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PYRIDOXAMINE DERIVATIVES AS NONENZYMATIC GLYCATION INHIBITORS: THE CONCEPTUAL DFT VIEWPOINT

Juan Frau[1] and Daniel Glossman-Mitnik[1, 2, *]

1 Departament de Química, Universitat de les Illes Balears, Palma de Mallorca 07122, Spain

2 Laboratorio Virtual NANOCOSMOS, Departamento de Medio Ambiente y Energía, Centro de Investigación en Materiales Avanzados, Chihuahua, Chih 31136, Mexico

ABSTRACT: The role of pyridoxamine and some derivatives as nonenzymatic glycation inhibitors have been studied through the calculation of Conceptual DFT descriptors. Several density functionals from the Minnesota family have been considered for the determination of the reaction sites like the Fukui function indices, the condensed dual descriptor $\Delta f(r)$, and the electrophilic and nucleophilic Parr functions. The calculation of the global descriptors: electronegativity χ, chemical hardness η, electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers, and the net electrophilicity $\Delta\omega^{\pm}$ through a ΔSCF technique has been compared with the results arising from the HOMO and LUMO energies in order to assess the fulfillment of the "Koopmans in DFT" (KID) procedure.

KEYWORDS: Pyridoxamine, AGEs, Conceptual DFT, Global Descriptors, Local Descriptors

***Corresponding Author: Dr. Daniel Glossman-Mitnik** Ph. D.

Centro de Investigación en Materiales Avanzados, Departamento de Medio Ambiente y Energía, Laboratorio Virtual NANOCOSMOS, Miguel de Cervantes 120, Complejo Industrial Chihuahua, Chihuahua, Chih 31136, Mexico.

* Email Address: daniel.glossman@cimav.edu.mx

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1. INTRODUCTION

It is well known that the nonenzymatic glycation of amino acids and proteins involves a group of reactions leading to structural and functional changes. These reactions are initiated by a nucleophilic addition (nonenzymatic glycation or Maillard reaction), a reaction between a free amino group from a protein and a carbonyl group from a reducing sugar to form a freely reversible Schiff base [1]. The Schiff base (or Amadori compound) can undergo a series of complex reactions leading to the formation of advanced glycation end products (AGEs) [1–3]. Accumulation of advanced glycation endproducts (AGEs) plays a crucial part in the development of age-related diseases and diabetic complications [4]. Thus, it is of fundamental importance to understand how different carbohydrates and carbonyl reducing compounds react with the amino acids and proteins and to obtain a measure of the extent of this reaction in each case. Ortega-Castro et al have recently presented a DFT study on the Schiff base formation of Vitamin B6 analogues through the reaction between a Pyridoxamine-analogue and carbonyl compounds [5]. Following the pioneering work of Parr and others [6], a useful number of concepts have been derived from the analysis of the density of any molecular system through DFT. These concepts that allow a researcher to make qualitative predictions about the chemical reactivity of a given system, can also be quantified and are collectively known as Conceptual DFT Descriptors. In order to obtain quantitative values of the Conceptual DFT Descriptors, it is necessary to resort to the Kohn-Sham theory trough calculations of the molecular density, the energy of the system, and the orbital energies, in particular, those related to the frontier orbitals, that is, HOMO and LUMO [7–10]. The usual way to proceed implies as a first step the choice of a model chemistry for the study of the molecular system or chemical reaction of interest. A model chemistry is a combination of a density functional, a basis set, and an implicit solvent model that one considers that can be adequate for the problem under study. There is a plethora of information in the literature about how to choose this model chemistry and one generally follows the experience of previous researchers and his/her own work.These concepts are associated to the vertical ionization potential I and electron affinity A, and can be obtained through energy calculations of the neutral species as well as the radical cation and anion. However, an alternative approach is to use an approximation that we have called KID procedure (for ”Koopmans in DFT”) that consists in the identification of I with $-\varepsilon_H$ (the energy of the HOMO) and A with $-\varepsilon_L$ (the energy of the LUMO). This KID procedure is an approximation because it is well known that the Koopmans’ theorem is not valid within DFT. Notwithstanding, it can be useful for faster calculations of Conceptual DFT descriptors for large molecular systems where the determination of the electronic energy of the radical cation and anion could be computationally costly and difficult to converge. This means that the goodness of a

given density functional for the prediction of Conceptual DFT descriptors can be estimated by checking how well it fulfills the KID procedure. Thus, it is of interest to consider several recently proposed density functionals that have shown great accuracy across a broad spectrum of databases in chemistry and physics [11] to see how well they behave through the KID procedure for the molecular systems under study. The objective of this work is twofold: i) to conduct a comparative study of the performance of some of the latest Minnesota family of density functionals for the description of the chemical reactivity of pyridoxamine (PM) and some analogues like 3-hydroxy-4-methylaminopyridine (PMa), pyridoxamine-5'-phosphate (PMP) and pyridoxal-5'-phosphate (PLP) which molecular structures are shown in Figure 1; and ii) to establish a comparative scale of the studied compounds as inhibitors of the formation of AGEs.

