic of reactivity is the Fukui function. Fukui functions, $f(r)$, as originally defined by Parr and Yang within DFT, are the first derivative of the chemical potential μ with respect to the external potential $v(r)$, or, equivalently, the first derivative of the electron density $\rho(r)$ with respect to the number of electrons N

$$f(\mathbf{r}) = \left[\frac{\delta \mu}{\delta v(\mathbf{r})}\right]_N = \left[\frac{\partial \rho(\mathbf{r})}{\partial N}\right]_v \tag{7}$$

Comparing eq 4 and eq 7, it is seen that the Fukui function is related directly to the local softness.

Computations of the local reactivity indices in the real molecular space are a very demanding task, but the above derivatives are discontinuous for molecular or atomic systems and difficult to evaluate without further approximations. Usually, the local quantities are obtained from integration over atomic regions in the molecules.[12,15,18,30,31,45,46] For the Fukui function computations, Koopmans theorem is often adopted and $f(r)$ is identified with the electron density of the frontier orbitals.[27]

The wide range of applications of these approximations has unambiguously demonstrated that, despite the accuracy of the SCF method, the reliability of the local reactivity indices depends strongly on the basis set quality.[2,27,46] Other problems inherent to these approximations are related to the fact that usually whole-electron occupation change is employed, whereas the exact definition demands an infinitesimal change of the number of electrons; moreover, generally only the frontier orbital densities are considered. Reactivity is, however, largely determined by the response of all valence electrons and is governed by the whole spectrum and not just the frontier orbitals.[49] Thus, in the present study, we have employed an original algorithm[23,24] based on the use of fractional occupation numbers in the energy derivative computations in orbital representation, not in the real molecular space. An advantage of this approach is the fact that the global and local reactivity indices obtained from the orbitally resolved hardness tensor (ORHT) are nearly independent of the basis sets and exchange-correlation functionals.[47] Although the computational schemes employed in the present study are described in details elsewhere,[39,48,50] we will briefly recall the basic ideas and formulas bellow.

Reactivity Indices from Orbitally Resolved Hardness Tensor. In Janak's formulation,[42] the Kohn−Sham (KS) one-electron orbital energies are defined as the first derivatives of the total energy with respect to the occupation numbers n_i. The study of a density change caused by external perturbation (i.e., the approach of a reagent to the system, the attachment of an electron, an ionization process, etc.) is explored in KS-DFT through Taylor's expansion of the total energy functional around the number of electrons N. Following Janak's extension of DFT for fractional occupations, the energy functional can be expanded around the state, characterized by the corresponding set of occupation numbers n^0 (n_1^0, n_2^0, ..., n_k^0) and by the relevant KS eigenvalues $\epsilon^0 = (\epsilon_1^0 ... \epsilon_k^0)$. The first derivatives of the total energy with respect to the occupation numbers give the KS-eigenvalues and the second derivatives give the hardness matrix elements as defined by Liu and Parr[14] $\eta_{ij} = \partial^2 E/\partial n_i \partial n_j$ (eq 8). Thus, the hardness matrix elements are positive and the hardness matrix is symmetric. Since the KS-eigenvalues are defined through Janak's theorem as first derivatives of the total DF-energy, the ij-th element of the hardness matrix can be obtained as the first derivative of ϵ_i with respect to n_j:[23,24] $\eta_{ij} = \partial \epsilon_i/\partial n_j$. The latter equation is numerically approximated with the finite difference formula

$$\eta_{ij} = \frac{\partial^2 \mathrm{E}}{\partial \mathrm{n}_i \partial \mathrm{n}_j} = \frac{\partial \epsilon_i}{\partial \mathrm{n}_j} = \lim_{\Delta n_j \to 0} \frac{\epsilon_i(n_j - \Delta n_j) - \epsilon_i(n_j)}{\Delta n_j} \tag{8}$$

It is worth emphasizing that the use of Janak's extension of DFT in this reactivity indices approach has two advantages: (1) the DF-energy functional can be expanded over the noninteger occupation numbers and (2) in the calculation of hardness matrix elements one takes only first order derivatives, thus diminishing the numerical errors. Therefore, the condition of having a symmetric hardness matrix is fulfilled with fair accuracy (mostly up to the third digit) depending, of course, on the particular molecular system. Hardness tensor elements are themselves approximations to the hardness kernel (eq 5).

