

Molecular Structure and Reactive Sites of Substituted Di-(4-hydroxycoumarin)s Derived from DFT Calculations

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Abstract

Motivation. Substituted di-(4-hydroxycoumarin)s possess distinct biological properties. The activity of this class of compound is closely related to their stereochemistry. To reveal the specific character of the structure-activity relationship of di-(4-hydroxycoumarin) derivatives, their molecular and electronic structures have to be known in details. Therefore, we present accurate DFT calculations of benzyl- and pyridyl substituted di-(4-hydroxycoumarin)s. Electron density distribution, molecular electrostatic potential, hardness, electrophilicity index and reactive sites of the compounds are also calculated and discussed.

Method. The calculations were performed with DFT(B3LYP) method. Different basis sets were tested in the course of the calculations: 6-31G*, 6-31+G** and 6-311G*.

Results. According to the calculated molecular electrostatic potential and Fukui functions, the most probable reactive sites for electrophilic attack and hydrogen bonds were predicted. All the species studied showed two O-H...O asymmetrical intramolecular hydrogen bonds. The HB strengths were evaluated in the frame of the classical method as well as using the rotational barrier method. The effects of the methylene substituent (benzyl and pyridyl) on the HB strengths and on the electron density distribution in the coumarin fragments were evaluated.

Conclusions. Steric, electronic and electrostatic factors (through the oxygens charge changes) were found to be responsible for the HB asymmetry in the compounds studied. The highest electronegativity, hardness and electrophilicity were found for p-pyhc and the lowest ones for o-pyhc, respectively. The Fukui functions and MEP calculations showed that the carbonyl oxygen atoms are the most probable sites for electrophilic attack.

Keywords. coumarins; reactive sites; molecular structure; DFT; PM3.

Abbreviations and notations

bhc, 3,3'-(benzylidene)-di-(4-hydroxycoumarin)	m-pyhc, 3,3'-(meta-pyridinomethylene)-di-(4-hydroxycoumarin)
B3LYP, Becke's three parameter method with correlation functional of Lee, Yang and Parr	o-pyhc, 3,3'-(ortho-pyridinomethylene)-di-(4-hydroxycoumarin)
DFT, density functional theory	p-pyhc, 3,3'-(para-pyridinomethylene)-di-(4-hydroxycoumarin)
HB, hydrogen bond	
MEP, molecular electrostatic potential	

1 INTRODUCTION

The coumarins derivatives possess diverse biological properties. They have been described as enzyme inhibitors or as agents with anticoagulant [1-4] spasmolytic [5-8] and anticancer activity [9-12]. A large number of structurally novel coumarin derivatives have been reported to show substantial in vitro and in vivo cytotoxic activity [13]. Recently, the hydroxycoumarin derivatives were reported as promising inhibitors of HIV integrase [14] and HIV1 protease [15]. It was found that the minimum active pharmacophore consisted of a 4-hydroxycoumarin dimmer containing an aryl substituent on the central linker methylene, Fig. 1 [14-19]. Due to the presence of carbonyl and

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hydroxyl groups in di-(4-hydroxycoumarin) fragment, two intramolecular O-H...O HBs were formed. The simplest compound of this class, with unsubstituted central linker, di-(4-hydroxycoumarin), has two equal in strength and symmetrical HBs [20]. The replacement of one methylene H atom of di-(4-hydroxycoumarin) with a benzyl substituent in bhc, led to asymmetrical molecular structure and different in strength, asymmetrical HBs, Fig. 1 (1) [21]. Very recently, a new series of pyridyl substituted di-(4-hydroxycoumarin)s were synthesized (o-pyhc, m-pyhc and p-pyhc) and their lanthanide complexes showed significant biological activity [22]. In pyridyl substituted di-(4-hydroxycoumarin)s two different in strength O-H...O HBs were also expected and their strengths will depend on the nature and dimension of the methylene substituent. Due to the similarity of pyhc with some known HIV integrase inhibitors, it was also interesting to study their relative chemical reactivity. In this paper we perform accurate DFT calculations of the molecular and electronic structure of a series of benzyl- and pyridyl substituted di-(4-hydroxycoumarin)s. The molecular quantities as vertical ionization potential, electron affinity, electronegativity, hardness, electrophilicity indices and Fukui functions were calculated and discussed. Molecular electrostatic potential was considered as additional molecular characteristic.