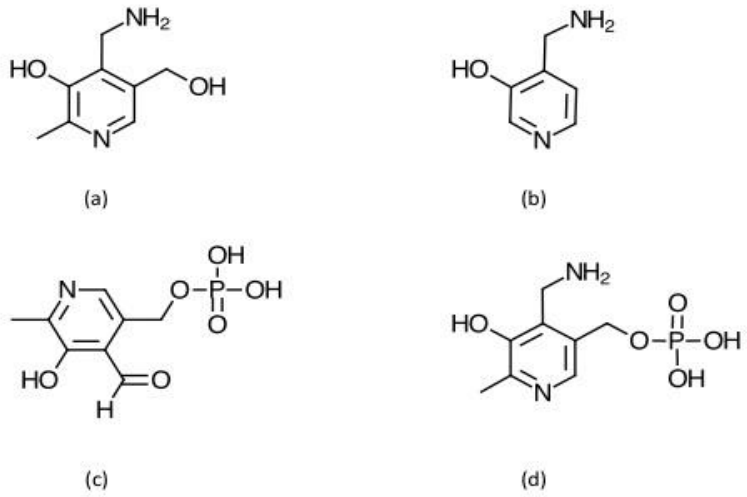

Figure 1: Molecular structures of a) PM, b) PMa, c) PLP and d) PMP

2 Theoretical Backgrounds

As this work is part of an ongoing project, the theoretical background will be analog to that presented in previous research [12–18] and will be shown here for the sake of completeness. Within the conceptual framework of DFT [19,20], the chemical potential μ is defined as:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = -\chi \tag{1}$$

where χ is the electronegativity, while the global hardness η is:

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} \tag{2}$$

Using a finite difference approximation and the KID procedure, the above expressions can be written

as:

$$\mu = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_H + \varepsilon_L) = \chi_K \tag{3}$$

$$\eta = (I - A) \approx (\varepsilon_L - \varepsilon_H) = \eta_K \tag{4}$$

where ε_H and ε_L are the energies of the highest occupied and the lowest unoccupied molecular orbitals, HOMO and LUMO, respectively.

The electrophilicity index ω has been defined as [21]:

$$\omega = \frac{\mu^2}{2\eta} = \frac{(I + A)^2}{4(I - A)} \approx \frac{(\varepsilon_H + \varepsilon_L)^2}{4(\varepsilon_L - \varepsilon_H)} = \omega_K \tag{5}$$

The electrodonating ω^- and electroaccepting ω^+ powers have been defined as [22]:

$$\omega^- = \frac{(3I + A)^2}{4(I - A)} \approx \frac{(3\varepsilon_H + \varepsilon_L)^2}{16\eta_K} = \omega_K^- \tag{6}$$

$$\omega^+ = \frac{(I + 3A)^2}{4(I - A)} \approx \frac{(\varepsilon_H + 3\varepsilon_L)^2}{16\eta_K} = \omega_K^+ \tag{7}$$

It follows that a larger ω^+ value corresponds to a better capability of accepting charge, whereas a smaller value of ω^- makes it a better electron donor. In order to compare ω^+ with $-\omega^-$, the following definition of net electrophilicity has been proposed [23]:

$$\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^- \approx \omega_K^+ - (-\omega_K^-) = \omega_K^+ + \omega_K^- = \Delta\omega_K^{\pm} \tag{8}$$

that is, the electroaccepting power relative to the electrodonating power.

The Fukui function is defined in terms of the derivative of ρ(r) with respect to N [20]:

$$f(r) = \left(\frac{\partial\rho(r)}{\partial N}\right)_{v(r)} \tag{9}$$

The function $f(r)$ reflects the ability of a molecular site to accept or donate electrons. High values of $f(r)$ are related to a high reactivity at point r [20].