It is not difficult to obtain local, orbital and global softness, global hardness and the Fukui indices from η_{ij}. As hardness and softness are reciprocal in the sense that $\int s(\mathbf{r})\eta(\mathbf{r}) = 1$, by inverting the hardness tensor one acquires the softness tensor ($[s_{ij}] = [\eta_{ij}]^{-1}$). Then the total softness (S), the total hardness (η) can be expressed from the orbital softnesses s_{ij} approximating the softness kernel (eq 6)

$$S = \sum_{ij} s_{ij}$$

$$\eta = \frac{1}{S} = \frac{1}{\sum_{ij} s_{ij}} \tag{9}$$

It is also straightforward to obtain a working definition of the orbital Fukui indices within the ORHT formalism: $f_i = \partial\mu/\partial\epsilon_i = \partial n_i/\partial N$ and the relation between orbital f_i and orbital softness s_i is given by

$$f_i = \left(\frac{\partial n_i}{\partial \mu}\right)\left(\frac{\partial \mu}{\partial N}\right) = \eta s_i \tag{10}$$

In this approximation, the sum of the Fukui indices for all of the orbitals considered in a particular molecular system equals 1. It is worth emphasizing that an important advantage of computing the reactivity indices in the orbital representation within KS-DFT is the negligible influence of the basis set quality and exchange-correlation functionals on the reactivity index numbers.[47]

Reactivity Indices from Atomically Resolved Hardness Tensor (ARHT). We calculate the atomic reactivity indices by using the same scheme as in the ORHT approach. The difference consists in the way of computing the hardness tensor elements. In atomic approximation, the diagonal elements η_{ii} are the total hardness values of each atom in the molecule. The latter are calculated applying the ORHT scheme. The off-diagonal elements in the hardness tensor (ARHT) are now taken from Ohno's[51] empirical formula

$$\eta_{ij} = \frac{1}{\sqrt{b_{ij}^2 + R_{ij}}}$$

$$b_{ij} = \frac{2}{\eta_{ii} + \eta_{jj}} \tag{11}$$

where R_{ij} is the distance between any two atoms i and j in the molecule. In this way the atoms are allowed to "interact" with each other within the molecule.

AIM Softnesses from Mayer Valences. The expression for the AIM softness is derived within an approximate scheme as simple functions of the Mayer bond-order indices.[41] The AIM is defined through the magnitude of the regional charge−charge fluctuations $\lambda(\Omega)$[39,40]

$$\lambda(\Omega) = \frac{1}{N(\Omega)}\langle \tilde{N}(\Omega)\tilde{N}(\Omega)\rangle - N(\Omega)^2$$

where the averaging $\langle\cdots\rangle$ is done with respect to the molecular ground state, and $N(\Omega)$ is the average electron occupancy in the molecular subdomain Ω. The regional charge−charge fluctuation is directly related to the regional (AIM) softness, $S(\Omega)$, which was shown[40] to equal the Mayer valence, V_A, of atom A

$$\lambda(\Omega) \approx \frac{S(\Omega)}{q_{\mathrm{MULL}}} = \frac{V_A}{q_{\mathrm{MULL}}} \tag{12}$$

In the above q_{MULL} stands for the Mulliken charges.

The Mayer atomic valence, V_A, can be expressed as a function of the Mayer bond-order index $P(AB)$

$$V_A = \sum_B P(AB) \tag{13}$$

the summation carried out over all bonds of atom A.

