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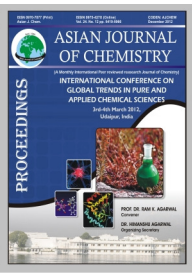

Application of Density Functional Approximation for Investigation of Reactive Sites, Molecular and Electronic Structure of Coumarins and Their Lanthanide(III) Complexes†

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DFT approximation was applied for investigation of a series di-[4-hydroxycoumain]s. Different basis sets were tested in the course of the calculations. The calculated hydrogen bond energies revealed two equivalent hydrogen bonds in DC and two different in strengths hydrogen bonds in PhDC and PyDC. Further, the effect of the substutient on the hydrogen bond asymmetry and the electron density distribution was evaluated. Molecular quantities as vertical ionization potential, electron affinity, electronegativity, hardness and electrophilicity indices of the neutral species, were calculated and discussed at the optimized geometries. Molecular electrostatic potential was applied for predicting the most probable sites for electrophilic attack. Since the active forms of the compounds studied are their ionic species, next, the molecular and electronic structures as well as the reactive sites of the dianionic species were studied. The theoretical results suggested that both carbonyl and both hydroxyl oxygen atoms are preferred binding sites for electrophilic attack for a metal coordination.

Key Words: Di-[4-hydroxycoumarin], DFT, AIM, Molecular electrostatic potential, Reactive sites.

INTRODUCTION

Di-[4-hydroxycoumarin] and its derivatives have revealed biological activity such as enzyme inhibition, hypotoxicity as well as carcinogenicity, anticoagulant and antibiotic action and these experimental findings have become the subject of growing theoretical interest[1]. In the last years, di-[4-hydroxycoumarin]s were reported as promising inhibitors of HIV integrase. Further, di-[4-hydroxycoumarin] derivatives are known to have good complexing ability and in some cases the complexes obtained showed distinct biological activity[1]. X-ray and NMR studies showed that in di-[4-hydroxycoumarin]s the carbonyl and hydroxyl groups are involved in two intramolecular O-H…O hydrogen bonds (HBs). In DC the O-H…O intramolecular hydrogen bonds are symmetrical and equivalent[1]. The replacement of one methylene H atom of DC with a phenyl substituent, PhDC, leads to two asymmetrical intramolecular hydrogen bonds[1]. The carbonyl and hydroxyl groups in the parent compound, 4-hydroxycoumarin (4-HC) are free and thus the compound can surve as a suitable model for comparison[1]. Since for 4-hydroxycoumarin, DC and PhDC structural data are available, DFT approach can be tested for accuracy in predicting geometrical parameters, vibrational frequencies and hydrogen bond strengths of di-[4-hydroxycoumarin]s. In the course of the calculations, different basis sets are applied (especially for the atoms, involved in the hydrogen bondings) requiring better agreement with experiment. To suggest the most probable binding sites of the compounds studied, the molecular quantities as vertical ionization potential, electron affinity, electronegativity, hardness, electrophilicity indices, Fukui functions as well as the molecular electrostatic potential of the neutral and double deprotonated species ($PhDC^{2-}$, $PyDC^{2-}$) were calculated and discussed.

EXPERIMENTAL

All calculations were performed using GAUSSIAN98 program package. Density functional calculations with Becke's three parameter hybrid method using the correlation functional of Lee, Yang and Parr (B3LYP) have proved quite useful in this regard for studying system with hydrogen bonds[2-4]. This method has been tested with different basis sets and has successfully been applied for estimation of the relative strengths and preferred geometries of hydrogen bonds in different systems. Due to the size of the systems studied, the cost advantage that

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offers B3LYP method in comparison with MP2 was significant. Moreover, the lower computational cost of B3LYP compared to other correlated methods allowed us to calculate the harmonic vibrational frequencies of the large systems. Due to the similarity of PyDC molecular structure with that of PhDC, the same method and basis sets were applied for *o*-PyDC, *m*-PyDC and *p*-PyDC isomers. All stationary points were confirmed as minima via vibrational frequency calculations. A conformational analysis of PhDC was performed at the same level and thirteen conformers were localized as minima on the potential energy surface. Further, net atomic charges and electron density have been obtained using the natural population analysis of Weinhold and Mulliken scheme (MPA), respectively. The electronic structure and bonding features of the compounds studied were analyzed using the natural bond orbital analysis[5]. The NBO analysis allowed us to describe the bonding in terms of the natural hybrids centered on each atom.

Molecular electrostatic potential (MEP) is rigorously related to the electronic density and can be regarded as another fundamental determinant of atomic and molecular properties. The condensed Fukui functions, f_k, were calculated using the simple procedure (based on Mulliken population analysis) given by Yang and Mortier[6]. The frontier-electron theory of chemical reactivity can be rationalized from DFT study of the electronic structure[7].

