Chemistry: Bulgarian Journal of Science Education *Volume 24 Number 3, 2015* *Природните науки в образованието*

Sixth International Conference
South-West University
Faculty of Mathematics & Natural Sciences
Blagoevgrad, Bulgaria 10 - 14 June, 2015

MONOHYDROXY FLAVONES. PART III: THE MULLIKEN ANALYSIS

Maria Vakarelska-Popovska, Zhivko Velkov
South-West University "Neofit Rilski", Bulgaria

Abstract. The purpose of this article is to compare Mulliken charges in monohydroxy flavones in order to assess the intramolecular reasons determining the electron density distribution and reactivity in all ten isomers. What would also be estimated is the role of the position of the hydroxyl group in the radical-scavenging activity. The optimization procedure was performed on a DFT/B3LYP level and on a large orbital basis.

Keywords: Mulliken population analysis, monohydroxy flavones.

Introduction

The disadvantages of Mulliken population analysis are well known. They come from the fundamental assumption in the Mulliken scheme: the overlap between two orbitals is shared equally in the partitioning of the wave function. This assumption doesn't reflect the electronegativity of the atoms. In addition, when large bases are used, it may give confusing partial charges. The occupation of an orbital may exceed two electrons or accept negative values. The last one is mainly due to the use of diffuse functions in orbital basis (Mulliken, 1955a; 1955b).

Mulliken population analysis is by default available in Gaussian and it is cheap. When, however, we do not care for the absolute values of the charges, this approach gives sufficiently reliable results and it is widely used for assessment of reactivity or QSAR investigations even for radical-scavenging description (Alov et al., 2015; Amir et al., 2011).

The properties of the monohydroxy flavones (Fig. 1) are a subject of our interest in the recent years (Vakarelska-Popovska & Velkov, 2013; 2014).[1] Investigation of monohydroxy flavones allows to determine how important is the position of the hydroxyl group in flavones on their radical-scavenging activity. In all previous studies we are interested in the structure reasons determining electron density distribution and their ability to react with active radicals.

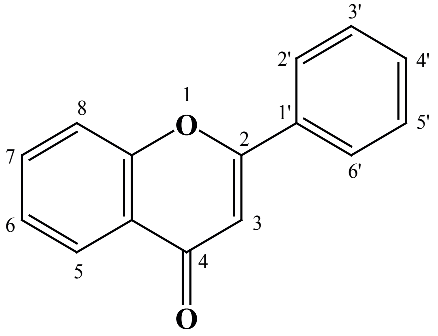

Fig. 1. 2-Phenyl-1-benzopyran-4-one (2-1-phenyl-4-oxo-chromen)

Therefore, in this work we will scrutinize the Mulliken charges in the evaluation of the internal molecular causes determining reactivity of all ten isomeric monohydroxy flavones.

Computational details

The calculations were carried out using the DFT, as implemented in the Gaussian09 program package (Frisch et al., 2009). The optimization of the geometry was performed with the Becke 3-parameter hybrid exchange functional combined with the Lee-Yang-Parr correlation functional (B3LYP), and with the standard 6-311++G(d,p) basis set (Parr & Yang, 1989). The optimization was achieved without any geometry constraints. For all structures the harmonic vibrational frequencies were computed to confirm the true minima on the calculated potential surface.

All possible intra-molecular interactions were taken into account in the initial geometries.

Discussion

The oxygen atom in position 1 (see **Fig. 1**) carries a negligible charge in all isomers. Only in isomers F-2‘ and F-8 at O1 it has negligible negative charge. Most likely it is formed in counterbalance to a standing nearby hydrogen atom with a partial positive charge. The Mulliken charges in unsubstituted flavon (**Fig. 1**) have also been examined. The charge at O1 therein is 0.035 in vacuo and 0.023 in water, almost as in most monohydroxy flavones, i. e. the addition of a hydroxyl group does not affect the electron density in this oxygen atom. Obviously, the oxygen atom in first position is a constant donor of electron density to carbon oxygen and to the rest of the molecule.

