Effect of aqueous environment in chemical reactivity of monolignols. A New Fukui Function Study

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ABSTRACT

The free radical reactivity of monolignols can be explained in terms of the Fukui function and the local hard and soft acids and bases (HSAB) principle to determine the potential linkages among them for reactions involving free radicals. Our results in gas-phase and aqueous environment elucidate the most probable free radical resonance structures in monolignols. Their reactivity toward nucleophilic or electrophilic species was described applying the Fukui function after a second analysis of the selected resonance structures. Methodology herein described could differentiate the inherent nature of one radical from another.

1. Introduction

Generally, three trans-hydroxycinnamyl alcohols (*p*-coumarol, coniferol and sinapol) are considered to be the main precursors in lignin formation models [1]. Those alcohols are named mono-lignols [2] (Fig. 1) and have been extensively studied [3], yielding insights for addressing the control synthesis of neolignans [4]. Lignin formation is a randomly free radical polymerization of monoligniols catalyzed by the enzymes lacasses or peroxydases, primordially at the middle lamellae of plant cells [5].

The monolignols are oxidized by enzymes to form five different free radical resonance structures (Fig. 2). Since the properties of monolignol radicals are fundamental for lignin, lignan or neolignan structures, resonance theory has been applied as a qualitative method using chemical intuition to describe their reactivity [6]. Their random combination is the responsible of the complex lignin structure due to the fact that free radicals have twenty-five different ways of forming bonds between them. The most frequent free radicals are β-O-4′, β-5′, β-β′, β-1′, 5-5′ and 5-O-4′ [7], however, their relative abundance has not been established because the extraction process used to isolate lignin from plant tissues modifies most of the original bonds [8].

Several attempts to obtain lignins *in vitro* have been developed [9] for achieving oligolignols that reproduce some of the linkages; however, the interpretation from the intrinsic chemical reactivity of lignin precursors has not been included. Furthermore, the 5-5′ and 5-O-4′ dimers do not actually arise in any significant way from monomer dimerization reactions [10]. In addition, several computational studies were carried out for establishing the predominant resonance structures of free radicals [11] and to propose the initial linkages occurred during lignification. Those studies have used a frontier orbital and energetic framework to correlate the linkage formation with the resonance structures of monolignols radicals [12], however, a description between radical interactions was not mentioned. Recently, the hard and soft acids and bases (HSAB) principle [13] was applied as a new approach to elucidate the intrinsic reactivity of lignin precursors [14].

The conceptual framework of density functional theory (DFT) [15] may reveal the underlying mechanism to explain how a molecular system responds to electronic perturbation, considering the structure–property relationship. DFT provides a rigorous theoretical framework for the analysis and interpretation of electronic structure of molecules. An electron density-based concept is the *Fukui function*, which describes the responding sensitivity of a molecular system to electronic perturbations [16].

The purpose of the present study is to determine the potential free radical sites of monolignols and their intrinsic reactivity toward another monolignol free radical, both in gas-phase and in

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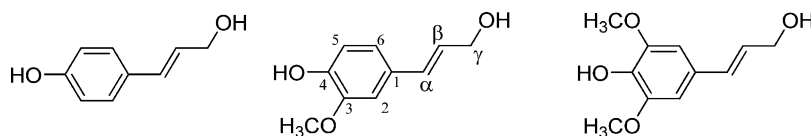E-mail address: plopez@umich.mx (P. Lopez).

Fig. 1. Lignin precursors: *p*-coumarol, coniferol and sinapol, respectively, showed in their predominant (*E*)-monolignol configuration. Typical numbering is shown over the coniferol structure.
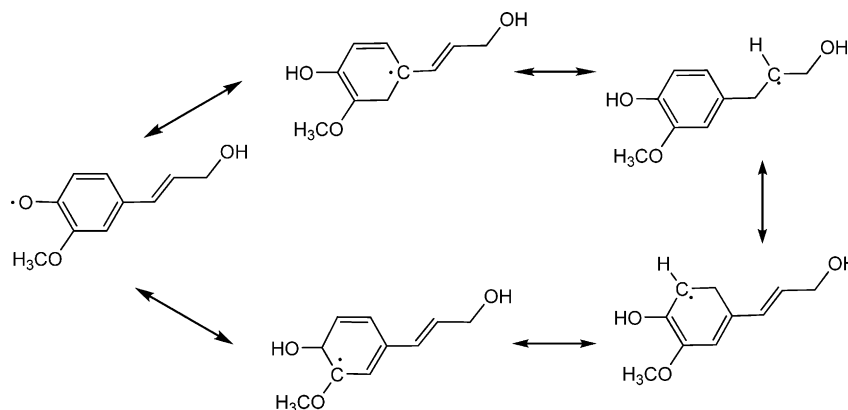