Thus, the AIM softness, S_{AIM}, defined as

$$S_{\mathrm{AIM}} = |V_A - V| \tag{14}$$

where V is the formal atomic valence, is practically a function of the Mayer bond order indices.

III. Method of Calculations

The electronic structures and geometries of the investigated objects were calculated with the Gaussian 03W program package.[52] All calculations presented below were performed at density functional level of theory with Becke's[53] exchange and Perdew[54] gradient corrected functionals (BP86) and a basis set of double-ζ quality.

Vibrational frequency calculation for each optimized structure was carried out to confirm that it was located at the minimum of the potential energy surface.

The computed Mulliken charges indicated that the lithiated structures **2** and **3** feature typical ionic bond polarization.

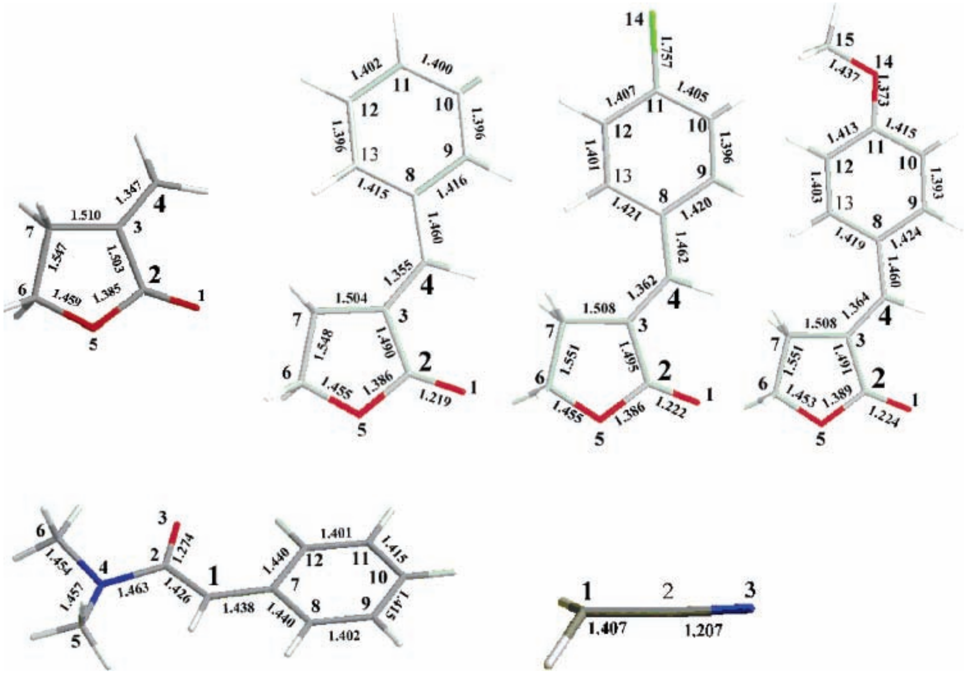

Figure 2. Optimized geometries and atomic numbering of the investigated structures.

Therefore, in all further studies, only the ambident nucleophilic part of the compounds was considered.

The Gaussian-optimized structures were used for the computation of reactivity descriptors (S_{AIM}, f_i) by means of the deMon program code.[55,56] The same nonlocal gradient corrected functional (BP86) and orbital DZVP basis sets[57] augmented with polarization functions were used for C, N, O and H atoms. The auxiliary basis[57] set used to fit the exchange-correlation potential were as follows: (4,3; 4,3) for C, N, O atoms and (4;4) for H atoms.

The variation in the occupation number Δn was set to be 0.0002. The elements of the hardness matrices were calculated by taking into account the occupied valence orbitals, together with the LUMO of each species. For the constituent atoms of the considered molecules we obtained the total hardnesses (in eV), η, equal to H, 12.47; C, 10.43; O, 13.25; N, 11.97; Cl, 6.30. These values were the diagonal elements in the atomically resolved hardness tensor.

