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Theoretical investigation of the selectivity in intramolecular cyclizations of some 2'–aminochalcones to dihydroquinolin–8–ones and indolin–3–ones

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Abstract The selectivity of the intramolecular cyclizations of a series of 2'–aminochalcones was investigated with an approach that combines spin–polarized conceptual density functional theory and energy calculations. To that aim, condensed–to–atoms electrophilic Fukui functions, $f_{NN}^{+}(\mathbf{r})$, were utilized as descriptors of the proclivity for nucleophilic attack of the NH$_2$ group on the unsaturated α and β carbons. The results of our model are in excellent agreement with the experimental available evidence permitting us in all cases to predict when the cyclization processes led to the formation of 5–exo and 6–endo products.

Keywords 2'–aminochalcones · 6–endo–end and 5–exo–trig closures · SP–DFT Fukui function

Introduction

Chalcones have been widely used as building blocks in combinatorial and diversity-oriented synthesis, because they are excellent 1,3-dielectrophilic systems. These systems offer a wide range of bioactivities and the possibility of multifunctionalization [1–3]. In fact, many synthetic routes toward obtaining of 2–aryl–2,3-dihydroquinolin-4(1H)-one derivatives for the synthesis of medicinally relevant compounds [4–6], start from 2'–aminochalcones as precursors bearing varied substituents in the aromatic rings [7–9].

Chalcones can react with nucleophiles at both the carbonyl group (1,2–addition) and the β–carbon (1,4–or Michael's addition). The intramolecular cyclization relies primarily on the success of aza-Michael reaction processes catalyzed by either acids or bases, under somewhat specialized reaction conditions [10–17]. In a recent study on the chemical transformation of chalcones, Abonia and co-workers reported the synthesis of a series of dihydroquinolin–8–ones via aza–Michael intramolecular cyclization of 2'-aminochalcones as precursors [18]. In that study, the nucleophilic attack of the amino group on the β–carbon led, as predicted from Baldwin's rules [19, 20], to the formation of six–membered heterocyclic systems. On the other hand, in a more recent investigation on the cyclization of some 2'–aminochalcones derived from 2– and 4–pyridinecarboxaldehydes in acidic media, Abonia and co-workers reported that the nucleophilic attack of the amino group occurred at the α–carbon, via a 5–exo–trig cyclization yielding indolin–3–ones derivatives [21]. These unexpected results contradicted the commonly observed 6-endo–trig cyclization for these type of systems, because Michael's addition products were not observed during the development of the reactions. Correspondingly, a four-step reaction scheme was proposed to explain this unusual behavior. It began with the protonation of the pyridine followed by the generation of a positive charge that became delocalized on the α-carbon after multiple resonant structures. It was inferred that this delocalization dramatically increased the α-carbon reactivity toward a nucleophilic attack of the amino group favoring the formation of the unexpected five-membered ring [21].

Given the importance of derivatization toward five- or six-membered heterocycle intermediates from chalcone templates