2 METHODS

All calculations were performed using density functional method with non-local three-parameter hybrid exchange B3LYP density functional [23,24] as implemented in the Gaussian98 package, Revision A7 [25]. The adequacy of B3LYP methods for studying hydrogen-bonding structures like bhc and pyhc, conformational behaviour, electron density distribution and other molecular properties, has been proved in some recent investigations [26-29]. To verify the reliability of the B3LYP/6-31G(d) results, in our study larger basis set, 6-31+G(d,p) was used to optimize the neutral bhc molecule (as it was obtained from X-ray diffraction data [21]).

A conformational analysis of the species studied was firstly done to obtain the lowest energy structures. The geometry optimization of the systems studied were performed without constraints. The minima on the potential energy surfaces were qualified by the absence of negative eigenvalues in the diagonalized Hessian matrix, giving imaginary normal vibrational mode.

Net atomic charges have been obtained using the natural population analysis scheme of Weinhold [30]. The electronic structure and bonding features of the compounds studied were analysed using natural bond orbital analysis [30,31]. The natural bond orbital analysis allowed us to describe the bonding in terms of the natural hybrids centred on each atom. For estimation of the probable reactive sites in the systems studied, two molecular descriptors were used, MEP and the

Fukui functions. MEP is related to the electronic density and is considered as a fundamental determinant of atomic and molecular properties. Therefore, MEP has largely been used as a molecular descriptor of the chemical reactivity of a number of biological systems, which take part in both electrophilic and nucleophilic reactions as well as hydrogen bonding interactions [32-35]. MEP, $V(r)$, at a given point $r(x,y,z)$ in the vicinity of a molecule, is defined in terms of the interaction energy between the electrical charge generated from the molecule electrons and nuclei and a positive test charge (a proton) located at r . For the systems studied the MEP values were calculated as described previously, using the equation [36]:

$$V(r) = \sum_A Z_A / R_{A-r} - \int \rho(r') / |r' - r| dr' \quad (1)$$

where Z_A is the charge of nucleus A , located at R_A , $\rho(r')$ is the electron density function of the molecule, and r' is the dummy integration variable.

The condensed Fukui functions, f_k , were calculated using the simple procedure (based on Mulliken population analysis) given by Yang and Mortier [37]. For a system of N electrons, independent calculations are to be made for corresponding $N-1$, N , and $N+1$ electron systems with the same molecular geometry. Mulliken population analysis yields (gross charges) $q_k(N-1)$, $q_k(N)$, and $q_k(N+1)$ for all atoms k . In a finite-difference approximation, the condensed Fukui functions were given by the equations:

$$\text{for nucleophilic attack } f_k^+ = q_k(N+1) - q_k(N) \quad (2)$$

$$\text{for electrophilic attack } f_k^- = q_k(N) - q_k(N-1) \quad (3)$$

$$\text{for radical attack } f_k^0 = 1/2[q_k(N+1) - q_k(N-1)]. \quad (4)$$

The condensed-to-atom quantity, ω_k^α corresponding to local electrophilicity index, $\omega(r)$, was obtained as described previously [38]:

$$\omega_k^\alpha = \omega f_k^\alpha \quad (5)$$

where $\alpha = +, -, \text{ and } 0$ refer to nucleophilic, electrophilic and radical reactions, respectively.