By applying a finite difference approximation to Eq (9), two definitions of Fukui functions depending on total electronic densities are obtained:

$$f^+(r) = \left(\frac{\partial\rho(r)}{\partial N}\right)^+_{v(r)} = \rho_{N+1}(r) - \rho_N(r) \tag{10}$$

$$f^{-}(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)^{-}_{v(r)} = \rho_N(r) - \rho_{N-1}(r) \quad (11)$$

where $\rho_{N+1}(r)$, $\rho_N(r)$ and $\rho_{N-1}(r)$ are the electronic densities at point r for the system with N+1, N and N−1 electrons, respectively. The first one, $f^{+}(r)$, has been associated to reactivity for a nucleophilic attack so that it measures the intramolecular reactivity at the site r towards a nucleophilic reagent. The second one, $f^{-}(r)$, has been associated to reactivity for an electrophilic attack so that this function measures the intramolecular reactivity at the site r towards an electrophilic reagent [19]. Morell et al. [24–30] have proposed a local reactivity descriptor (LRD) which is called the dual descriptor $\Delta f(r)$. The definition of $\Delta f(r)$ is [24,25]:

$$\Delta f(r) = \left(\frac{\partial f(r)}{\partial N}\right)_{v(r)} \quad (12)$$

The dual descriptor can be condensed over the atomic sites: When $\Delta f_k > 0$ the process is driven by a nucleophilic attack on atom k and then that atom acts as an electrophilic species; conversely, when $\Delta f_k < 0$ the process is driven by an electrophilic attack over atom k and therefore atom k acts as a nucleophilic species. In 2014, Domingo proposed the nucleophilic and electrophilic Parr functions $P(r)$ [31,32] which are given by the following equations:

$$P^{-}(r) = \rho_s^{rc}(r) \quad (13)$$

for electrophilic attacks, and

$$P^{+}(r) = \rho_s^{ra}(r) \quad (14)$$

for nucleophilic attacks, which are related to the atomic spin density (ASD) at the r atom of the radical cation or anion of a given molecule, respectively. The ASD over each atom of the radical cation and radical anion of the molecule gives the local nucleophilic P_k^{-} and electrophilic P_k^{+} Parr functions of the neutral molecule [33].

2. MATERIAL AND METHODS

Computational Methodologies

Following the lines of our previous work [12–18], the computational studies were performed with the Gaussian 09 [34] series of programs with density functional methods as implemented in the computational package. The equilibrium geometries of the molecules were determined by means of the gradient technique. The force constants and vibrational frequencies were determined by computing analytical frequencies on the stationary points obtained after the optimization to check if there were true minima. The basis set used in this work was Def2SVP for geometry optimization and frequencies while Def2TZVP was considered for the calculation of the electronic properties [35,36]. For the calculation of the molecular structure and properties of the studied systems, we have chosen

several density functionals from the latest Minnesota density functionals family, which consistently provide satisfactory results for several structural and thermodynamic properties [11]: M11, which is a is a range-separated hybrid meta-GGA [37], M11L, which is a dual-range local meta-GGA [38], MN12L, which is a nonseparable local meta-NGA [39], MN12SX, which is a range-separated hybrid nonseparable meta-NGA [40], N12, which is a nonseparable gradient approximation [41], N12SX, which is a range-separated hybrid nonseparable gradient approximation [40], SOGGA11, which is a GGA density functional [42] and SOGGA11X, which is a hybrid GGA density functional [43]. In these functionals, GGA stands for generalized gradient approximation (in which the density functional depends on the up and down spin densities and their reduced gradient) and NGA stands for nonseparable gradient approximation (in which the density functional depends on the up/down spin densities and their reduced gradient, and also adopts a nonseparable form). All the calculations were performed in the presence of water as a solvent, by doing IEF-PCM computations according to the SMD solvation model [44].

3. RESULTS AND DISCUSSION

3.1 Global Descriptors

The molecular structures of pyridoxamine (PM), 3-hydroxy-4-methylaminopyridine (PMa), pyridoxamine-5'-phosphate (PMP) and pyridoxal-5'-phosphate (PLP) were preoptimized by starting with the readily available MOL structures (ChemSpider: www.chemspider.com, PubChem: https://pubchem.ncbi.nlm.nih.gov/), and finding the most stable conformers by means of the Avogadro 1.2.0 program [45,46] through a random sampling with molecular mechanics techniques and a consideration of all the torsional angles through the general AMBER force field [47]. The structures of the resulting conformers were then reoptimized with the eight density functionals mentioned in the previous section in connection with the Def2SVP basis set and the SMD solvation model, using water as a solvent. The HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of the PM, PMa, PMP and PLP calculated with the M11, M11L, MN12L, MN12SX, N12, N12SX, SOGGA11 and SOGGA11X density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model are presented in Tables D1A to D8A. The upper part of the tables shows the results derived assuming the validity of KID procedure (hence the subscript K) and the lower part shows the results derived from the calculated ΔSCF energies.