Fig. 2. Free radical resonance structures of monolignols, according to the resonance theory. Only coniferol is illustrated.

the presence of water. The Fukui function, defined as a reactivity index in the conceptual framework of DFT, was applied for explaining the stability of resonance structures I–V and the reactivity between them in order to predict the most probable initial linkages. We aim to find out whether the Fukui function for the unperturbed substrates is able to explain or predict the observed regioselectivity of the radical addition reaction between monolignols. To the best of our knowledge, the present work is the first attempt to characterize the intrinsic chemical reactivity of monolignols applying the Fukui function twice, first, to determine their most predominant free radical resonance structures and, in a second step, to describe their reactivity toward radical addition reactions between them. We hope this theoretical study of the monolignol free radical reactions opens the possibility of assessing the utility of the Fukui function as a reactivity descriptor in the study of free radical reactions involving resonance structures and their intrinsic reactivity in terms of the electron density.

2. Theoretical basis

One of the most accepted criteria for reactivity is the HSAB principle. It was originally developed to describe most of the acid–base reactions through the concept of hardness [17], however, due to its applicability and simplicity it has been widely used to predict the nature of different chemical phenomena and has become popular among the community of chemists [18]. Many useful and important chemical concepts (i.e. electronegativity, hardness and softness) are described naturally within the density functional theory (DFT) framework. The Fukui function is defined as the change of the electronic density with respect to number of electrons (N), considering the nuclei position fixed, i.e. constant external potential $V(r)$:

$$f(r) \equiv \left(\frac{\partial \rho(r)}{\partial N}\right)_{V(r)}$$

Due to the discontinuity of the derivative expression with respect to N, the following three functions can be defined in a finite difference approximation:

$$f^+(r) = \rho(r)_{N+1} - \rho(r)_N \tag{1}$$

$$f^-(r) = \rho(r)_N - \rho(r)_{N-1} \tag{2}$$

$$f^0(r) = \frac{1}{2}\left[\rho(r)_{N+1} - \rho(r)_{N-1}\right] \tag{3}$$

where $\rho(r)_{N+1}$, $\rho(r)_N$ and $\rho(r)_{N-1}$ are the electronic densities of the system with $N + 1$, N, and $N - 1$ electrons, respectively, all with the ground state geometry of the N electron system. Although the finite difference approximation to the Fukui functions is exact only for exact calculations (i.e., full configuration interaction) [19], in most cases they are considered a reliable descriptor to indicate how the incoming or outcoming electron is redistributed in regions of the molecule [20]. Expressions 1, 2 and 3 are respectively evaluated for: nucleophilic attack, where molecule gains an electron; electrophilic attack, where molecule loses an electron; and free radical attacks [21]. This treatment of chemical reactivity is based on the assumption that when molecules A and B interact in order to form a product AB, a mutual perturbation of the molecular densities of both reactants occurs [22]. Since the electronic density contains all the information, chemical reactivity should be reflected in its sensitivity to perturbations. The Fukui function is also defined as the *initial* response in $\rho(r)$ due to an infinitesimal perturbation in the total N, at constant external potential $V(r)$. The "frozen core" [23] approximation assumes that a perturbation in the electronic density of a molecule occurs mainly in the external regions; therefore, errors in Eqs. (1), (2) and (3) should be small since the interaction of reagents begins when they approach. It is known that in a real chemical process this condition is never satisfied, however, the "frozen core" approximation is useful to predict and describe the intrinsic chemical reactivity of chemical species.

Supported by the principle that molecules with regions where the Fukui function is larger are chemically softer than those regions where the same function is smaller and considering the HSAB principle in a local sense, the hard or soft behavior of different sites inside the molecules can be established. The HSAB principle can then be applied considering the magnitude of the Fukui function in each site in the molecule, postulating that "The maxima of $f^+(r)$ indicate regions in the molecule suitable for attack by a nucleophile or an upcoming charge, whereas regions with

$f^-(r)$ maxima are suitable for attack by an electrophile or an outgoing charge and $f^0(r)$ maxima indicate regions suitable for radical attack" [24].