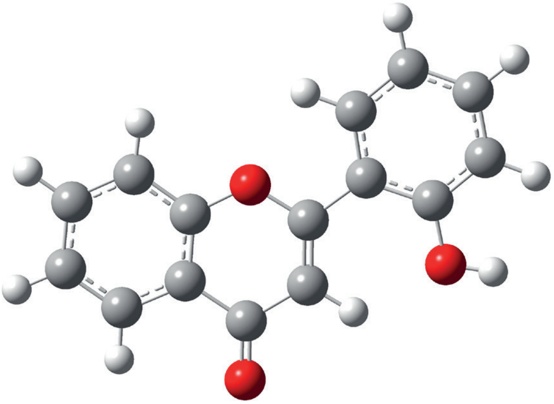

Fig. 2. The optimized structure of 6′-hydroxy-flavone.

The charges of the carbon atom on second position are very sensitive to the location of the hydroxyl group. There is a significant positive charge at C2 in the isomers with hydroxyl groups in ring B. Ring B is usually not coplanar to ring C and the withdrawal of electron density to the carbonyl group is realized mainly from rings C and A. When the hydroxyl group is in rings A and C, there is less withdrawal from position 2 and 1.

The charges at C3 are also very sensitive to a position of the hydroxyl group. In isomers with hydroxyl group in ring B the charges are negative or close to zero. In isomers with hydroxyl group in ring A, the charges are close to zero or positive. The polarizing effect of the water is considerable for the isomers F-6′ and F-4′.

The charge accumulation at C4 is greater in the isomers in which the hydroxyl groups are in ring A and less in the isomers in which the hydroxyl groups are in ring B. The negative charge in the isomer F-3 was significantly lower than all, probably due to the induction of the oxygen atom from the hydroxyl group

In earlier studies we came to the conclusion that the transfer to the carbonyl oxigen atom is one of the important reasons for stabilizing monohydroxy flavonoid. Therefore, the charges of the carbonyl oxygen atomes are the most telling ones. Let‘s see how the charges at carbonyl oxygen atoms change. Surprisingly, in vacuo, the charges at the carbonyl oxygen varies marginally (around -0.300). Only in isomers F-3 and F-5 there is a higher negative charge (-0.350 and -0.344 correspondingly). The only reason for that is the presence of strong hydrogen bonds in these isomers, which leads to an accumulation of charge at the carbonyl oxygen. Obviously, the charge at this atom is not so sensitive to the position of the hydroxyl group in monohydroxy flavones.

Table 1. Mulliken charges in all ten monohydroxy flavones (*Numbers show the position of the hydroxyl group in 2-phenyl-1-benzopyran-4-one structure on Fig. 1)