Table D1A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the M11 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-6.43	-2.75	4.59	3.68	2.86	8.25	3.66	11.91
PMa	-6.45	-2.84	4.65	3.61	2.99	8.53	3.89	12.42
PLP	-6.92	-3.86	5.39	3.06	4.74	12.37	6.98	19.34
PMP	-6.46	-2.82	4.64	3.64	2.96	8.48	3.83	12.31
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
PM	6.92	2.37	4.65	4.54	2.38	7.36	2.71	10.07
PMa	6.93	2.46	4.69	4.47	2.46	7.55	2.86	10.41
PLP	7.19	3.51	5.35	3.68	3.88	10.67	5.32	15.98
PMP	6.86	2.44	4.65	4.42	2.45	7.49	2.84	10.33

Table D2A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the M11L density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-9.70	-0.05	4.87	9.65	1.23	5.50	0.63	6.13
PMa	-9.94	-0.09	5.01	9.85	1.28	5.68	0.66	6.34
PLP	-9.94	-1.20	5.57	8.73	1.78	6.89	1.31	8.20
PMP	-9.76	-0.11	4.93	9.64	1.26	5.60	0.66	6.26
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
PM	7.22	2.44	4.83	4.77	2.44	7.60	2.77	10.37
PMa	7.63	2.53	5.08	5.11	2.53	7.91	2.83	10.74
PLP	7.50	3.52	5.51	3.98	3.81	10.63	5.12	15.76
PMP	7.28	2.49	4.89	4.79	2.49	7.72	2.84	10.56

Table D3A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the MN12L density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-6.36	-2.38	4.37	3.98	2.40	7.24	2.87	10.10
PMa	-6.36	-2.47	4.41	3.90	2.50	7.45	3.04	10.49
PLP	-6.72	-3.48	5.10	3.24	4.01	10.76	5.67	16.43
PMP	-6.38	-2.44	4.41	3.94	2.47	7.39	2.98	10.37
Property	**I**	**A**	**χ**	**η**	**ω**	ω^-	ω^+	$\Delta\omega^\pm$
PM	6.68	2.07	4.37	4.61	2.08	6.63	2.26	8.89
PMa	6.78	2.16	4.47	4.62	2.16	6.84	2.37	9.21
PLP	7.01	3.15	5.08	3.86	3.34	9.47	4.39	13.85
PMP	6.79	2.11	4.45	4.67	2.12	6.76	2.31	9.06

Table D4A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the MN12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-7.07	-2.28	4.68	4.79	2.28	7.20	2.53	9.73
PMa	-7.13	-2.35	4.74	4.79	2.35	7.36	2.62	9.99
PLP	-7.34	-3.41	5.38	5.38	3.68	10.29	4.91	15.20
PMP	-7.13	-2.36	4.75	4.75	2.36	7.39	2.65	10.04
Property	**I**	**A**	**χ**	**η**	**ω**	ω^-	ω^+	$\Delta\omega^\pm$
PM	7.04	2.32	4.68	4.68	2.32	7.27	2.59	9.87
PMa	6.99	2.39	4.69	4.69	2.39	7.42	2.73	10.15
PLP	7.31	3.44	5.37	5.37	3.73	10.38	5.01	15.39
PMP	6.99	2.39	4.69	4.69	2.39	7.41	2.72	10.14

Table D5A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the N12 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-5.50	-2.64	4.12	2.95	2.87	7.99	3.87	11.87
PMa	-5.65	-2.74	4.20	2.91	3.03	8.33	4.13	12.47
PLP	-6.37	-3.78	5.08	2.59	4.98	12.67	7.59	20.26
PMP	-5.63	-2.70	4.17	2.93	2.97	8.20	4.03	12.23
Property	**I**	**A**	**χ**	**η**	**ω**	ω^-	ω^+	$\Delta\omega^\pm$
PM	6.26	2.15	4.21	4.11	2.15	6.66	2.46	9.12
PMa	6.44	2.33	4.34	4.22	2.23	6.89	2.55	9.44
PLP	6.84	3.32	5.08	3.52	3.66	10.09	5.01	15.10
PMP	6.33	2.21	4.27	4.12	2.21	6.81	2.54	9.35

Table D6A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the N12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-6.71	-2.29	4.50	4.43	2.29	7.10	2.60	9.70
PMa	-6.77	-2.36	4.57	4.41	2.37	7.29	2.72	10.01
PLP	-7.24	-3.44	5.34	3.80	3.76	10.43	5.08	15.51
PMP	-6.74	-2.35	4.54	4.39	2.35	7.25	2.70	9.95
Property	**I**	**A**	**χ**	**η**	**ω**	ω^-	ω^+	$\Delta\omega^\pm$
PM	6.72	2.34	4.53	4.38	2.34	7.22	2.69	9.92
PMa	6.77	2.42	4.60	4.35	2.43	7.42	2.83	10.25
PLP	7.21	3.47	5.34	3.75	3.81	10.52	5.18	15.70
PMP	6.76	2.39	4.58	4.37	2.40	7.36	2.78	10.14