The frontier-electron theory of chemical reactivity can be rationalized from DFT study of the electronic structure [39]. The electron density distribution is the fundamental concept for understanding the chemical reactivity and can explain the phenomena nucleophilic, electrophilic and radical attacks on a molecule. For a system of N electrons with ground-state energy $E[n,v]$, where v is the potential energy acting on an electron due to the presence of all nuclei, several quantities of fundamental importance were defined. The chemical potential μ of the electrons (the

negative of the electronegativity χ is given by $\mu = (\partial E/\partial N)_{v(r)}$ and has the same value everywhere [40]. In a finite-difference approximation:

$$\chi = -\mu = (I + A)/2, \quad (6)$$

where I and A are the ionization potential and electron affinity. The change of μ with the number of electrons was defined by Parr and Pearson as a measure for the “absolute hardness” as $\eta = \frac{1}{2}(\partial\mu/\partial N)_{v(r)} = \frac{1}{2}(\partial^2 E/\partial N^2)_{v(r)}$ [41]. The corresponding finite-difference formula is:

$$\eta = (I - A)/2. \quad (7)$$

The electrophilicity index was estimated as previously suggested [42,43]:

$$\omega = \mu^2 / 2\eta. \quad (8)$$

3 RESULTS AND DISCUSSION

3.1 Conformational Analysis of bhc, o-, m- and p-pyhc

A conformational search for bhc at PM3 level showed that among the thirteen possible bhc structures, localized as minima on potential energy surface, only one was stabilized by two HBs and its energy was the lowest one [44]. Two high-energy structures were stabilized with one HB. All other structures of bhc have not revealed HBs and hence they showed significantly higher relative energy as compared to that with one and two HBs. B3LYP calculations confirmed the stabilization of bhc by two HBs with different O...O distances and strengths. The B3LYP/6-31G(d) optimized molecular structure of the lowest energy conformer of bhc is shown in Fig. 1 (1).

For pyhc the conformational search showed one p-pyhc (4-pyhc), two m-pyhc (3- and 5-pyhc) and two o-pyhc (2- and 6-pyhc) conformers, localized as minima on potential energy surface. The stability order of pyhc conformers was found on the basis of the electronic energies, zero-point corrected electronic energies and Gibbs energies in gas phase. The B3LYP/6-31G(d) optimized molecular structures of the lowest energy structures of o-, m- and p-pyhc are shown in Fig. 1, structures 2, 3 and 4, respectively.

3.2 Molecular Asymmetry of bhc, o-, m- and p-pyhc Species

The B3LYP/6-31G(d) calculated geometry parameters for bhc agree with available experimental data [21]. Two asymmetrical O-H...O intramolecular HBs were calculated; each links a coumarin hydroxyl and carbonyl group (Fig. 1 (1)). The HB strengths were evaluated in the frame