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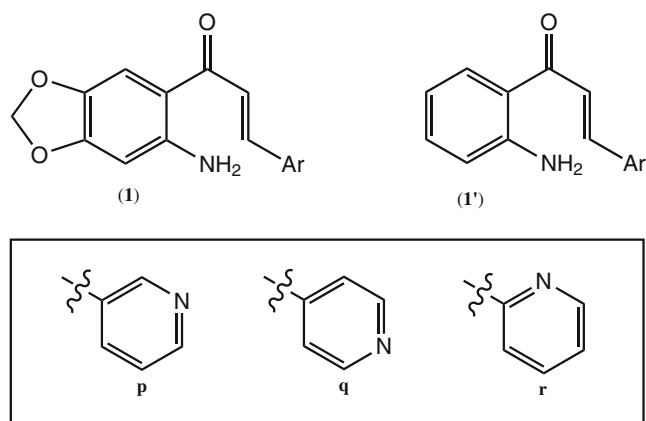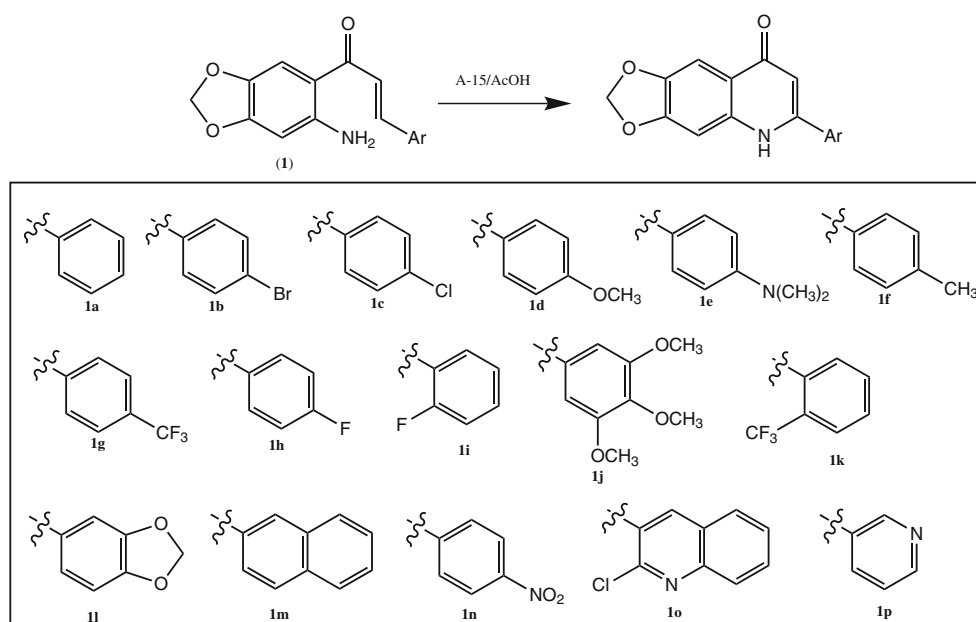
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[1, 4, 10, 21] it is desirable to develop methods that could provide a convenient estimation of the site selectivity in these systems. Following ongoing interests in the development and exploration of elements of a chemical reactivity theory based on the DFT framework [22–27], in the present contribution we focus on the proposed rationalizations concerning the selectivity in the acid-catalyzed intramolecular cyclization of the series of 2'–aminochalcones presented in Figs. 1 and 2. Experimental evidence for these reactions is available in refs. [18, 21]. According to these findings, the unexpected 5–exo cyclocondensation process yielding indolinone derivatives over the usual 6-endo pathway toward quinolinone ones, occurs only for chalcones with the aromatic 2– and 4–pyridinyl substituents. For the rest of the chalcones, including those with the 3-pyridinyl moiety, the 6–endo pathway appears as the usual and preferred route under the chosen experimental settings [18, 21].

Our exploration will be carried out in terms of *reactivity indexes* defined within the framework of spin-polarized DFT [23]. Our goal is simply to characterize the proclivity of the studied 2'–aminochalcone templates to undergo 6–endo and 5–exo ring closure reactions. The validity of the model will be determined by contrasting its predictions with the observed experimental results. It will be shown that our theoretical model properly predicts the cases where an unexpected 5–exo cyclocondensation process providing indolinone derivatives will prevail over the usual 6–endo mode producing quinolinones.

This paper is organized as follows: in Theoretical aspects we summarize the theory; in Computational details we present the computational details; in Results and discussion we present and discuss the results and in Conclusions we provide concluding remarks and perspectives.

Fig. 2 Pyridinyl substituted 2'–aminochalcones. For experimental details see ref. [21]

Theoretical aspects

Density functional theory provides a formal framework for the treatment of the chemical *reactivity* problem [22–24]. Within a perturbative approach [28–31], complete hierarchies of global, local, and non–local quantities, have been associated to different orders of response of a molecular system against perturbations in either its number of electrons, N, its external (i.e., due to the nuclei) potential, $v(\mathbf{r})$, or both [22–24]. A key example of these reactivity indexes is the Fukui function, $f(\mathbf{r})$, defined [32, 33] as the response of the system's electron density to a perturbation in its total number of electrons,

$$f(\mathbf{r}) = \left.\frac{\partial \rho(\mathbf{r})}{\partial N}\right|_{v(\mathbf{r})}. \tag{1}$$