Table D7A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the SOGGA11 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-5.68	-2.00	4.29	2.79	3.30	8.92	4.63	13.55
PMa	-5.73	-3.00	4.37	2.74	3.48	9.32	4.95	14.27
PLP	-6.38	-3.99	5.19	2.39	5.64	14.02	8.83	22.85
PMP	-5.71	-2.94	4.32	2.77	3.38	9.09	4.77	13.87
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
PM	6.47	2.43	4.45	4.04	2.45	7.39	2.93	10.32
PMa	6.61	2.50	4.56	4.11	2.53	7.59	3.04	10.63
PLP	6.99	3.52	5.25	3.48	3.97	10.78	5.53	16.31
PMP	6.53	2.47	4.50	4.05	2.50	7.50	3.00	10.49

Table D8A: HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electronegativity χ, total hardness η, global electrophilicity ω, electrodonating ω^- and electroaccepting ω^+ powers and net electrophilicity $\Delta\omega^\pm$ of PM, PMa, PLP and PMP calculated with the SOGGA11X density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω_K^-	ω_K^+	$\Delta\omega_K^\pm$
PM	-8.00	-1.44	4.72	6.56	1.70	6.17	1.45	7.62
PMa	-8.23	-1.50	4.87	6.74	1.76	6.37	1.50	7.87
PLP	-8.26	-2.57	5.41	5.69	2.58	8,22	2.80	11.02
PMP	-8.04	-1.50	4.77	6.54	1.74	6.26	1.50	7.76
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
PM	7.05	2.39	4.72	4.66	2.39	7.43	2.71	10.15
PMa	7.27	2.47	4.87	4.80	2.47	7.67	2.81	10.48
PLP	7.33	3.47	5.40	3.86	3.77	10.49	5.09	15.58
PMP	7.09	2.43	4.76	4.66	2.43	7.54	2.78	10.32

With the object of analyzing our results and to verify the fulfillment of the KID procedure, we have previously designed several descriptors that relate the results obtained through the HOMO and LUMO calculations with those obtained by means of a ΔSCF procedure. However, it must be stressed that it is not our intention to perform a gap-fitting by minimizing a descriptor by choosing optimal range-separation parameter γ, but to check if the density functionals considered in this study, in which, some of them contain a fixed range-separation parameter γ, obey the KID procedure. As a matter of fact, there is no range-separation parameter γ in our designed descriptors. Moreover, we have considered A as minus the energy of the LUMO of the neutral system instead of considering A as minus the energy of the HOMO of the N+1 electron system, as it was in the mentioned works [48,49].

The first three descriptors are related to the simplest fulfillment of the KID procedure by relating ε_H with -I, ε_L with -A, and the behavior of them in the description of the HOMO-LUMO gap:

$$J_I = \left|\epsilon_H + E_{gs}(N-1) - E_{gs}(N)\right| \tag{15}$$

$$J_A = \left|\epsilon_L + E_{gs}(N) - E_{gs}(N+1)\right| \tag{16}$$

$$J_{HL} = \sqrt{J_I^2 + J_A^2} \tag{17}$$

Next, we consider four other descriptors that analyze how well the studied density functionals are useful for the prediction of the electronegativityχ, the global hardness η and the global electrophilicity ω, and for a combination of these Conceptual DFT descriptors, just considering the energies of the HOMO and LUMO or the ΔSCF:

$$J_\chi = |\chi - \chi_K| \tag{18}$$

$$J_\eta = |\eta - \eta_K| \tag{19}$$

$$J_\omega = |\omega - \omega_K| \tag{20}$$

$$J_{D1} = \sqrt{J_\chi^2 + J_\eta^2 + J_\omega^2} \tag{21}$$

Where D1 stands for the first group of Conceptual DFT descriptors. Finally, we designed other four descriptors to verify the goodness of the studied density functionals for the prediction of the

electroaccepting power ω^+, the electrodonating power ω^-, the net electrophilicity $\Delta\omega^{\pm}$, and for a combination of these Conceptual DFT descriptors, just considering the energies of the HOMO and LUMO or the ΔSCF:

$$J_{\omega^+} = |\omega^+ - \omega_K^+| \tag{22}$$

$$J_{\omega^-} = |\omega^- - \omega_K^-| \tag{23}$$

$$J_{\Delta\omega^{\pm}} = \left|\Delta\omega^{\pm} - \Delta\omega_K^{\pm}\right| \tag{24}$$

$$J_{D2} = \sqrt{J_{\omega^+}^2 + J_{\omega^-}^2 + J_{\Delta\omega^{\pm}}^2} \tag{25}$$

where D2 stands for the second group of Conceptual DFT descriptors.