Atom № in F-6‘*	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	6‘-0	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	0.024	0.76	-0.68	-0.824	-0.303	0.112	-0.401	-0.278	-0.171	1.172	-0.5	-0.174	-0.677	-0.238	-0.354	-0.159
Charges/PCM	0.041	0.501	-0.079	-1.233	-0.412	0.133	-0.204	-0.475	-0.393	0.875	-0.388	-0.236	-0.439	-0.124	-0.459	-0.108
Atom № in F-5′	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	5‘-0	4‘-C	3‘-C	2‘-C
Charges/vac	0.042	0.627	-0.383	-0.926	-0.292	0.151	-0.08	-0.474	-0.303	1.435	-1.187	-0.518	-0.205	0.155	-0.353	-0.166
Charges/PCM	0.053	0.604	-0.421	-0.791	-0.401	0.196	-0.124	-0.513	-0.285	1.35	-1.181	-0.551	-0.254	0.165	-0.386	-0.581
Atom № in F-4‘	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	4‘-0	3‘-C	2‘-C
Charges/vac	0.038	0.683	-0.627	-0.880	-0.299	0.23	-0.081	-0.462	-0.305	1.127	-0.507	-0.44	-0.43	-0.218	-0.336	0.167
Charges /PCM	0.041	0.407	-0.218	-1.242	-0.414	0.109	-0.209	-0.503	-0.369	1.21	-0.824	-0.125	-0.331	-0.257	-0.437	0.149
Atom № in F-3‘	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	3‘-0	2‘-C
Charges/vac	0.025	0.301	-0.037	-1.507	-0.304	0.14	-0.159	-0.419	-0.384	1.226	-0.457	-0.414	0.179	-0.283	-0.251	-0.438
Charges/PCM	0.025	0.287	-0.045	-1.419	-0.404	0.154	-0.213	-0.462	-0.386	1.165	-0.453	-0.436	0.173	-0.31	-0.304	-0.438
Atom № in F-2‘	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C	2‘-0
Charges/vac	-0.045	0.355	0.103	-1.618	-0.295	0.077	-0.168	-0.416	-0.46	1.397	-0.437	-0.51	-0.145	-0.208	-0.459	-0.23
Charges /PCM	-0.020	0.358	0.08	-1.531	-0.4	0.087	-0.208	-0.466	-0.448	1.356	-0.435	-0.541	-0.194	-0.252	-0.401	-0.273
Atom № in F-3	1-0	2-C	3-C	3-0	4-C	4-0	5-C	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	0.035	-0.253	-0.485	-0.284	-0.35	-0.349	0.34	-0.227	-0.279	-0.187	1.325	-0.672	-0.344	-0.21	-0.374	0.077
Charges/PCM	0.038	0.118	-0.431	-0.265	-0.549	-0.424	0.269	-0.416	-0.248	-0.14	1.361	-0.644	-0.653	-0.367	-0.378	0.073
Atom № in F-5	1-0	2-C	3-C	4-C	4-0	5-C	5-0	6-C	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	0.045	0.194	0.177	-1.764	-0.344	-0.021	-0.279	0.091	-0.332	-0.796	1.189	-0.509	-0.403	-0.203	-0.307	-0.097
Charges/PCM	0.054	0.221	0.117	-1.691	-0.422	0.086	-0.333	0.02	-0.378	-0.816	1.242	-0.517	-0.432	-0.244	-0.345	-0.081
Atom № in F-6	1-0	2-C	3-C	4-C	4-0	5-C	6-C	6-0	7-C	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	0.033	0.342	-0.052	-1.471	-0.295	0.013	-0.446	-0.251	-0.032	-0.39	1.208	-0.482	-0.392	-0.218	-0.291	-0.164
Charges/PCM	0.039	0.348	-0.094	-1.326	-0.407	-0.013	-0.472	-0.262	-0.059	-0.363	1.143	-0.466	-0.416	-0.259	-0.322	-0.156
Atom № in F-7	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	7-0	8-C	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	0.031	0.382	0.052	-1.471	-0.304	0.06	0.209	-0.744	-0.204	-0.266	1.091	-0.578	-0.353	-0.25	-0.248	-0.16
Charges/PCM	0.038	0.379	0.016	-1.374	-0.415	0.04	0.285	-0.882	-0.235	-0.564	1.099	-0.508	-0.425	-0.257	-0.326	-0.101
Atom № in F-8	1-0	2-C	3-C	4-C	4-0	5-C	6-C	7-C	8-C	8-0	1‘-C	6‘-C	5‘-C	4‘-C	3‘-C	2‘-C
Charges/vac	-0.047	0.020	0.465	-1.877	-0.289	0.067	-0.205	-0.071	-0.703	-0.218	1.011	-0.511	-0.357	-0.217	-0.219	-0.179
Charges/PCM	-0.015	0.059	0.422	-1.821	-0.396	0.093	-0.264	-0.121	-0.681	-0.252	0.972	-0.516	-0.392	-0.254	-0.26	-0.142

Aquatic environment prevents the formation of hydrogen bonds with the hydroxyl group at position 3, but does not prevent the strong bond with the hydroxyl group in 5 position.

It is interesting to compare the charges at the oxygen atoms of the hydroxyl groups in all ten isomers.

The smallest negative charge in vacuo belongs to the hydroxyl oxigen in isomers F-6 (-0.174). The reasons are probably the following. The attraction between the oxygen of the hydroxyl group and the hydrogen at 3th position in ring C (see **Fig. 2**) leads to the formation of a planar geometry and efficient withdrawal of electron density from the first one. In all other isomers with hydroxyl groups in ring B there is no such efficient conjugation and all of them have higher negative charges at the hydroxyl oxigen. From those six isomers F-3 has the most significant negative charge. The oxygen atoms in isomers F-3 and F-5 have the greatest negative charges. The hydroxyl group in F-3 is non-phenolic. Obviously, the size of the charge of the hydroxyl oxygen in the F-5 is associated with the strong hydrogen bond in this isomer.