Fig. 1 Aza–Michael intramolecular cyclization 2–aminomethylendioxychalcones (1) in acid–catalyzed media. Aromatic substituents are shown for systems **1a**–**p**. For experimental details see ref. [18]

The Fukui function is a local (i.e., electronic position $\mathbf{r}$–dependent) descriptor, i.e., it gives a local response to a global perturbation [30, 32–34]. Hence, it is useful for describing *site selectivity* within the molecular framework. Because of the discontinuity of the electron density at integer N, we will have two different functions, $f^+(\mathbf{r})$ when the derivative is taken as N increases from N to $N+\delta N$, and $f^-(\mathbf{r})$ when the derivative is taken as N decreases from N to $N-\delta N$. This fact encloses the essence of the frontier orbital theory of reactivity of Fukui [35–38]. Under suitable approximations, the $f^+(\mathbf{r})$ response becomes associated with the lowest unoccupied molecular orbital (LUMO) and measures reactivity toward a donor reagent, whereas the $f^-(\mathbf{r})$ can be related to the highest occupied molecular orbital (HOMO) and measures reactivity toward an acceptor reagent. Fukui functions are the most important regioselectivity indicators for frontier controlled reactions in conceptual DFT [30, 31, 34].

These key descriptors are well-defined quantities within the general spin–polarized version of DFT (SP–DFT) [23, 39–41], an extended framework that enables the treatment of both charge transfer and spin polarization processes [23, 42–46]. In fact, two generalized local Fukui functions ($f_{NN}^{\pm}(\mathbf{r})$, and $f_{SN}^{\pm}(\mathbf{r})$), can be exclusively associated to *charge transfer* processes, and two more Fukui functions, ($f_{NS}^{\pm}(\mathbf{r})$, and $f_{SS}^{\pm}(\mathbf{r})$) are associated to spin-polarization. Note from this representation notation that each SP–DFT Fukui descriptor has two subscripts, N or S, which indicate if perturbations occurs on the number of electrons N and on the spin number N_S, respectively. The superscript ($\pm$) simply indicates if the associated responses (i.e., in the total $\rho(\mathbf{r})$, or spin $\rho_S(\mathbf{r})$ densities) are related to allocate decrease ($-$) or increase ($+$) of the values of the perturbed variables [23, 44].

We should note that several other representations of SP-DFT can be used [23]. For instance, we can use the number of electrons with each spin and the external potential as the basic variables, i.e., $[N_\alpha, N_\beta]$, or even the spin-densities, i.e., $[\rho_\alpha, \rho_\beta]$. These alternative representations are linearly related to those $[N, N_S]$ ones. Further development for the $[N_\alpha, N_\alpha]$ representation and its Legendre transforms has been recently proposed [23]. The choice of any specific type of SP-DFT representation will depend on the nature of the chemical process to be studied. Constrained *spin-polarization* and *charge-transfer* processes become better represented in terms of $[N, N_S]$ and related representations. As noted below, in this work we consistently use the simplest approximations to the $f_{NN}^+(\mathbf{r})$ descriptors, which we can consider of primary importance for describing an intramolecular cyclization reaction implying electron density reorganization occurring at constant spin number. Given that comprehensive discussions concerning the description of chemical reactivity within a SP-DFT framework are published elsewhere [23, 39, 43], here we briefly summarized only the essential details for completeness of the current discussion.

It has been previously proven with very interesting examples [47–50], that the regioselectivity of intramolecular ring closure processes can be properly predicted by considering a simple model where the number of electrons are considered to be changing from a local point of view (i.e., a charge transfer occurs from one part of the molecule to another one) at constant global spin number N_S (i.e., a pseudo-radical electronic reorganization, as treated within a simplified SP–DFT framework). The usefulness of this SP–DFT conceptual model to rationalize the intrinsic reactive path of 2'–aminochalcones, i.e., the propensity to undergo a *intramolecular* nucleophilic attacks from the NH_2 group to the α and β unsaturated carbons, will therefore be explored by using specifically the spin-polarized *nucleophilic* Fukui function $f_{NN}^+(\mathbf{r})$,

$$f_{NN}^+(\mathbf{r}) = \left.\frac{\partial \rho(\mathbf{r})}{\partial N}\right|_{N_S, v(\mathbf{r})}^+ \tag{2}$$

which provides, in principle, the desired response to the current problem at hand [23, 44, 47].