3. Methodology

Our proposal to study the intrinsic chemical reactivity of monolignols toward free radical reactions in gas-phase and aqueous environment is to predict and explain the formation of specific linkages between them, applying the methodology of Fukui functions twice. In a first step, we apply only the $f^0(r)$ Fukui function form over their neutral singlet configuration to elucidate the most predominant free radical resonance structure. Then, in a second step, we study the monolignols in a doublet open shell configuration applying the $f^+(r)$ and $f^-(r)$ forms of the Fukui function to describe the reactivity of the most predominant free radical resonance structures found in the first step.

3.1. Step one

As explained in theoretical basis above, any of the three Fukui function forms is a useful reactivity descriptor for a molecule *before* it reacts. Thus, it can be possible to elucidate how monolignols react toward a free radical attack through the evaluation of their $f^0(r)$ Fukui function form analyzing their neutral (singlet) configuration. Also, it can be considered that this form of the Fukui function is useful to observe the predominance of the free radical resonance structures of monolignols, because it indicates the most probable sites where a free radical interaction can occur. The neutral (singlet) configurations of monolignols were built and optimized by *ab initio* calculations using the GAUSSIAN03 software package [25]. The conformational analysis to obtain the equilibrium geometry was performed using the B3LYP hybrid density functional [26] and the 6-311G** basis set was selected in a restricted calculation. After optimization calculation, the electronic densities for each monolignol were computed at the frozen optimized geometries, i.e. assuming a constant external potential $V(r)$, required in the Fukui function definition. The electronic densities for their $\rho(r)_{N+1}$ and $\rho(r)_{N-1}$ forms with $N+1$ and $N-1$ electrons, respectively, were obtained at the UB3LYP/6-311++G** level through single point calculations. The 6-311++G** basis set was selected because it produces a better bond and density description. Each electron density was stored in a three dimensional grid-cube, to be manipulated according to equation 3 to determine the $f^0(r)$ Fukui function. The grid selected to calculate each side of the density cube had 12 points/Bohr. Both geometry optimization and single point calculations were carried out in gas-phase and aqueous environment, the effect of the water being incorporated using the Polarized Continuum Model (PCM) [27]. The graphical program Chemcraft [28] was used for visualization of computed results.
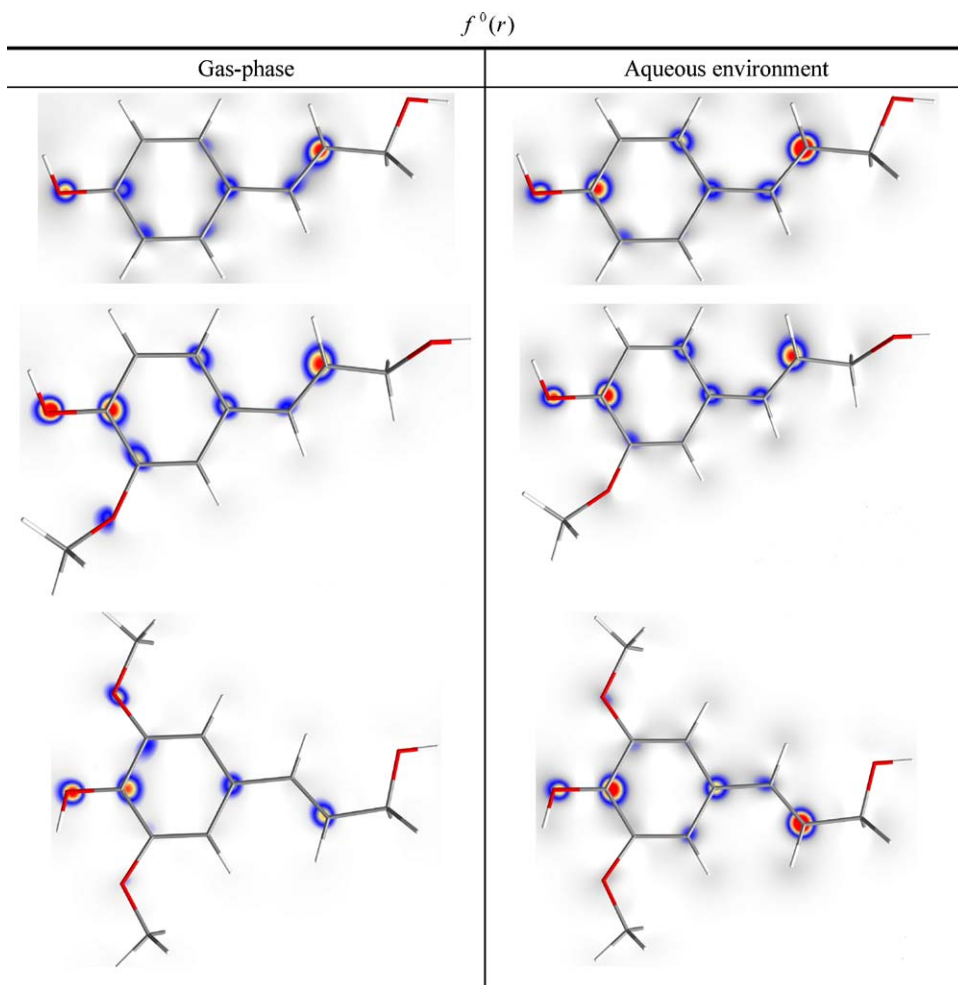