The results of the calculations of J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, J_{ω^-}, J_{ω^+}, $J_{\Delta\omega^{\pm}}$ and J_{D2} for the PM, PMa, PMP and PLP molecules considered in this work are displayed in Tables D1B to D8B.

Table D1B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, J_{ω^-}, J_{ω^+}, $J_{\Delta\omega^{\pm}}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D1A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	J_{ω^-}	J_{ω^+}	$J_{\Delta\omega^{\pm}}$	J_{D2}
PM	2.49	2.39	3.45	0.05	4.88	1.21	5.03	2.10	2.14	4.24	5.19
PMa	2.31	2.44	3.35	0.06	4.74	1.25	4.90	2.23	2.17	4.40	5.39
PLP	2.44	2.32	3.37	0.06	4.76	2.04	5.18	3.75	3.81	7.56	9.25
PMP	2.48	2.38	3.43	0.05	4.85	1.23	5.00	2.13	2.18	4.30	5.27
Average	2.43	2.38	3.40	0.06	4.81	1.43	5.03	2.55	2.55	5.13	6.28

Table D2B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, J_{ω^-}, J_{ω^+}, $J_{\Delta\omega^{\pm}}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D2A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	J_{ω^-}	J_{ω^+}	$J_{\Delta\omega^{\pm}}$	J_{D2}
PM	0.48	0.38	0.61	0.05	0.86	0.49	0.99	0.89	0.95	1.84	2.25
PMa	0.48	0.38	0.62	0.05	0.87	0.53	1.02	0.98	1.03	2.01	2.46
PLP	0.27	0.35	0.44	0.04	0.62	0.86	1.06	1.70	1.66	3.36	4.12
PMP	0.39	0.39	0.55	0.00	0.78	0.52	0.94	0.99	0.99	1.98	2.42
Average	0.41	0.37	0.56	0.04	0.78	0.60	1.00	1.14	1.16	2.30	2.81

Table D3B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D3A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.31	0.31	0.44	0.00	0.63	0.32	0.70	0.61	0.61	1.22	1.49
PMa	0.42	0.31	0.52	0.05	0.73	0.34	0.80	0.61	0.67	1.28	1.57
PLP	0.29	0.33	0.44	0.02	0.62	0.66	0.91	1.30	1.28	2.58	3.16
PMP	0.40	0.33	0.52	0.04	0.73	0.35	0.81	0.63	0.67	1.30	1.59
Average	0.36	0.32	0.48	0.03	0.67	0.42	0.81	0.79	0.81	1.59	1.95

Table D4B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D4A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.03	0.04	0.05	0.00	0.06	0.04	0.07	0.07	0.07	0.13	0.17
PMa	0.15	0.05	0.15	0.05	0.19	0.05	0.21	0.06	0.11	0.16	0.20
PLP	0.03	0.03	0.04	0.00	0.06	0.05	0.08	0.09	0.10	0.19	0.23
PMP	0.14	0.03	0.14	0.05	0.17	0.03	0.18	0.02	0.08	0.10	0.13
Average	0.09	0.03	0.10	0.03	0.12	0.04	0.13	0.06	0.09	0.15	0.18

Table D5B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D5A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.67	0.49	0.83	0.09	1.16	0.72	1.37	1.33	1.42	2.75	3.37
PMa	0.79	0.52	0.94	0.14	1.31	0.80	1.54	1.44	1.58	3.03	3.71
PLP	0.47	0.46	0.66	0.00	0.94	1.32	1.62	2.58	2.58	5.16	6.31
PMP	0.69	0.50	0.85	0.10	1.19	0.76	1.42	1.39	1.49	2.88	3.53
Average	0.66	0.49	0.82	0.08	1.15	0.90	1.48	1.69	1.77	3.45	4.23

Table D6B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D6A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.01	0.05	0.05	0.03	0.05	0.06	0.08	0.12	0.09	0.21	0.26
PMa	0.00	0.06	0.06	0.03	0.05	0.06	0.09	0.14	0.10	0.24	0.29
PLP	0.03	0.02	0.04	0.00	0.05	0.05	0.07	0.09	0.09	0.19	0.23
PMP	0.02	0.05	0.05	0.03	0.03	0.05	0.06	0.11	0.08	0.19	0.24
Average	0.02	0.04	0.05	0.02	0.04	0.05	0.08	0.12	0.09	0.21	0.25