Note that $f_{NN}^+(\mathbf{r})$ becomes equivalent to $f^+(\mathbf{r})$ for closed-shell systems, only within the framework of a frozen core orbital approximation. Note in Eq. (2) that $f_{NN}^+(\mathbf{r})$ includes the additional restriction in that spin number *should* remain constant along the entire process. Hence, $f_{NN}^+(\mathbf{r})$ will properly describe charge-transfer processes involving no change in the total spin multiplicity, as it is precisely the case of an intramolecular attack. The underlying model approximation should thereafter imply the use of descriptors intended to give the initial propensities of the system to a charge density reorganization upon removing (i.e., $f_{NN}^-(\mathbf{r})$) or adding (i.e., $f_{NN}^+(\mathbf{r})$) the same fraction of the number of electrons of both spin-up and spin-down symmetries [23, 47–50]. Henceforth, beyond the obvious difference of performing and unrestricted calculation instead of using the restricted methods, the natural choice of reactivity indicators for analyzing the reactions presented here, should feature SP-DFT quantities over the conventional ones.

Hence, within a frozen orbital core approximation Eq. (2) can be evaluated within a condensed-to-atom k scheme of approximation through [23, 44, 47],

$$f_{NN,k}^+ = \frac{1}{2}\left[\sigma_k^{LUMO\alpha} + \sigma_k^{LUMO\beta}\right], \tag{3}$$

where σ_k^{LUMO} represents the shape factor of LUMO orbital in each spin component at site k. The $f_{NN,k}^+$ distribution is normalized to one [44]. Orbital shape factors or "density per particle" exclusively carry the *relative* information on the electron orbital *distribution* [51–54] A higher value of f^+ is associated to a higher proclivity of center k to interact with nucleophiles. It is important to point out that there are different aspects of the selected system to be considered to

analyze its reactivity, including the pattern of substitution. The nucleophilic propensity of the attacking nitrogen atom has been evaluated thorough the corresponding local nucleophilic index using [23, 44, 47],

$$f_{NN,k}^{-} = \frac{1}{2}\left[\sigma_k^{HOMO\alpha} + \sigma_k^{HOMO\beta}\right]. \tag{4}$$

In the above context, our basic hypothesis is that, despite the underlying simple approximations behind the condensed–to–atom model [48, 55–60], the electronic effects of substituent can be effectively assessed by such descriptor of Eq. 3. As we will show later, results are consistent with the experimental evidence, determining the validity of our approximation for the prediction of the selectivity in the cyclization process in chalcones.

Computational details

Geometry optimization and frequency calculations were performed for the 2'–amino–chalcones depicted in Figs. 1 and 2. These calculations were carried out at the UB3LYP/6-31G(d, p) level of theory using the GAUSSIAN 09 suite of programs (G09) [61]. The reactivities of the 2'–aminochalcones presented in Tables 1, 2 and 3 were approached in terms of their intrinsic reactivities in vacuum of neutral and protonated species, respectively. Aiming at maintaining the simplicity of a semi-quantitative rationalization, the selected level of theory represents certainly a minimal suited one to deal with the effects

of both electron delocalization and protonated species (no anions) in the studied systems. Condensed-to-atoms Fukui functions, $f_{NN,k}^{+}$, were evaluated using Eq. 3 via simple computational routines processing single point G09 results including the options "SCF = Tight IOP(3/33 = 1) and POP = Full" [44].

Results and discussion

Formation of six–membered nitrogen heterocycles

The 6–endo cyclization reaction of the 2'-aminochalcones sketched in Fig. 1 is achieved in acidic conditions [18]. The cyclization process starts with the protonation of the oxygen atom of the carbonyl group. Upon protonation, there is an activation of the β–carbon toward the nucleophilic attack of the amino group, leading to the formation of six-membered heterocycles. As the nucleophilic reactivity of the attacking center remains constant along the series of compounds, our attention will focus primarily on the electrophilic responses at the unsaturated fragment. Note that from a conceptual and theoretical perspective, the observed changes in the electrophilic character at the α and β carbons of the 2'–aminochalcones 1a–1p can be deducted by analyzing the numerical values of the spin-polarized condensed-to-atoms electrophilic Fukui functions [44] of the neutral and protonated structures. High and low values will indicate the activation and deactivation of those positions toward the intramolecular nucleophilic attack.