$f^0(r)$

| Gas-phase | Aqueous environment |

Fig. 3. Contour plot of the free radical form of Fukui function, for the *p*-coumarol, coniferol and sinapol, respectively. The highest and lowest values are indicated in the scale by the white and red colors, respectively, middle values being indicated in blue. The red, gray, and white lines indicate the oxygen, carbon, and hydrogen atoms, respectively.

3.2. Step two

Nucleophilic ($f^+(r)$) and electrophilic ($f^-(r)$) versions of the Fukui function over the doublet open shell configuration for each monolignol were applied in order to elucidate the intrinsic reactivity of each predominant free radical structure. Therefore it should be possible to know if a free radical resonance structure behaves as donor or acceptor of the non-paired electron from another monolignol. Each monolignol in their doublet open shell configuration was optimized to obtain their equilibrium geometry applying the same conditions in step one for geometry optimization. Again, after optimization calculation the electronic densities for each monolignol were computed at the frozen optimized geometries, i.e. assuming a constant external potential $V(r)$, required in the Fukui function definition. Unlike step one, the $\rho(r)_{N+1}$, $\rho(r)_N$ and $\rho(r)_{N-1}$ electron densities with $N + 1$, N and $N - 1$ electrons, respectively, were calculated in single point calculations to obtain the nucleophilic ($f^+(r)$) and electrophilic ($f^-(r)$) version of the Fukui function, according to Eqs. (1) and (2), respectively. Additionally, the $\rho(r)_{N+1}$ and $\rho(r)_{N-1}$ electron densities were calculated at the RB3LYP/6-311++G** level, whereas the $\rho(r)_N$ electron density was calculated at the UB3LYP/6-311++G** level. Also, the Fukui functions were obtained through cube manipulation with the same calculation framework used in step one.

Although similar studies of Fukui indexes employ the "condensed" version for this type of functions [29], we take the advantage of using density cubes instead of atomic charges in order to avoid uncertainties included in the population analysis when estimating partial atomic charges [30].

4. Results and discussion

To visualize the results, a contour plane plot was selected over the phenylpropanoid plane of monolignols at 0.45 Å above in gas-phase and 0.60 Å above in aqueous environment because, at these distances, it was possible to observe the first occurrence of the highest value for the three forms of the Fukui function. The highest and lowest values are indicated in the scale by the white and red colors, respectively, whereas middle values are indicated in blue.

The $f^0(r)$ form of the Fukui function was applied as a stability descriptor of the free radical resonance structures, because it represents regions in the monolignols where an unpaired electron may be found after a redistribution of the initial electronic density. Results are presented in Fig. 3 where the highest values of $f^0(r)$ are shown in the red regions.