RESULTS AND DISCUSSION

Conformational stability: Preliminary conformational search at PM3 level showed that among all thirteen neutral PhDC structures, localized as minima on PES, only one was stabilized by two hydrogen bonds and its energy was the lowest one. All other structures of PhDC have not revealed hydrogen bonds and hence they showed significantly higher relative energy as compared to that with one and two hydrogen bonds. B3LYP/6-31G* calculations confirmed the stabilization of PhDC by two hydrogen bonds with different 9O–O···H distances and strengths. The calculated Laplacian of the charge density showed π-delocalization in the rings formed by the hydrogen bonds, which results into a smaller conformational flexibility and contributes to stabilization of the intramolecular hydrogen-bonded structure.

For PyDC isomers, the conformational search showed two *o*-PyDC (2-and 6-PyDC), two *m*-PyDC (3-and 5-PyDC) and one *p*-PyDC (4-PyDC) conformers, localized as minima on the potential energy surface. The stability order of PyDC isomers was found on the basis of the electronic energies, zero-point corrected electronic energies and Gibbs energies in gas phase. The results are summarized in Table-1.

Molecular geometries: X-ray diffraction analysis has shown that PhDC, which is not inherently chiral, crystallized in a polar space group and had an unusually high density. In full agreement with experiment, differences in the exocyclic angles about the coumarin points of attachment to the methylene carbon in PhDC were found with all basis sets applied. Due to participation in hydrogen bonding both hydroxyl and carbonyl groups in PhDC showed longer O-H and C=O bond lengths and shorter C-O bond length.

TABLE-1
TOTAL ELECTRONIC AND RELATIVE ENERGIES (kJ mol^{-1}) (ELECTRONIC, ZPVE CORRECTED, ΔE^{corr} AND GIBBS, ΔG) OF PyDC ISOMERS

Isomers	E (Hartree)	ΔE (kJ mol^{-1})	ΔE^{corr} (kJ mol^{-1})	ΔG (kJ mol^{-1})
p-PyDC				
4-PyDC	-1429.721323	8.62	9.32	9.34
m-PyDC				
5-PyDC	-1429.720304	11.30	11.96	11.84
3-PyDC	-1429.720319	11.25	11.94	12.07
o-PyDC				
6-PyDC	-1429.724183	1.13	1.17	0.73
2-PyDC	-1429.724614	0.0	0.0	0.0

All B3LYP/6-31G* energy minima of *o*-, *m*- and *p*-PyDC structures were stabilized by two intramolecular O–H···O hydrogen bonds like in the case of PhDC. The comparison of the geometry parameters for DC, PhDC and PyDC isomers showed that the substitution of methylene hydrogen atom with phenyl or pyridyl substituent caused lengthening of some C-C bonds. The largest bond length changes in PhDC and PyDC with respect to DC, were observed for *o*-PyDC isomers. It should be mentioned, however, that both carboxyl C-O and carbonyl C=O groups are included in intramolecular hydrogen bonds and their bond lengths could also be affected by the hydrogen bond strengths.

Hydrogen bonding strength estimated from calculation of the hydrogen bond energies: The calculated hydrogen bond energies in PhDC, *o*-PyDC, *m*-PyDC and *p*-PyDC species showed two asymmetrical O-H…O intramolecular hydrogen bonds, each linking the coumarin hydroxyl and carbonyl groups. To check the reliability of the hydrogen bond energies obtained, we estimated the hydrogen bond strengths using the rotational barrier method. Although the calculated hydrogen bond energies were more negative than those obtained using the classical method (with 9-17 kJ mol^{-1}) they also suggested different in strengths hydrogen bonds and confirmed the trends obtained with the classical method. On the basis of the results thus obtained one may conclude that steric, electronic as well as electrostatic factors are responsible for the asymmetrical hydrogen bonds in PyDC.

Reactive descriptors of neutral PhDC, *o*-PyDC, *m*-PyDC and *p*-PyDC species

Global reactivity parameters: The molecular quantities vertical ionization potential (I) and electron affinity (A), electronegativity (χ), hardness (η), softness and electrophilicity index (ω) for 2-, 3-, 4-, 5-, 6-PyDC and PhDC are presented in Table-2. The calculated I and A values for *o*-, *m*- and *p*-PyDC are close to those obtained for PhDC. Among the series of systems studied, only *o*-derivatives have lower electronegativity values with respect to PhDC. Among the pyridyl substituted isomers, χ decrease in the order: *p*-PyDC > *m*-PyDC > *o*-PyDC. The hardness of the systems studied increase in the order: *o*-PyDC < PhDC < *m*-PyDC < *p*-PyDC. As in the case of η, *p*-PyDC revealed the highest electrophilisity index ω, whereas *o*-PyDC had the lowest one.