Table 1 Spin-polarized condensed–to–atoms nucleophilic and electrophilic Fukui functions at the nitrogen attacking atom NH_2 and the α and β unsaturated carbons, respectively, of neutral and protonated 2–aminochalcones 1(a-p), evaluated at the UB3LYP/6-31G(d,p) level of theory

System	Neutral			O-protonated		
	$f_{NN,N}^{-}$	f_{NN,C_α}^{+}	f_{NN,C_β}^{+}	$f_{NN,N}^{-}$	f_{NN,C_α}^{+}	f_{NN,C_β}^{+}
1a	0.1577	0.1154	0.2025	0.1147	0.0135	0.2299
1b	0.1774	0.1359	0.1881	0.1214	0.0280	0.2036
1c	0.1532	0.1250	0.1920	0.1136	0.0163	0.2249
1d	0.1577	0.1044	0.2116	0.0905	0.0190	0.2084
1e	0.1259	0.0941	0.2131	0.0846	0.0074	0.2313
1f	0.1584	0.1111	0.2040	0.1126	0.0120	0.2313
1g	0.1525	0.1307	0.1797	0.1130	0.0170	0.2233
1h	0.1557	0.1148	0.2055	0.0977	0.0245	0.2018
1i	0.1562	0.1234	0.1964	0.1142	0.0153	0.2295
1j	0.1553	0.1095	0.2060	0.0745	0.0091	0.2302
1k	0.1525	0.1307	0.1798	0.0981	0.0303	0.1955
1l	0.1553	0.1097	0.2084	0.0747	0.0113	0.2319
1m	0.1809	0.1216	0.1628	0.0998	0.0224	0.2065
1n	0.1725	0.1023	0.0630	0.1233	0.0421	0.1823
1o	0.1651	0.1160	0.1208	0.1069	0.0181	0.2093
1p	0.1532	0.1250	0.1920	0.1136	0.0163	0.2249
Average	0.1581	0.1169	0.1829	0.1033	0.0189	0.2165

Table 2 Total energies and energy differences for neutral and protonated 2'–aminochalcones depicted in Fig. 2. Calculations were performed at the UB3LYP/6–31G(d,p) level of theory

System	Neutral (in a.u.)	N–protonated (in a.u.)	O–protonated (in a.u.)	PBE_N (in kcal mol⁻¹)	PBE_O (in kcal mol⁻¹)	PBE_N_PBE_O (in kcal mol⁻¹)
1p	−913.9738148	−914.3570144	−914.3590566	−240.5	−241.7	1.3
q	−913.9733758	−914.3628367	−914.3548183	−244.4	−239.4	−5.0
1r	−913.9742600	−914.3650643	−914.3630600	−245.2	−244.0	−1.3
1'p	−725.4415958	−725.8195020	−725.8165088	−237.1	−235.3	−1.9
1'q	−725.4417403	−725.8248479	−725.8120040	−240.4	−232.3	−8.1
1'r	−725.4454773	−725.8255913	−725.8261250	−238.5	−238.9	0.3

We first analyze the electrophilic character of the α and β carbons for neutral structures presented in Table 1. We note immediately that with exception of the case of structure labeled as 1**n**, the β carbon is on average only 1.5 more electrophilic than the α carbon. The opposite behavior in neutral 1**n** is explained in terms of activation that a p-nitro group exerts on the α center, which is properly assessed by the model in Eq. (3). From these results it can be inferred that if the cyclization reactions were successfully conducted in neutral medium, they would lead to the formation of 5– and 6–membered heterocycles. However, these reactions only occur in acidic conditions [18]. Therefore, we have also considered the Fukui functions of the protonated structures. In Table 1 we observe that the protonation of the carbonyl group results in an average decrease of 35 % in the nucleophilic character of the attacking nitrogen atom, an increase of 18 % in electrophilic character of the β carbon and an average reduction of 84 % in electrophilic character of the α carbon. The latter result clearly indicates that the α carbon is practically deactivated toward the nucleophilic attack by the amino group. These predictions are in good agreement with the experimental results emphasizing a selective acid–catalyzed cyclization of the 2'–aminochalcones (Table 1) at the β carbon, resulting in the formation of the dihydroquinolinones [18].