In p-coumarol and sinapol there are significant differences caused by the aqueous environment. As seen in Fig. 2, the non-paired electron in structure IV is located around the carbon atom at the β-position, and this is the most probable free radical resonance structure for p-coumarol and sinapol in aqueous environment. These results can be considered representative of lignin formation because monolignol polymerization occurs inside and between wood cells. In aqueous environment, sinapol preferentially presents structure IV and less frequently, structure I, whereas in
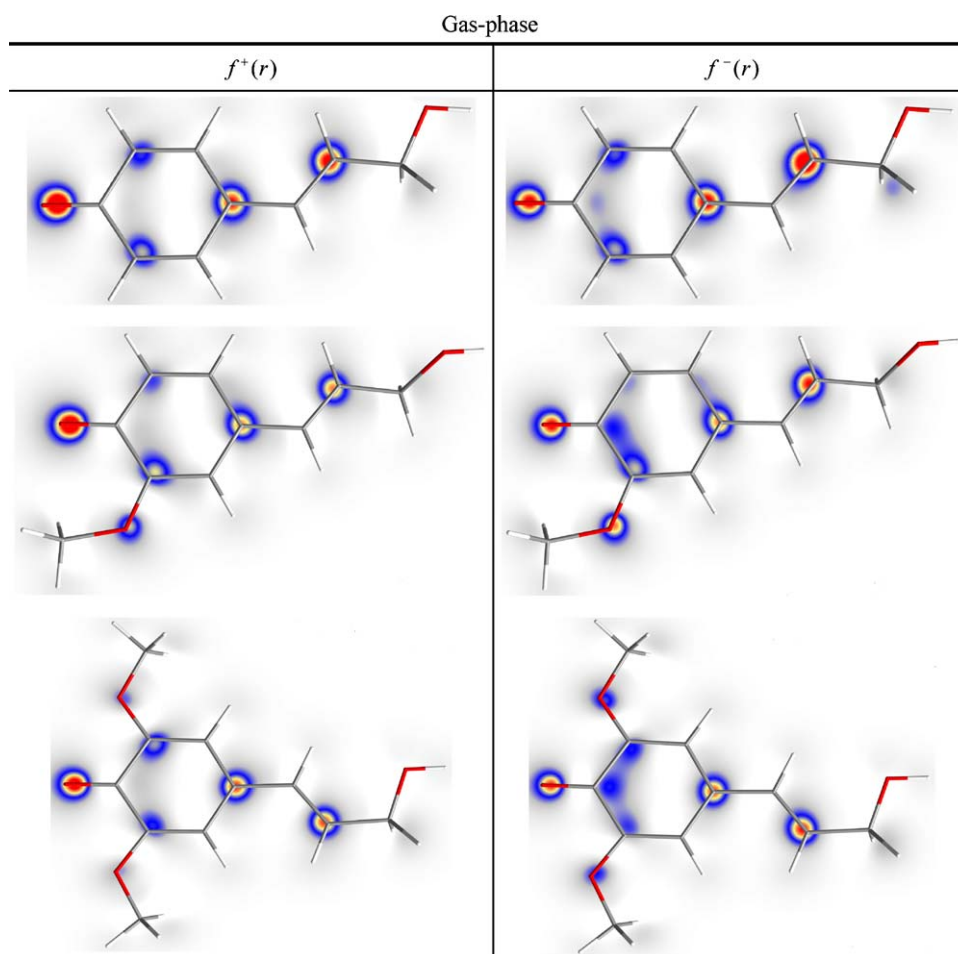

Fig. 4. Contour plots for the nucleophilic and electrophilic forms of the Fukui function in vacuum environment, showing intrinsic chemical reactivity for the p-coumarol, coniferol and sinapol, respectively. The highest and lowest values are indicated in the scale by the white and red colors, respectively, middle values being indicated in blue. The red, gray, and white lines indicate the oxygen, carbon, and hydrogen atoms, respectively.