IV. Results and Discussion

AIM Softness from Mayer Atomic Valences. The optimized structures and the atomic numbering of the reactants involved in the Michael addition reaction under study (vide supra) are given in Figure 2.

As a simple and quick estimation of selectivity we have computed first the AIM softnesses (S_{AIM}), expressed in mixed LCAO representation of second quantization as functions of Mayer atomic valences. These quantities reflect the charge fluctuations within the molecule:[39,40,58,59] the larger the charge fluctuation in a particular atomic region of a molecule, the more this atom is engaged in bonds with other atoms; that is, the electrons belonging to the atom are less localized in this atomic region. Atoms characterized by lower values of S_{AIM} exhibit higher degree of electron localization. The definition of AIM softnesses implies that AIM valences are often close to those expected from the classical valence picture.

To explain the witnessed regioselectivity on S_{AIM} grounds, we compare the S_{AIM} values for the two competing centers **C2** and **C4** of the 2-arylmethylene-1,4-butanolides on one hand and those of the active α-carbon sites in the ambident nucleophiles on the other hand. Our S_{AIM} results (collected in Table 1) reveal that in all the 1,4-butanolides considered the **C4** shows a larger degree of electron localization (smaller S_{AIM} value) compared to the degree of electron localization of **C2**. This may favor the nucleophilic attack on the **C4** center than on the **C2** one.

TABLE 1: Atom-in-Molecule Softnesses (S_{AIM}) from Mayer Atomic Valences for 2-Arylmethylene-1,4-butanolides (1a−1d)

number of atoms	S_{AIM}			
	1a	1b	1c	1d
O1	0.262	0.258	0.258	0.253
C2	0.241	0.232	0.229	0.232
C3	0.495	0.253	0.239	0.233
C4	0.047	0.017	0.017	0.015
O5	0.308	0.313	0.315	0.309
C6	0.0	0.034	0.029	0.029
C7	0.029	0.104	0.097	0.100
C8		0.414	0.370	0.398
C9		0.104	0.057	0.034
C10		0.073	0.069	0.009
C11		0.041	0.121	0.197
C12		0.067	0.069	0.064
C13		0.092	0.062	0.072
O(Cl)14			0.140	0.304
C15				0.056

Comparing the **C4** AIM softness in structures **1a − 1d**, we note the considerable difference between the S_{AIM} of 1a (0.047) and S_{AIM} in the other structures (ranging from 0.017 to 0.015). This correlates well with the fact that the aryl substituent leads to an extension of the π-electron system, thus increasing the order of the bond with **C4**. The chlorine in **1c** and the methoxy group (−OMe) in **1d** appear to have negligible influence on the C4 S_{AIM} values, although the −OMe group, as an electron-donating group via the benzene ring, decreases slightly the S_{AIM} of C4. As evidenced by the AIM softness values, the **C2** center is less sensitive to the substitution effect. It is worthwhile to note that **C4** is characterized as less bonded center compared to **C2** in all the 1,4-butanolides studied.

In conclusion, the AIM softness data imply that the reaction goes through 1,4-addition because the electron localization is

TABLE 2: Atomic Fukui Indices (f_i) from the Atomically Resolved Hardness Tensor for All Structures (1a−d, 2, and 3)

	f_i					
number of atoms	**1a** $\eta = 8.54$	**1b** $\eta = 7.60$	**1c** $\eta = 4.78$	**1d** $\eta = 7.29$	**2** $\eta = 7.50$	**3** $\eta = 9.42$
1	0.044	0.026	−0.072	0.022	0.092	0.342
2	0.232	0.195	0.204	0.185	0.130	0.275
3	0.012	−0.004	0.023	−0.002	−0.048	0.221
4	0.249	0.090	0.124	0.087	−0.127	
5	−0.087	−0.070	−0.124	−0.067	0.243	
6	0.241	0.207	0.248	0.198	0.249	
7	0.149	0.124	0.198	0.120	−0.005	
8		−0.010	0.017	0.006	0.081	
9		0.084	0.152	0.082	0.093	
10		0.097	0.087	0.096	0.095	
11		0.095	0.503	0.067	0.093	
12		0.097	0.091	0.081	0.076	
13		0.075	0.148	0.076		
14			1.846	−0.099		
15				0.275		