Unexpected cyclization

We are now in a better position to analyze the electrophilicity of the α and β carbons of the structures 1p–1r and 1'(p–r) depicted in Fig. 2. As shown in ref. [21] pyridinyl chalcones **1q**, **1r**, **1'q** and **1'r** presented an unexpected cyclization on the α–carbon leading to the formation of 5-membered rings when the reactions proceeded in an acidic medium. In contrast to the 2'–aminochalcones listed in Fig. 1, protonation of these molecules may occur on either the carbonyl group or the pyridinic nitrogen. Therefore, before arriving at conclusions on the electrophilic character of the α and β carbons we have also analyzed the magnitudes of the proton binding energies, PBE, for both the carbonyl and pyridinyl moieties. With the aim of maintaining the simplicity of the current semi quantitative rationalization, these PBEs were calculated in terms of differences in total energies between neutral and protonated species on either the carbonyl or the pyridinyl groups.

Table 2 reports the total energies of the neutral and protonated systems, the oxygen and nitrogen proton binding energies, PBE_N and PBE_O, respectively, as well as the PBE difference PBE_N-PBE_O. Negative and positive PBEs will indicate that the protonation is better stabilized on N and O respectively. Note immediately from Table 2 that in the case of structure 1p (i.e., 3-pyridinil pattern of substitution), the

Table 3 Spin-polarized condensed-to-atoms nucleophilic and electrophilic Fukui functions at the attacking nitrogen atom NH_2 and the $\alpha−\beta$ unsaturated fragment, respectively, at both neutral and protonated 2–aminochalcones depicted in Fig. 2, evaluated at the UB3LYP/6-31G(d,p) level of theory

System	Neutral			N-protonated			O-protonated		
	$f^-_{NN,N}$	f^+_{NN,C_α}	f^+_{NN,C_β}	$f^-_{NN,N}$	f^+_{NN,C_α}	f^+_{NN,C_β}	$f^-_{NN,N}$	f^+_{NN,C_α}	f^+_{NN,C_β}
1p	0.1532	0.1250	0.1920	0.0943	0.0576	0.0117	0.1136	0.0163	0.2249
1q	0.1522	0.1369	0.1850	0.0900	0.1897	0.0229	0.1136	0.0197	0.2208
1r	0.1550	0.1297	0.1866	0.0879	0.1862	0.0337	0.0988	0.0306	0.1975
1'p	0.3140	0.1602	0.1888	0.2793	0.0202	0.0008	0.2702	0.0257	0.2351
1'q	0.3131	0.1711	0.1786	0.2795	0.1874	0.0202	0.2637	0.0309	0.2218
1'r	0.3147	0.1684	0.1668	0.2785	0.1603	0.0349	0.2669	0.0301	0.2259

protonation is preferred on the carbonyl oxygen which favors the formation of the corresponding dihydroquinolinone template (i.e., a 6-membered ring) depicted in Fig. 1 [21]. In contrast, the protonation of structure 1'p is preferred on the N atom of the pyridinic ring. As also observed in Table 2, protonation on the N atom is favored for structures 1q, 1r, and 1'q, whereas for 1'r both sites present the same preference for protonation under the identical conditions of the current computational analysis. Remarkably, these results are in agreement with the protonation sites proposed in reference [21] for the 4- and 2-pyridinyl aromatic patterns of substitution exhibited by structures **q** and **r**.