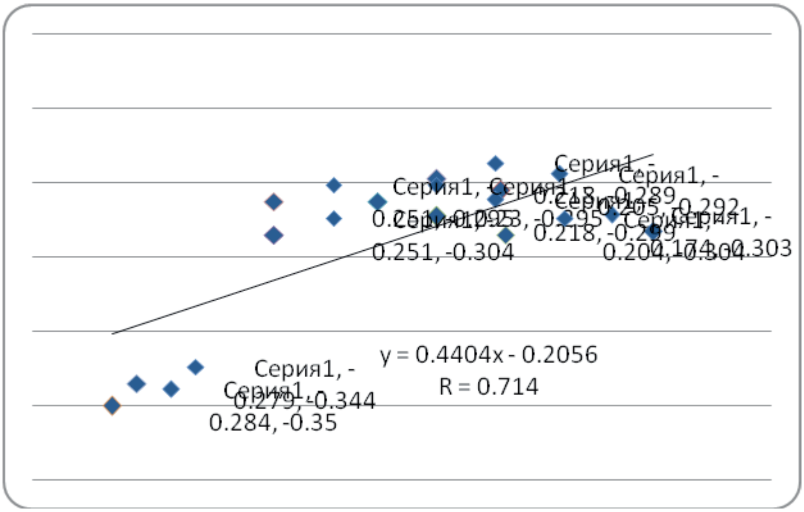

Fig. 3. Correlation between charges at hydroxyl and carbonyl oxygen atoms. This is an unusual result. We expected that by reducing the charge of the hydroxyl oxygen this will increase the charge of the carbonyl oxygen. There is no correlation between these charges in aqueous media

When reporting the polarizing effect of the water, the charges at the hydroxyl groups oxygens grow to about 0.1. Only the charge of the oxygen atom in F-3 significantly decreases.

It is interesting to note that the charges of the oxygen atoms of the hydroxyl groups in vacuo correlate with the charges at the oxygen atoms of the carbonyl groups. Hence, the larger the negative charge of first oxygen atom is, the greater is at the other.

Conclusions

We have always believed that the charge transfer to the carbonyl oxygen is the determining structural feature for the properties of the flavones. The Mulliken population analysis, however, shows that this is not entirely so.

The withdrawal of electron density from the oxygen at position 1 and the lack of flatness in the molecules hinder it. In all cases, a comprehensive analysis of the electron density needs to be done in the near future.

NOTES

1. Velkov & Vakarelska-Popovska, unpublished results.

REFERENCES

Alov, P., Tsakovska, I. & Pajeva, I. (2015). Computational studies of free radical-scavenging properties of phenolic compounds. *Curr. Top. Med. Chem., 15,* 85-104.

Frisch, M. J. , Trucks, G.W. , Schlegel, H.B. , Scuseria, G. E. , Robb, M.A. , Cheeseman, J.R., Scalmani, G., Barone V., Mennucci, B., Peterson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montomery, Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazeev, O., Austin, A.J., Cammi, R., Romelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrewski, V.G., Voth, G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, O., Foresman, J.B., Ortiz, J.V., Cioslowski, J. & Fox, D.J. (2009). *Gaussian, Inc.*Wallingford.

Mulliken, R.S. (1955a). Electronic population analysis on LCAO-MO molecular wave functions I. *J. Chem. Phys., 23*, 1833-1840.

Mulliken, R.S. (1955b). Electronic population analysis on LCAO–MO molecular wave functions II: overlap populations, bond orders, and covalent bond energies. *J. Chem. Phys*, *23*, 1841-1845.

Parr, R.G. & Yang, W. (1989). *Density-functional theory of atoms and molecules*. Oxford: Oxford University Press.

Vakarelska-Popovska, M. & Velkov, Z. (2013). Quantum-chemical calculation of O-H bond dissociation enthalpy in flavones. *Proc 5th Int. Scientific Conf. – FMNS*, v. 4, pp. 10-16.

Vakarelska-Popovska, M.H. & Velkov, Z.A. (2014). Structure of flavones and flavonols, part II: role of position on the O-H bond dissociation enthalpy. *Comp. Chem.*, *2*, 1-5.

✉ **Dr. Zhivko Velkov** (corresponding author)
Department of Chemistry,
South-West University "Neofit Rilski"
66 Ivan Michailov Str.
2700 Blagoevgrad, Bulgaria
E-mail**:** jivko_av@swu.bg