Fig. 5. Contour plots for the nucleophilic and electrophilic forms of the Fukui function in aqueous environment, showing the effect of water in the intrinsic chemical reactivity for the *p*-coumarol, coniferol and sinapol, respectively. The highest and lowest values are indicated in the scale by the white and red colors, respectively, middle values being indicated in blue. The red, gray, and white lines indicate the oxygen, carbon, and hydrogen atoms, respectively.
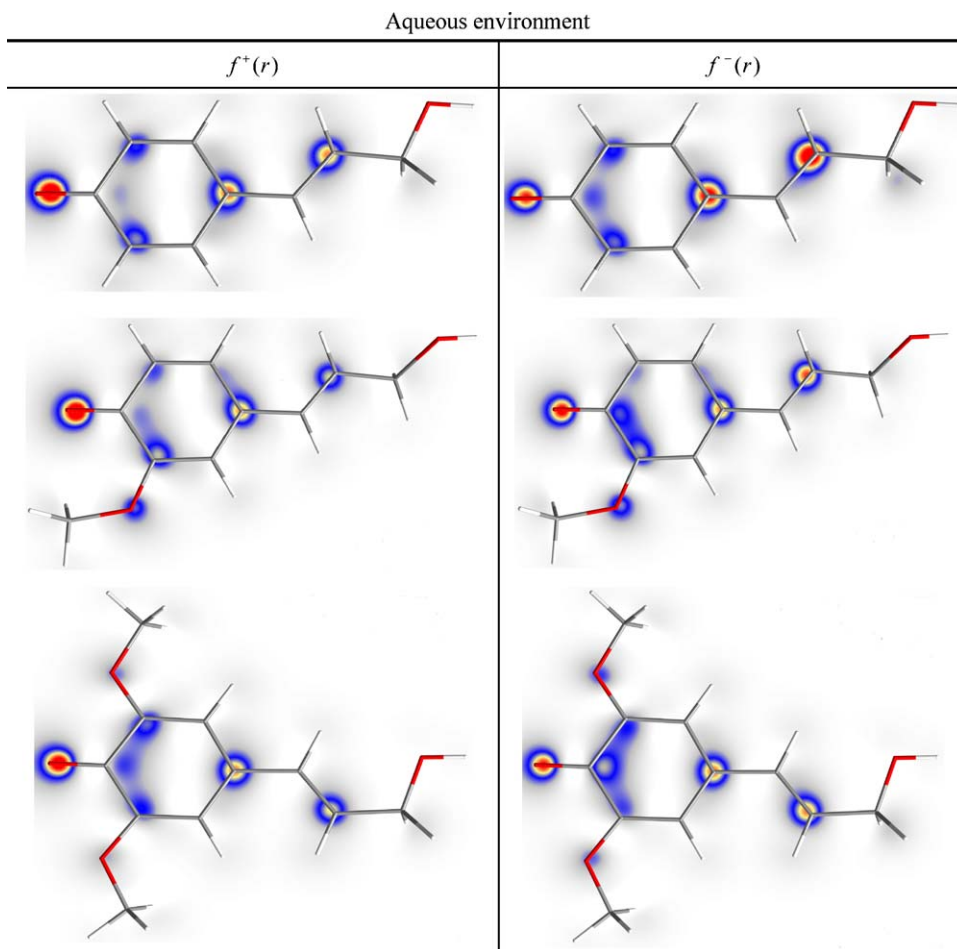
gas-phase, structure I predominates. Coniferol showed similar trends in gas-phase and aqueous environment, however, under water the carbon atom at the β-position and the carbon–oxygen bond in the hydroxyl region had the highest value of $f^0(r)$, indicating the predominance of structures I and IV. The red-highlighted contour associated to the 4-carbon in the hydroxyl groups should be carefully interpreted due to the electronegativity of the oxygen, which tends to accumulate charge. In coniferol this observation could be explained considering that the hydroxyl group in the phenol ring is surrounded by water molecules, decreasing its reactivity and transferring it to the carbon at position 4, however, this atom is not considered to participate in the representative lignin bonds.

After obtaining the most probable free radical structures for each monolignol in step one, the following analysis in step two is to determine the reactivity between them. The non-paired electron in the doublet open shell configuration for each monolignol could behave as an acceptor ($f^+(r)$ maximum) or as a donor ($f^-(r)$ maximum) in a free radical reaction, the results being shown in Figs. 4 and 5. Although the maxima in vacuum and water environment present different intensity, results showed similar reactivity sites.

Comparing contours for sinapol in aqueous environment, we observe that $f^+(r)$ maximum occurs at the phenolic oxygen where an incoming electron prefers to form a bond. On the other hand, sinapol presents the ability to donate an electron to form a bond at the carbon in the β-position, because it was there where the maximum $f^-(r)$ was found. It was not possible to determine the

reactivity of carbon at the β-position in gas-phase, because the nucleophilic ($f^+(r)$) and electrophilic ($f^-(r)$) versions of the Fukui function showed similar results over the β-carbon; thus, the unpaired electron does not present a specific reactivity toward a free radical attack.