For a proper prediction of the electrophilic character of the α and β carbons, the energy data presented above must be contrasted with the calculated spin-polarized condensed-to-atoms electrophilic Fukui functions for the α and β carbons of neutral and protonated 2'–aminochalcones 1p–1r and 1'p–1'r. Note also that in these cases, the nucleophilic reactivity at the nitrogen attacking center in neutral compounds of systems 1' is twice that of systems 1. This difference is indeed enhanced in both N- and O-protonated species. As shown in Table 3 the electrophilicity of the neutral species is predicted to be centered on the β carbon by about a factor of 1.5–1.4, favoring a 6-endo pathway toward quinolinonic derivatives. Correspondingly, cyclization is not observed experimentally in the absence of catalyst. Note also from Table 3 that such proclivity is enhanced at structures 1 as compared with structures 1'. Thus, in the case of neutral compounds 1 the preference of the β position over the α one is predicted to be in the range 35 %–44 %, whereas in neutral compounds 1', such a selectivity is considerably diminished to be in the range 1 %–18 %.

After protonation on the N, the scenario is common for all compounds, indicating a complete deactivation of the β carbon. These results are accompanied by a strong activation of the α center except for the structures 1p and 1'p as noted in Table 3. In those cases both the α and β electrophilic centers are predicted to be in fact strongly deactivated. In contrast, when protonation occurs on the carbonyl oxygen, for all systems, there is complete deactivation of the α center accompanied by a strong activation of the β center.

We are now in a better position to predict the reactivity of the α and β carbons toward a nucleophilic attack of the amino group. As reported in Table 2 the protonation on the N atom is better stabilized for structures 1q–r, 1'q; and as is shown in Table 3, protonation on this site will enhance the electrophilic character of the α carbon while simultaneously deactivating the β carbon. Therefore, we predict that in acidic environment the nucleophilic attack of the amino group will only occur on the α carbon and will lead to an unexpected 5–exo cyclization. This prediction is in excellent agreement with the reported experimental data [21].

We now turn our attention to structure 1p. Table 2 shows that the protonation is better stabilized when it occurs on the oxygen atom. As observed in Table 3 this protonation activates the β carbon while deactivating α carbon. Therefore, we predict that in acidic media the cyclization will occur on the β carbon leading to formation of a 6-membered ring. This prediction is also in excellent agreement with experimental available data [21].

Finally, we analyze structure 1'p. Table 2 shows that the protonation is better stabilized when it occurs on the nitrogen atom. As observed in Table 3 this protonation will deactivate both the α and β carbons. As a result, we predict if the reaction was performed in acidic media, it would be very difficult for the cyclization to take place on either the α or β carbons. To the best of our knowledge, this reaction has not been reported yet. We should note however that given the small difference between PBE_N and PBE_O, both protonations are likely to occur, being the possible product of cyclization (i.e., 5-membered or 6-membered) being predicted by the highest f_{NN}^+ values reported in Table 3.

The predictions of our analysis for regular and unexpected cyclizations are in perfect agreement with the experimental data. The results presented so far confirm the potential of the proposed methodology as a tool for predicting the reactivity of 2'–aminochalcones.

Conclusions

We have calculated condensed–to–atoms Fukui functions for a series of 2'–amino chalcones simulating neutral and acidic conditions. The calculated indexes revealed that reactions occurring in neutral media should lead to the formation of 6-membered heterocycles. Our results in protonated species have shown that the 6-membered heterocycles will be formed except for 2'–aminochalcones containing 2– and 4–pyridyl substituents. These results are in excellent agreement with the experimental observations related to the cyclization processes of 2'–aminochalcones toward the synthesis of the dihydroquinolin-8-one systems and the unexpected 3-indolinone structures via 6–endo–trig and 5–exo–trig cyclization mechanisms, respectively. The results obtained so far allow us to conclude that the simple theoretical methodology employed in this study [23, 44] is highly suitable for predicting the selectivity of the cyclization process for this family of systems. Despite the underlying basic approximations behind such models, the usefulness of the condensed–to–atom SP–DFT Fukui descriptor properly provides insights concerning the categorization of *electronic* effects driving the experimental reactivity trends. We hope this work further extends the range of applications of conceptual DFT and broadens the possibility of new interpretations of chemical reactivity in the context of density-functional theory. Additional research on this direction is now in progress, by applying the proposed methodology to the study

of open challenges associated to intramolecular reaction processes in chalcone templates as well as other 1,3–dielectrophilic systems.

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