Table D7B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D7A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.79	0.46	0.91	0.16	1.25	0.85	1.52	1.54	1.70	3.23	3.96
PMa	0.88	0.49	1.01	0.19	1.37	0.95	1.68	1.72	1.92	3.64	4.46
PLP	0.62	0.48	0.78	0.07	1.09	1.67	2.00	3.24	3.31	6.54	8.01
PMP	0.82	0.47	0.94	0.18	1.29	0.88	1.57	1.60	1.77	3.37	4.13
Average	0.78	0.48	0.91	0.15	1.25	1.09	1.69	2.02	2.17	4.20	5.14

Table D8B: Descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, $J_{\omega-}$, $J_{\omega+}$, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PLP and PMP molecules calculated from the results of Table D8A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
PM	0.95	0.95	1.34	0.00	1.90	0.69	2.02	1.26	1.26	2.52	3.09
PMa	0.97	0.97	1.37	0.00	1.94	0.71	2.07	1.30	1.30	2.61	3.19
PLP	0.93	0.90	1.29	0.02	1.83	1.20	2.18	2.27	2.29	4.56	5.59
PMP	0.95	0.94	1.33	0.00	1.88	0.70	2.01	1.28	1.28	2.56	3.13
Average	0.95	0.94	1.33	0.01	1.89	0.82	2.07	1.53	1.53	3.06	3.75

On the basis of the results for the descriptors presented on Tables D1B to D8B, we have compiled the average values for each density functional for PM, PMa, PMP and PLP, and the calculated

results are displayed on Table 1.

Table 1: Average descriptors J_I, J_A, J_{HL}, J_χ, J_η, J_ω, J_{D1}, J_{ω^-}, J_{ω^+}, $J_{\Delta\omega\pm}$ and J_{D2} for the PM, PMa, PMP and PLP molecules calculated with the M11, M11L, MN12L, MN12SX, N12, N12SX, SOGGA11 and SOGGA11X density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	J_{ω^-}	J_{ω^+}	$J_{\Delta\omega\pm}$	J_{D2}
M11	2.43	2.38	3.40	0.06	4.81	1.43	5.03	2.55	2.57	5.13	6.28
M11L	0.41	0.37	0.56	0.04	0.78	0.60	1.00	1.14	1.16	2.30	2.81
MN12L	0.36	0.32	0.48	0.03	0.67	0.42	0.81	0.79	0.81	1.59	1.95
MN12SX	0.09	0.03	0.10	0.03	0.12	0.04	0.13	0.06	0.09	0.15	0.18
N12	0.66	0.49	0.82	0.08	1.15	0.90	1.48	1.69	1.77	3.45	4.23
N12SX	0.02	0.04	0.05	0.02	0.04	0.05	0.08	0.12	0.09	0.21	0.25
SOGGA11	0.78	0.48	0.91	0.15	1.25	1.09	1.69	2.02	2.17	4.20	5.14
SOGGA11X	0.95	0.94	1.33	0.01	1.89	0.82	2.07	1.53	1.53	3.06	3.75

As can be seen from Table 1, the "Koopmans in DFT" (KID) procedure holds with great accuracy for the MN12SX and N12SX density functionals, which are a range-separated hybrid meta-NGA and a range-separated hybrid NGA density functionals, respectively. Indeed, the values of J_I, J_A and J_{HL} are not exactly zero. However, their values can be favorably compared with the results presented for these quantities in the work of Lima et al [49], where the minima have been obtained by choosing a parameter that enforces that behavior.It is interesting that the same density functionals also fulfill the KID procedure for the other descriptors, namely J_χ, J_η, J_ω, and J_{D1}, as well as for J_{ω^-}, J_{ω^+}, $J_{\Delta\omega\pm}$, and J_{D2}. These results are very important, because they show that it is not enough to rely only in J_I, J_A and J_{HL}. For example, if we consider only J_χ, for all the density functionals considered, the values are very close to zero. As for the other descriptors, only the HSEh1PBE, MN12SX and N12SX density functionals show this behavior. That means that the results for J_χ are due to a fortuitous cancellation of errors.The usual GGA (SOGGA11) and hybrid-GGA (SOGGA11X) are not good for the fulfillment of the KID procedure, and the same conclusion is valid for the local functionals M11L, MN12L and N12. An important fact is that although the range-separated hybrid NGA and range-separated hybrid meta-NGA density functionals can be useful for the calculation of the Conceptual DFT descriptors, it is not the same for the range-separated hybrid GGA (M11) density functional. An inspection of Table D1A shows

that this is because this functional describes inadequately the energy of the LUMO, leading to negative values of A, which are in contradiction with the ΔSCF results.