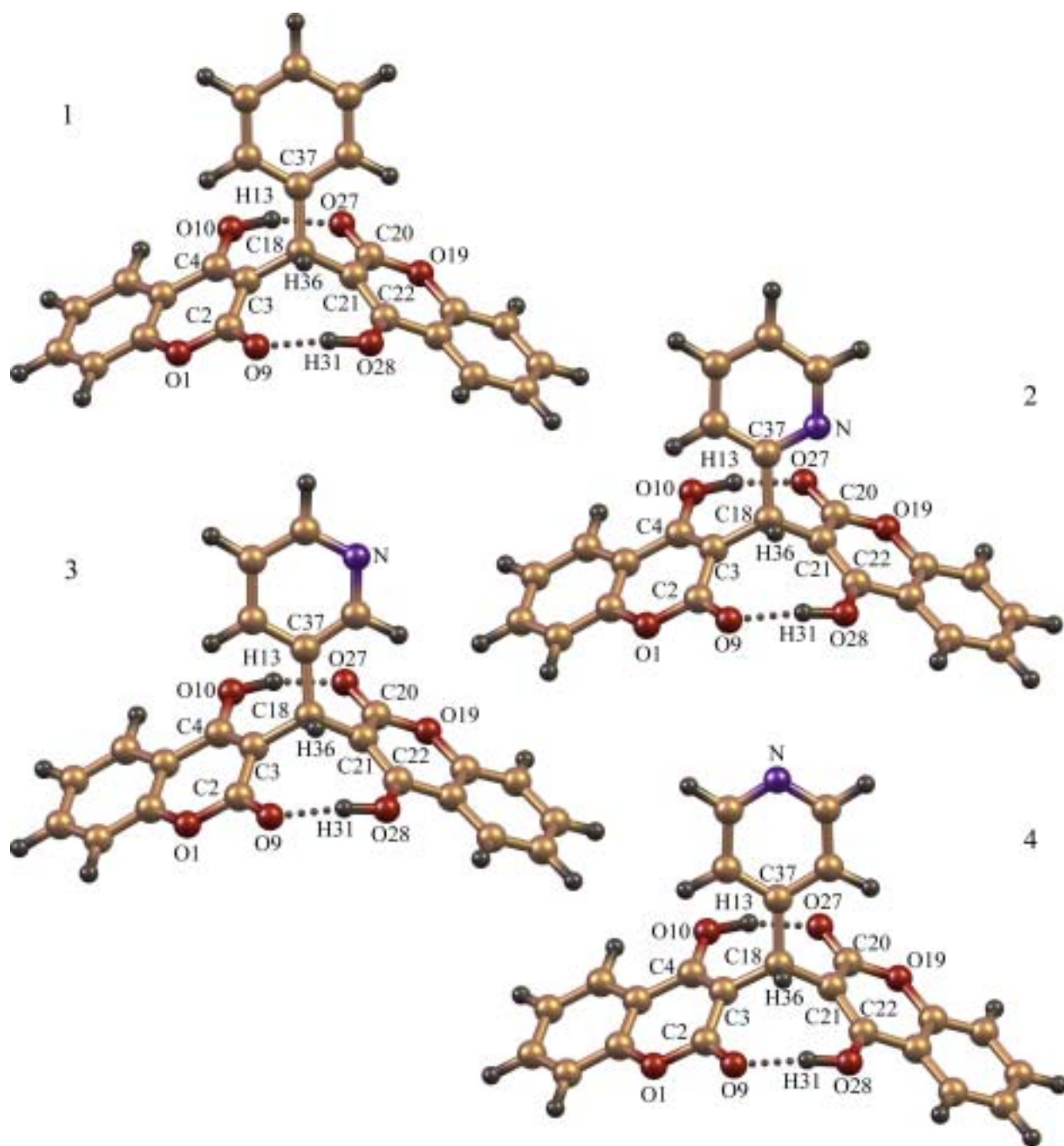


Figure 1. B3LYP/6-31G(d) optimized geometries of bhc (1), 2-pyhc (2), 3-pyhc (3) and 4-pyhc (4)

of the classical method as well as using the rotational barrier method [29,45,46]. The HB energies of bhc obtained in the frame of the classical method were estimated of $-55.46 \text{ kJ mol}^{-1}$ and $-52.32 \text{ kJ mol}^{-1}$ for O10-H13...O27 HB and O9...H31-O28, respectively [44].

The values obtained correlated with the calculated (2.638 \AA and 2.696 \AA) and experimental (2.624 \AA and 2.720 \AA) O...O distances and predicted difference in the hydrogen bonding strengths in bhc. The calculated HB energies for O10-H13...O27 HB and O9...H31-O28 HBs in pyhc