found to be higher for the **C4** center compared to **C2**. This result might be used as a possible explanation of the observed 1,4-addition, but it cannot answer the question why the reaction goes through 1,2-addition with $LiCH_2CN$ (**3**). To get a better understanding of the studied reaction mechanism, another quality of the local reactivity indices has to be considered and rationalized in terms of the HSAB principle.

Fukui Indices from Atomically Resolved Hardness Tensor. Fukui indices derived from the atomically or orbitally resolved hardness tensor are directly proportional to the local softnesses (s_i) as follows from eq 10. In this aspect, the smaller the Fukui index, the harder an atom or an orbital. The local hardness is related to electron localization: an atom in the molecule that is characterized with higher degree of electron localization exhibits a larger value of the local hardness. According to the HSAB principle, the preferred reaction site in the 2-arylmethylene-1,4-butanolides would be the atom characterized by a Fukui index which is closer to the f_i of the α-carbon in the corresponding ambident nucleophile.

Computed atomic Fukui indices for all molecular structures are listed in Table 2 together with the total hardness values obtained at the same level of approximation. Comparison of the AFIs, f_i, for the aryl substituted 1,4-butanolides (**1b**−**1d**) indicates that **C4** is harder than **C2**. The presence of an electron acceptor like **Cl** (structure **1c**) in *para*-position in the aryl substituent results in an increase of the **C4** Fukui index, i.e., **C4** becomes a softer atom, compared to the corresponding one in 2-phenylmethylene-1,4-butanolide (**1b**). As expected from chemical point of view, the electron acceptor will soften the **C4** center. On the contrary, for structure **1d**, where the electron-donating group (−OMe) is in para position, we notice a slight decrease in f_i of **C4**; that is, the **C4** atom turns somewhat harder than in **1b**. The degree of localization of the active carbon in *N*,*N*-dimethyl-phenylacetamide (structure 2) falls in the same range ($f_i = 0.092$) as the Fukui indices of **C4** in structures **1b**−**1d**. Interpreting these results in the spirit of the HSAB principle, we conclude that the hard **C4** atom will be the preferred site in the addition reaction with *N*,*N*-dimethyl-phenylacetamide (compared to the soft **C2** center). Thus, the products obtained are a result of a 1,4-addition.[35]

An exception in this series is structure **1a**, for which the Fukui indices of **C4** and **C2** have almost equal values. Therefore, these two centers will feature similar activity in the addition reaction. This can be attributed to the lack of aryl substituent in **1a**.

Nucleophile **3** is classified as a hard nucleophile in organic chemistry. As seen from Table 2, our computations of the total hardness values also prove that this is the hardest species considered. However, the total hardness/softness is not informative in selectivity studies. In fact, the active α-carbon atom in **3** is found to be a soft center ($f_i = 0.342$). This can be expected intuitively from the chemical structure: the absence of a benzene ring adjacent to the active C-atom in **3** prevents delocalization of the negative charge, unlike in 2. On the other hand, the **C2** atoms in **1b**−**1d** are all characterized by their f_i values as soft centers as well. Therefore, the soft center in **3** reacts with the soft center **C2** in **1b**−**1d**, thus explaining the observed[38] 1,2-addition reaction of $LiCH_2CN$ with 2-arylmethylene-1,4-butanolides.