Table 2: Nucleophilic Fukui functions, condensed dual descriptors and nucleophilic Parr functions for the PM, PMa and PMP molecules calculated with the MN12SX and N12SX density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model. MPA: Mulliken Population Analysis - HPA: Hirshfeld Population Analysis.

	MN12SX				**N12SX**			
	f_k^+	Δf_k	$P_k^+(MPA)$	$P_k^+(HPA)$	f_k^+	Δf_k	$P_k^+(MPA)$	$P_k^+(HPA)$
PM	0.75	-0.75	0.84	0.81	0.75	-0.75	0.82	0.79
PMa	0.73	-0.74	0.85	0.82	0.78	-0.77	0.85	0.81
PMP	0.73	-0.75	0.84	0.82	0.74	-0.74	0.82	0.78

3.2 Local Descriptors

The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. The corresponding condensed functions are given by $f_k^+ = q_k(N+1) - q_k(N)$ (for nucleophilic attack), $f_k^- = q_k(N) - q_k(N-1)$ (for electrophilic attack), and $f_k^0 = [q_k(N+1) + q_k(N-1)]/2$ (for radical attack), where q_k is the gross charge of atom k in the molecule. The condensed Fukui functions have been calculated using the AOMix molecular analysis program [50,51] starting from single-point energy calculations. The condensed dual descriptor has been defined as $\Delta f_k = f_k^+ - f_k^-$ [24,25]. From the interpretation given to the Fukui function, one can note that the sign of the dual descriptor is very important to characterize the reactivity of a site within a molecule toward a nucleophilic or an electrophilic attack. That is, if $\Delta f_k > 0$, then the site is favored for a nucleophilic attack, whereas if $\Delta f_k < 0$, then the site may be favored for an electrophilic attack [24,25,52]. The nucleophilic Fukui function f_k^+, the condensed dual descriptor Δf_k and the nucleophilic Parr function P_k^+ over the amino N atoms of the PM, PMa, PLP and PMP molecules calculated with the MN12SX and N12SX density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model are shown in Table 2. For the calculation of the ASD, we have considered both a Mulliken Population Analysis (MPA) [7–10] or a Hirshfeld Population Analysis (HSA) [53–55] modified to render CM5 atomic charges [56]. As the values of the descriptors that arise from Table 2 are very similar, it is hard to say which of the derivatives of PM will be more effective as as inhibitor of the glycation process. However, as the studied systems behave as electrodonating

molecules, we can use the values of the electrodonating power in Tables D3A and D5A to obtain the following trend for their ability to perform as AGEs inhibitors: PMa > PMP >PM. Thus, the modified forms of pyridoxamine (PM), that is, PMa and PMP, will be better glycation inhibitors than the original system.

4. CONCLUSION

The Minnesota family of density functionals (M11, M11L, MN12L, MN12SX, N12, N12SX, SOGGA11 and SOGGA11X) as well as sixteen other usual density functionals have been tested for the fulfillment of the KID procedure by comparison of the HOMO- and LUMO-derived values with those obtained through a ΔSCF procedure. It has been shown that the range-separated hybrid meta-NGA density functional (MN12SX) and the range-separated hybrid NGA density functional (N12SX) are the best for the accomplishment of this objective. As such, they are a good alternative to those density functionals whose behavior have been tuned through a gap-fitting procedure and a good prospect for their usefulness in the description of the chemical reactivity of molecular systems of large size. From the whole of the results presented in this work, it can be say that the sites of interaction of the pyridoxamine molecule and its derivatives can be predicted by using DFT-based reactivity descriptors such as the electronegativity, global hardness, global electrophilicity, electrodonating and electroaccepting powers, net electrophilicity as well as Fukui function, condensed dual descriptor and Parr functions calculations. These descriptors were used in the characterization and successfully description of the preferred reactive sites and provide a firm explanation for the reactivity of those molecules.Moreover, a comparative scale could be established for the ability of the studied compounds in the inhibition of the formation of AGEs. This is based on calculations performed with the MN12SX density functional in connection with the Def2TZVP basis set and the SMD parametrization of the IEF-PCM model using water as a solvent. It can be concluded that this model chemistry (MN12SX/Def2TZVP/SMD(Water)) is the best for fulfilling the KID procedure and for the prediction of the behavior of molecules as potential inhibitors of the formation of AGEs.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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