species are: in 4-pyhc (-57.23 kJ mol⁻¹ and -51.65 kJ mol⁻¹), for 3-pyhc (-59.27 kJ mol⁻¹ and -51.33 kJ mol⁻¹), for 2-pyhc (-62.56 kJ mol⁻¹ and -50.48 kJ mol⁻¹), for 5-pyhc (-55.90 kJ mol⁻¹ and -52.16 kJ mol⁻¹) and for 6-pyhc (-47.53 kJ mol⁻¹ and -56.25 kJ mol⁻¹). With the exception of 6-pyhc, the calculated HB energies for pyhc isomers predicted that the O10-H13...O27 HB was stronger than the O9...H31-O28 one as it was already found in bhc [46]. The highest HB stabilization energy was calculated for ortho (2-pyhc) and it was in agreement with its conformational stability. To check the reliability of the HB energies obtained, we estimated the HB strengths using the rotational barrier method. Although the calculated HB energies were more negative than those obtained using the classical method (with 9-17 kJ mol⁻¹) they also suggested different in strengths HBs and confirmed the trends obtained with the classical method.

The molecular asymmetry observed for the compounds studied was explained with different substituent effect on the HB rings. The calculated bond lengths showed that the substituent produced larger changes in the upper HB ring (H13-O10-C4-C3-C18-C21-C20=O27) as compared to the changes in the lower one (O9-C2-C3-C18-C21-C22-O28-H31) (Fig. 1). Due to the substituent withdrawing effect, the C4-O10 and C20=O27 bond lengths became shorter, the O10 and O27 atomic charges were less negative and the electron repulsion between them weakened. As a result, O10...O27 distance decreased and the corresponding O10-H13...O27 HB in bhc and p-pyhc became stronger.

At the same time, the benzyl- and p-pyridyl substituents produced smaller changes in the lower HB ring (O9-C2-C3-C18-C21-C22-O28-H31). Conversely to the trends obtained for the upper HB ring, the C2=O9 and C22-O28 bond lengths were longer, O9 and O28 atomic charges were more negative and due to the larger repulsion, the O9...O28 distance became longer. As a result, the corresponding O9...H31-O28 HB was weaker. Hence, the electron density on the O atoms, involved in the HBs changed upon the benzyl- and p-pyridyl substituents and through the O...O electrostatic effect contributed to strengthening of O10-H13...O27 HB and to weakening of O9...H31-O28 one. On the basis of the results thus obtained one may conclude that steric, electronic and electrostatic factors are responsible for the asymmetrical HBs in bhc and p-pyhc.

3.3 Reactive Descriptors of bhc and pyhc Species

3.3.1 Global reactivity parameters

The molecular quantities vertical ionization potential (I) and electron affinity (A), electronegativity (χ , eq. 6), hardness (η , eq. 7), and electrophilicity index (ω , eq. 8) for 2-, 3-, 4-, 5-, 6-pyhc and bhc are presented in Table 1.

Table 1. Calculated vertical ionization potential (I , eV), electron affinity (A , eV), electronegativity (χ , eV), hardness (η , eV) and electrophilicity index (ω , eV) for the systems studied

Species	I	A	χ	η	ω
bhc	7.52	0.41	3.97	3.56	2.21
2-pyhc	7.40	0.33	3.87	3.53	2.12
6-pyhc	7.58	0.33	3.86	3.53	2.11
3-pyhc	7.63	0.51	4.07	3.56	2.33
5-pyhc	7.62	0.51	4.07	3.56	2.32
4-pyhc	7.69	0.57	4.12	3.57	2.38

The calculated I and A values for o-, m, and p-pyhc are close to those obtained for bhc. Hence, the substitution of benzyl with pyridyl substituent did not lead to significant changes of the electronegativity and hardness (eq. 6, 7). The electronic chemical potential has the same equalization property as the macroscopic chemical potential. If free flow is allowed, electrons go from a region of high chemical potential to a region of low chemical potential, until both regions have the same chemical potential value [40]. The larger the difference in chemical potential between two molecules, the easier the reaction will be [47]. As it seen from Table 1, among the series of the systems studied, only ortho-derivatives have lower electronegativity values with respect to bhc. Among the pyridyl substituted isomers, χ decrease in the order: p-pyhc > m-pyhc > o-pyhc.