In gas-phase, *p*-coumarol showed similar results in the $f^+(r)$ and $f^-(r)$ Fukui function forms; however, the behavior of its unpaired electron around the carbon at the β-position showed a slight difference. Only the phenolic oxygen showed a clear reactivity, being subject to a nucleophilic attack. The aqueous environment clarifies the reactivity of *p*-coumarol, yielding specific sites to accept an electron at the phenolic oxygen, where the $f^+(r)$ maximum occurred and to donate an electron from the carbon at the β-position, where the $f^-(r)$ maximum occurred.

Coniferol showed a very specific reactivity: a nucleophilic attack from free radical species could mainly occur at the phenolic oxygen, both in gas-phase and in aqueous environment, whereas an electrophilic attack could be feasible in the carbon at the β-position.

5. Conclusions

The presence of water significantly modifies the reactivity of monolignols and promotes three of the most abundant linkages (β-O-4', β-5', β-β', β-1'). The 5-5' and 5-O-4' dimers in coniferol-lignans are less abundant since the Fukui function did not shown significant values over the 5-carbon in the coniferol, although the graphical results put it at the middle in the presented reactivity

scale, the structure V is not possible or probable in the initial dimerization, considering the intrinsic reactivity of coniferol.

The methodology applied to obtain our results was useful to observe the effect of aqueous environment in the chemical reactivity of monolignols, assessing the utility of the Fukui function in a DFT framework as a descriptor of the stability and reactivity of monolignol radical species.

Acknowledgments

References

[1] A. Sakakibara, Y. Sano, Lignin, in: D.N.S. Hon, N. Shirasi (Eds.), Wood and Cellulosic Chemistry, CRC Press, New York, 2007, , pp. 109–174, Chapter 4.

[2] K. Freudenberg, Lignin: its constitution and formation from p-hydroxycinnamyl alcohols, Science 148 (1965) 595–600.

[3] (a) R.S. Ward, The synthesis of lignans and neolignans, Chem. Soc. Rev. 11 (1982) 75–125;
(b) S. Barsberg, P. Matousek, M. Towrie, H. Jorgensen, C. Felby, Lignin radicals in the plant cell wall probed by Kerr-gated resonance Raman spectroscopy, Biophys. J. 90 (2006) 2978–2986.

[4] (a) S. Zacchino, G. Rodríguez, G. Pezzenati, G. Orellana, In vitro evaluation of antifungal properties of 8,O,4′-neolignans, J. Nat. Prod. 60 (1997) 659–662;
(b) L. Juhásza, Z. Dinyaa, S. Antus, T.E. Gunda, A new approach for the synthesis of naturally occurring dihydrobenzo[b]furan-type neolignans of potential biological activity, Tetrahedron Lett. 41 (2000) 2491–2494.

[5] T. Higuchi, Lignin biochemistry: biosynthesis and biodegradation, Wood Sci. Technol. 24 (1990) 23–63.

[6] T. Higuchi, in: T. Higuchi (Ed.), Biosynthesis of Lignin. Biosynthesis and Biodegradation of Wood Components, Academic Press, Orlando, 1985, pp. 141–160.

[7] B. Monties, Plant phenolics, in: P.M. Dey, J.B. Harborne (Eds.), Methods in Plant Biochemistry, Academic Press, New York, 1989, pp. 113–157.

[8] D. Fengel, G. Wegener, Lignin, in: De Gruyter (Ed.), Wood Chemistry, Ultrastructure, Reactions, Berlin, 1989, pp. 132–181, Chapter 6.

[9] (a) J. Ralph, Y. Zhang, A new synthesis of (Z)-coniferyl alcohol, and characterization of its derived synthetic lignin, Tetrahedron 58 (1998) 1349–1354;
(b) L.J. Landucci, Reaction of p-hydroxy cinnamyl alcohols with transition-metal salts. 1. Oligolignols and polylignols (DHPS) from coniferyl alcohol, Wood. Chem. Tech. 15 (1995) 349–368.

[10] W. Boerjan, J. Ralph, M. Baucher, Lignin biosynthesis, Annu. Rev. Plant. Biol. 54 (2003) 519–546.