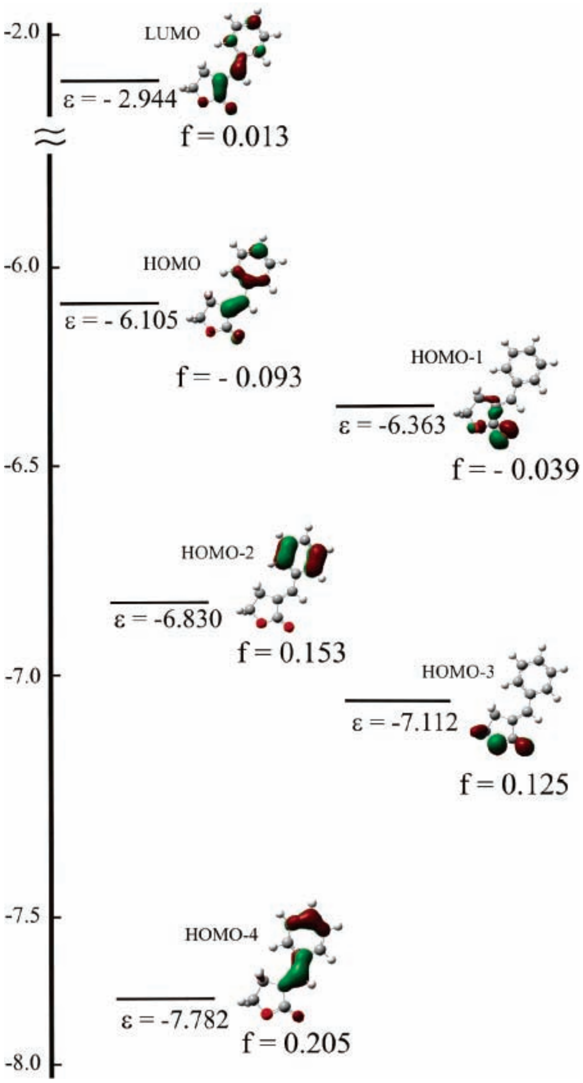

Figure 3. Computed molecular orbitals with their f_i of 2-phenylmethylene-1,4-butanolide (**1b**).

Fukui Indices from Orbitally Resolved Hardness Tensor. We continue further with analysis of the orbital Fukui indices mainly for the HOMO and LUMO of the reactants. The considered Michael 1,4-addition is a typical nucleophilic reaction (A_N). Thus the 1,4-butanolides LUMOs interact with the nucleophiles' HOMOs. To follow the reactivity of the substituted 1,4-butanolide acceptors (**1a**−**1d**), it is important to know the character of their LUMO and the HOMOs of the nucleophiles **2** and **3**, i.e., the orbital coefficients.

A set of computed f_i of LUMO down to HOMO-4 for 2-phenylmethylene-1,4-butanolide (**1b**) are given in Figure 3 as an example. It is seen that the orbitals are rather delocalized due to the presence of the π-conjugated system. Therefore, it is