Local reactivity indices: The presence of substituent (benzyl or pyridyl) linked to methylene C-atom provokes

asymmetry in di-(4-hydroxycoumarin) fragment. Thus, different substituents will produce smaller or larger differences in the charges of the two carbonyl or two hydroxyl oxygens. In PhDC and PyDC isomers there is more than one donor atom suitable for electrophilic attack. Thus, the condensed Fukui functions, f^-_k and electrophilisity indices, ω^-_k governing electrophilic attack were calculated and discussed. In *o*-PyDC isomers, the *N*-centers have negative ω^-k values, whereas in m- and *p*-PyDC, the ω^-k values are higher then those of O_1 and O_{19}. For all the molecules studied, the ω^-_k values of the carbonyl oxygens are higher then those obtained for hydroxyl oxygen, lacton oxygen and nitrogen atoms *i.e.* they could be considered as the most favourable atomic sites for electrophilic attack.

TABLE-2
CALCULATED VERTICAL IONIZATION POTENTIAL (I, eV), ELECTRON AFFINITY (*A*, eV), ELECTRONEGATIVITY (χ, eV), HARDNESS (η, eV) AND ELECTROPHILISITY INDEX (ω, eV) FOR THE SYSTEMS STUDIED

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

Molecular electrostatic potential of neutral 4-hydroxycoumarin, DC, PhDC and PyDC species: In dealing with noncovalent interactions, it seems reasonable to look at the electrostatic potential on the three-dimensional surfaces of the molecules. The molecular electrostatic potential was used to predict reactive sites for electrophilic and nucleophilic attack in the systems studied. Each of the molecules studied has several possible sites for electrophilic attack and V(r) calculations have provided insights into the order of preference. The negative regions in the molecules studied were found around the carbonyl, hydroxyl and lactone oxygen atoms and in PyDC isomers around the N atom in addition. In *o*-PyDC, the most negative value of V(r) was found for the carbonyl O atoms, followed by N and hydroxyl O atoms (Fig. 1, structure 1). In *p*-PyDC and *m*-PyDC isomers, the most negative V(r) values were associated with the N atom and they decreased in the order: *p*-PyDC > *m*-PyDC > *o*-PyDC (Fig. 1, structure 2).

We have estimated several molecular descriptors of the compounds studied since they are biologically active and could take part in different interactions (donor-acceptor, electrostatic). The molecular descriptors used pointed out to different active sites: for *p*- and *m*-PyDC neutral species, molecular electrostatic potential predicted that the nitrogen atom should be preferred for electrophilic attack. At the same time, the condensed Fukui functions predicted the carbonyl oxygen atoms followed by the hydroxyl oxygen atoms as the preferred for electrophylic attack. In the particular case of metal coordination, however, it is more important to consider the behaviour of the species in solution, where a deprotonation occur and the active forms are the double deprotonated species ($PyDC^{2-}$).

Deprotonated species: In all deprotonated forms of the compound studied, the hydrogen bondings are absent and simultaneous rotations of the coumarin moieties occurred to avoid repulsion between the negative charges of the hydroxyl and carbonyl oxygen atoms. Due to the rotation the geometries of the corresponding low-energy dianionic species are different from those of the neutral forms.

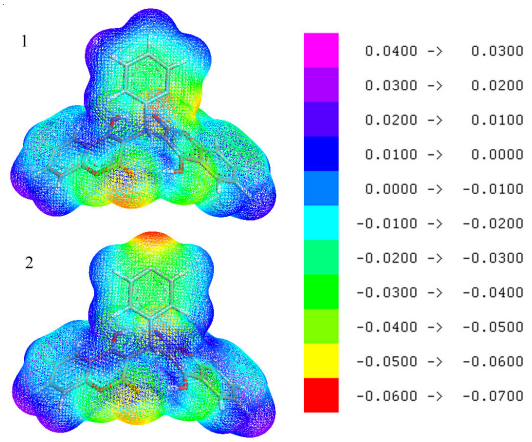

Fig. 1. MEP colour map of *o*-PyDC (1) and *p*-PyDC (2). The scale values (hartree) correspond to the interaction energy between the molecular electrical charge and the positive test charge (a proton) located at r

The electronic energy (E), the relative energy (ΔE), the ZPVE corrected energy (E^{corr}) and the free energy (G) of the structures studied were calculated in gas-phase. The solvent (water) effect on the stability of deprotonated species was also considered.

Conclusion

The geometric structures of DC, PhDC and *o*-, *m*- and *p*-PyDC were optimized at B3LYP level, using different basis sets for the atoms involved in hydrogen bonds, 6-31G*, 6-31+G** and 6-311G*. The trends obtained were confirmed from the calculated ν(O-H) vibrational shifts. The highest hydrogen bond stabilization energy was calculated for *o*-PyDC and it was in agreement with its conformational stability. The hydrogen bond asymmetry was explained with the withdrowing effect of the substituent in the CH_2 group which connects the coumarin fragments. The calculated molecular electrostatic potential and Fukui functions for the double deprotonated species indicated that the most prefered sites for electrophilic attack, in particular for metal coordination are the carbonyl and hydroxyl oxigen atoms.

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