[11] (a) B. Durbeej, L.A. Eriksson, Formation of β-O-4 lignin models—a theoretical study, Holzforschung 57 (2003) 466–478;
(b) L. Jurasek, Morphology of computer-modeled lignin structures: fractal dimensions, orientation and porosity, J. Pulp Paper Sci. 22 (1996) 376–380;
(c) M. Roussel, C. Lim, Dynamic model of lignin growing in restricted spaces, Macromology 28 (1995) 370–376.

[12] B. Durbeej, L.A. Eriksson, A density functional theory study of coniferyl alcohol intermonomeric cross linkages in lignin—three-dimensional structures, stabilities and the thermodynamic control hypothesis, Holzforschung 57 (2003) 150–164.

[13] R.G. Pearson, HSAB principle, J. Am. Chem. Soc. 85 (1963) 3533–3539.

[14] C. Martinez, J.L. Rivera, R. Herrera, J.L. Rico, F. Flores, J.G. Rutiaga, P. López, Evaluation of the chemical reactivity in lignin precursors using the Fukui function, J. Mol. Mod. 14 (2008) 77–81.

[15] R.G. Parr, W. Yang, In Density Functional Theory of Atoms and Molecules, Oxford University Press, New York, 1989, pp. 70–84.

[16] R.G. Parr, W. Yang, Density functional approach to the frontier-electron theory of chemical reactivity, J. Am. Chem. Soc. 106 (1984) 4049–4050.

[17] W. Yang, R.G. Parr, Hardness, softness, and the Fukui function in the electronic theory of metals and catalysis, Proc. Natl. Acad. Sci. U.S.A. 82 (1985) 6723–6726.

[18] (a) P.W. Ayers, R.G. Parr, Variational principles for describing chemical reactions: the fukui function and chemical hardness revisited, J. Am. Chem. Soc. 122 (2000) 2010–2018;
(b) M.E. Beck, Do fukui function maxima relate to sites of metabolism? A critical case study, J. Chem. Inf. Model. 45 (2005) 273–282.

[19] P.W. Ayers, F. De Proft, A. Borgoo, P. Geerlings, Computing Fukui functions without differentiating with respect to electron number. I. Fundamentals, J. Chem. Phys. 126 (2007) 224107-1–224107-13..

[20] H. Chermette, P. Boulet, S. Portmann, in: K.D. Sen (Ed.), Reviews in Modern Quantum Chemistry: A Celebration of the Contributions of Robert G. Parr, World Scientific, Singapore, 2002.

[21] W. Yang, W.J. Mortier, The use of global and local molecular parameters for the analysis of the gas-phase basicity of amines, J. Am. Chem. Soc. 108 (1986) 5708–5711.

[22] J.L. Gázquez, in: K.D. Sen (Ed.), Chemical hardness. Structure and Bonding, Springer-Verlag, Berlin, 1993, pp. 27–42.

[23] U. von Barth, C.D. Gelatt, Validity of the frozen-core approximation and pseudopotential theory for cohesive energy calculations, Phys. Rev. B 21 (1980) 2222–2228 (and references therein).

[24] P. López, F. Méndez, Fukui Function as a descriptor of the imidazolium protonated cation resonance hybrid structure, Org. Lett. 6 (2004) 1781–1783.

[25] Gaussian 03, Revision E.01, 2004, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian, Inc., Wallingford, CT.

[26] A.D. Becke, Density functional thermochemistry. III. The role of exact exchange, J. Chem. Phys. 98 (1993) 5648–5652.

[27] (a) S. Miertus, J. Tomasi, Approximate evaluations of the electrostatic free energy and internal energy changes in solution processes, Chem. Phys. 65 (1982) 239–241;
(b) S. Miertus, E. Scrocco, J. Tomasi, Electrostatic interaction of a solute with a continuum. A direct utilization of ab-initio molecular potentials for the prevision of solvent effects, Chem. Phys. 55 (1981) 117–120.

[28] Chemcraft is a graphical program for working with quantum chemistry computations. http://www.chemcraftprog.com.

[29] R. Balawender, L. Komorowski, Atomic Fukui function indices and local softness ab initio, J. Chem. Phys. 109 (1998) 5203–5211.

[30] P. Fuentealba, P. Pérez, R. Contreras, On the condensed Fukui function, J. Chem. Phys. 113 (2000) 2544–2551.