It is generally accepted that a variety of acid-base reactions can be described by the principle: "Hard likes hard and soft likes soft". In agreement with this principle, it is expected that benzyl and pyridyl substituted di-(4-hydroxycoumarine)s will prefer to react with compounds having the same η values (Table 1). The hardness of the systems studied increase in the order: o-pyhc < bhc < m-pyhc < p-pyhc.

Another useful reactivity descriptor is the electrophilicity index ω . When two molecules react, which one will behave as an electrophile will depend on that which one has higher electrophilicity index [38]. As in case of μ and η , p-pyhc revealed the highest ω value, whereas o-pyhc, the lowest one.

3.3.2 Local reactivity indices - condensed Fukui functions and electrophilicities

As it was mentioned above the presence of substituent (benzyl or pyridyl) linked to methylene C-atom (C18) provokes asymmetry in di-(4-hydroxycoumarin) fragment. Thus, different substituents will produce smaller or larger differences between the charges of the two carbonyl or two hydroxyl oxygens. It is interesting to trace how the substituent effects change the reactivity indices as condensed-to-atom Fukui functions and electrophilicity indices. In bhc and pyhc isomers there is more than one donor atom suitable for electrophilic attack. To point out to the most probable sites, the condensed Fukui functions, f_k^- (according to eq. 3, using Mulliken atomic charges) and electrophilicity indices, ω_k^- (eq. 5) governing electrophilic attack were calculated and discussed (Table 2).

Table 2. Condensed Fukui functions (f_k^-) and electrophilicity indices (ω_k^-) at selected atoms k in bhc and pyhc species

Species	O1	O9	O10	N	O19	O27	O28
bhc							
f_k^-	0.016	0.052	0.041		0.016	0.050	0.040
ω_k^-	0.035	0.114	0.091		0.035	0.110	0.088
2-pyhc							
f_k^-	0.015	0.044	0.039	-0.003	0.017	0.054	0.046
ω_k^-	0.032	0.093	0.083	-0.006	0.036	0.114	0.097
6-pyhc							
f_k^-	0.016	0.062	0.044	-0.008	0.015	0.044	0.039
ω_k^-	0.034	0.131	0.093	-0.017	0.032	0.093	0.082
3-pyhc							
f_k^-	0.015	0.048	0.038	0.030	0.016	0.052	0.043
ω_k^-	0.035	0.112	0.088	0.070	0.037	0.121	0.100
5-pyhc							
f_k^-	0.016	0.056	0.043	0.028	0.015	0.044	0.039
ω_k^-	0.037	0.130	0.100	0.065	0.035	0.102	0.090
4-pyhc							
f_k^-	0.016	0.054	0.043	0.025	0.016	0.054	0.041
ω_k^-	0.038	0.128	0.102	0.060	0.038	0.128	0.098

The results obtained showed that for bhc, 6-, 5-, and 4-pyhc, ω_k^- has the highest value in O9-center indicating that this site would be the most favorable one for electrophilic attack. For 2- and 3-pyhc, ω_k^- has the highest value in O27-center indicating that this is the most reactive site for electrophilic attack. In o-pyhc isomers, the N-centers have negative ω_k^- values, whereas in m-, and p-pyhc, the ω_k^- values are higher than those of O1 and O19. For all the molecules studied, the ω_k^- values of the carbonyl oxygens are higher than those obtained for hydroxyl oxygen, lacton oxygen and nitrogen atoms i. e. they could be considered as the most favorable atomic sites for electrophilic attack.

3.3.3 Molecular electrostatic potential

To predict reactive sites for electrophilic and nucleophilic attack in the systems studied, MEP was calculated at the B3LYP/6-31G(d) optimised geometries. The negative regions of $V(r)$ were related to electrophilic reactivity and the positive ones - to nucleophilic reactivity (Fig. 2).