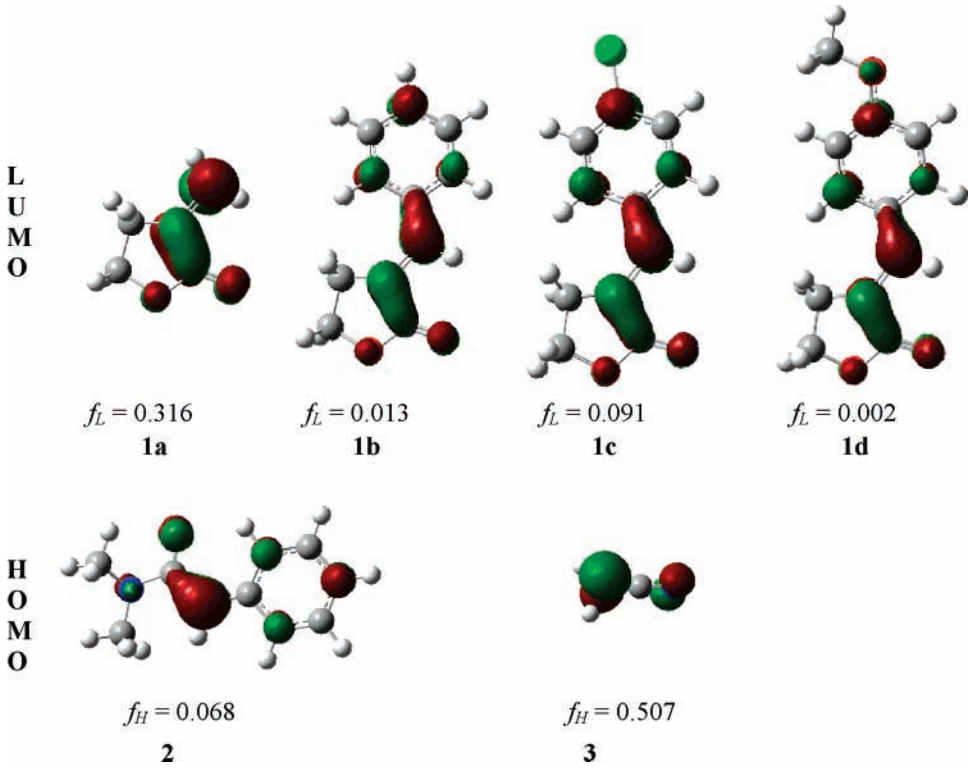

Figure 4. Fukui indices of LUMOs (f_L)of **1a−d** and HOMOs (f_H) of **2** and **3**.

difficult to assign the orbital Fukui index to a specific atomic center in the molecule. We see, however, that the main contribution to LUMO belongs to **C4** followed by **C3**. The **C2** coefficient in LUMO is roughly half the one of **C4**. The LUMO composition of all of the 1,4-butanolides is analogous (see Figure 4): the main contribution is from **C4**. These orbitals are hard orbitals as evidenced by the Fukui index values also shown in Figure 4.

The only exception is again **1a** featuring soft LUMO (f_i = 0.316). In the same figure are plotted the HOMOs of the nucleophiles (**2** and **3**), too. Their OFIs characterize the HOMO of the *N*,*N*-dimethyl-phenylacetamide **2** as a hard orbital (f_i = 0.068), whereas the HOMO of the acetonitrile anion **3** as a soft one (f_i = 0.507). For both ambident nucleophiles **2** and **3**, the main contribution to HOMO originates from the active α-carbon center. In the framework of the HSAB principle, one can expect higher reactivity of *N*,*N*-dimethyl-phenylacetamide **2** toward 1,4-addition of aryl substituted 1,4-butanolides (**1b**−**1d**). The soft LUMO of structure **1a** would be easily accessible for the soft HOMO electrons of the acetonitrile anion **3**, hence, 1,2-addition occurs.

V. Conclusions

We have employed three DFT approaches to study selectivity descriptors for 1,4-Michael addition reaction. From the relatively easily accessible AIM softness data we have made the first estimation showing that the carbonyl carbon atom in 2-arylmethylene-1,4-butanolides is less active compared to the methylene carbon. This approximate result has been substantiated by the atomic Fukui index values. Moreover, using the conceptual power of these local selectivity descriptors we have been able to assign the soft/hard characteristic to each atomic center. So, the **C4** atom in 2-arylmethylene-1,4-butanolides **1b**−**d** and the active α-carbon atom in **2** have been found to be hard centers. Finally, summarizing these results within the HSAB principle, we have been able to confirm quantitatively the hypothesis given in the experimental work.[35] We have gathered additional information for the reactivity exploiting the orbital Fukui indices: hard LUMOs in the aryl substituted butanolides prefer to accept hard HOMO electrons of the *N*,*N*-dimethyl-phenylacetamide nucleophile.

The atomic and orbital *local* reactivity indices used in this work are powerful tools for mechanism prediction of the Michael addition reaction. The knowledge of the reactivity and selectivity descriptors can be used additionally to design new γ-lactons with functionalized side-chains.

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