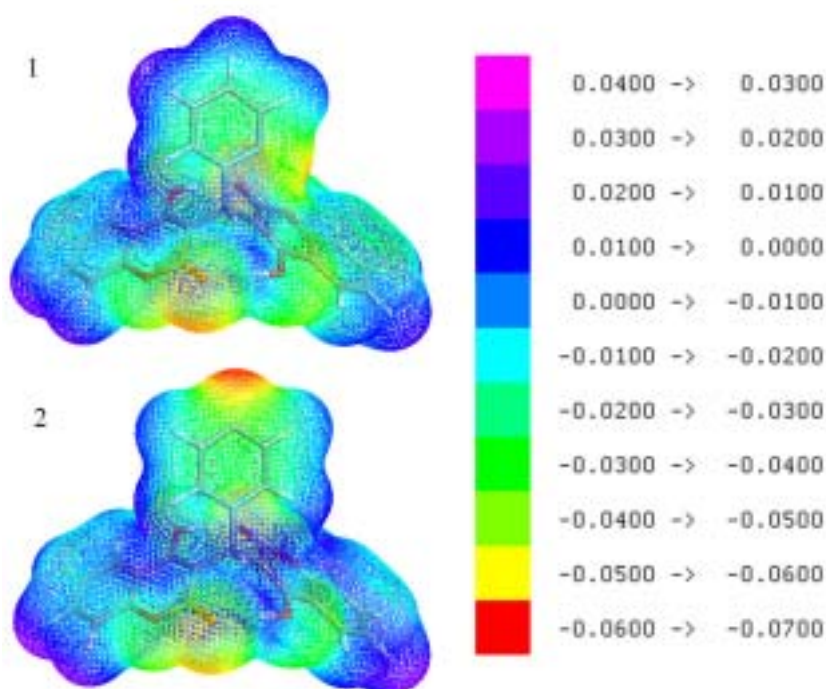


Figure 2. MEP colour map of o-pyhc (1) and p-pyhc (2). The scale values (in hartree) correspond to the interaction energy between the molecular electrical charge and the positive test charge (a proton) located at r .

The $V(r)$ values were obtained on molecular surface defined by electron density with 0.001 electron/bohr³. The negative regions in the molecules studied were found around the carbonyl O9,

O27, hydroxyl O10, O28 and lactone O1, O19 atoms and in pyhc isomers around the N atom in addition. In p-pyhc and m-pyhc isomers, the most negative $V(r)$ values were associated with the N atom, $-0.065 \div -0.064$ and hence, it is expected that it will be preferred for electrophilic attack. The nitrogen was the most negative site in p-pyhc, Fig. 2 (2), and it became less negative in m-pyhc. In o-pyhc, however, the most negative value of $V(r)$ was found for the carbonyl O atoms (-0.057 and -0.059) and the nitrogen $V(r)$ value was less negative (-0.052), Fig.2 (1). Therefore, in o-pyhc, the preferred electrophilic sites are the carbonyl oxygens. It was further found that the $V(r)$ values of N atoms in p- and m-pyhc(s) are more negative than that of pyridine ($V(r) = -0.060$). Thus, it could be concluded that the electrophilic power of the nitrogen atoms increased in p- and m-pyhc(s), but not in o-pyhc. In all the systems studied, the hydroxyl O10 and O28 revealed also significant negative $V(r)$ values ($-0.028 \div -0.039$) and hence, they could be considered as the next candidates for electrophilic attack. It is interesting to note further that the negative regions on the lactone O ($-0.027 \div -0.035$ a.u.) were not well defined being extended to the carbonyl group.

4 CONCLUSIONS

Steric, electronic and electrostatic factors (through the oxygens charge changes) were found to be responsible for the HB asymmetry in the compounds studied. The highest electronegativity, hardness and electrophilicity were found for p-pyhc and the lowest ones for o-pyhc respectively. The Fukui functions and MEP calculations showed that the carbonyl oxygen atoms are the most probable sites for electrophilic attack.

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