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Molecular modeling of the structures, properties and glycating power of some reducing disaccharides

Abstract

The molecular structures, properties and glycating power of some reducing disaccharides (Cellobiose, Gentiobiose, Isomaltose, Lactose, Laminaribiose, Maltose, Mannobiose and Xylobiose) have been studied by resorting to Chemical Reactivity Theory including Conceptual DFT and Molecular Electron Density Theory (MEDT). The reactivity sites for nucleophilic and electrophilic attacks have been chosen by relating them to the Fukui function indices, the condensed dual descriptor Δf(r) and the Parr functions. The glycating power of the reducing disaccharides is compared with that of simple hexoses and pentoses through the values of the calculated reactivity descriptors.

Keywords: conceptual DFT, reducing disaccharides, glycating power

Volume 1 Issue 1 - 2017

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Received: February 10, 2017 | **Published:** March 31, 2017

Abbreviations: AGEs, advanced glycation end products; DFT, density functional theory; ASD, atomic spin density

Introduction

The nonenzymatic reaction between amino groups of proteins, lipids and nucleic acids with carbonyl group of reducing sugars is called glycation. Glycation primarily occurs at intra- chain lysine residues of proteins and involves the condensation reaction of the carbonyl group of reducing sugar aldehydes with the amino groups of lysine residues. Several other carbonyl compounds bearing a reducing carbon C atom can behave as glycating agents. The Schiff base formed in the nucleophilic addition reaction if followed by a molecular rearrangement and later to the formation of the so called Advanced Glycation End products (AGEs).

This kind of reactions is amenable of being studied through Conceptual Density Functional Theory (DFT). Conceptual DFT or Chemical Reactivity Theory (as it is also known) is a powerful tool for the prediction, analysis and interpretation of the outcome of chemical reactions.[1–4] Following the works of Adrover et al.[5,6] we have previously studied the chemical reactivity of simple carbohydrates and other glycating carbonyl compounds and found a relationship between the glycating power and the calculated Conceptual DFT descriptors.

From an empirical and practical point of view, for the calculation of the Conceptual DFT descriptors it is meaningful to follow the procedure of assigning the KS HOMO as equal to and opposite of the vertical ionization potential, ε_H=-I and the KS LUMO as equal to and opposite of the vertical electron affinity, ε_L=-A. We have coined the acronym KID for this empirical procedure (for "Koopmans in DFT"). By vertical ionization potential and vertical electron affinity we mean the differences between the energies of the radical cation and the neutral molecule and between the neutral molecule and anion radical respectively, all of them calculated at the geometry of the neutral. This is a necessary condition because the Conceptual DFT descriptors are defined and calculated at constant external potential v(r).

Therefore, we believe that it is worth to extend this kind of studies in order to understand the chemical reactivity of reducing disaccharides (Cellobiose, Gentiobiose, Isomaltose, Lactose, Laminaribiose, Maltose, Mannobiose and Xylobiose). Thus, the objective of this work is to conduct a comparative study of the performance of some recently proposed density functionals[7] for the description of the molecular properties and chemical reactivity of those reducing disaccharides.

Theoretical background

As this work is part of an ongoing project, the theoretical background is similar to that presented in previous research and has been described in detail before[8–16], the chemical potential μ is defined as:

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

Where χ is the electro negativity.

The global chemical hardness is:

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

Using a finite difference approximation and the "Koopmans in DFT" procedure (KID), the former expressions can be written as:

$$\mu = -1/2\left(I + A\right) = 1/2\left(\varepsilon_L + \varepsilon_H\right) = \chi_K \quad (3)$$

$$\eta = \left(I - A\right) = \left(\varepsilon_L - \varepsilon_H\right) = -\eta_K \quad (4)$$

where ε_H and ε_L are the highest occupied and the lowest

unoccupied molecular orbitals, HOMO and LUMO, respectively. In turn, the electrophilicity index ω has been defined as:[17]

$$\omega = \mu^2 / 2\eta = (I+A)^2 / 4(I-A) = (\varepsilon_L + \varepsilon_H)^2 / 4(\varepsilon_L - \varepsilon_H) = \omega_K \quad (5)$$

The condensed Fukui functions can be employed to determine the reactivity of each atom in the molecule. The corresponding condensed functions are given by

$$f_k^+ = q_k(N+1) - q_k(N) \quad (6)$$

(For nucleophilic attack),

$$f_k^- = q_k(N) - q_k(N-1) \quad (7)$$

(for electrophilic attack), and

$$f_k^0 = \left[q_k(N+1) - q_k(N-1)\right] / 2 \quad (7)$$

(for radical attack), where q_k is the gross charge of atom k in the molecule.

The condensed dual descriptor has been defined as[18,19]

$$\Delta f_k = f_k^+ - f_k^- \quad (8)$$

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.[18–20]

In 2013, Domingo proposed the Parr functions P(r)[21,22] which are given by the following equations:

$$P^-(r) = \rho^{rc}(r) \quad \text{(for electrophilic attacks)}$$

and

$$P^+(r) = \rho^{ra}(r)$$

(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.[23]

Settings and computational methods

Following the lines of our previous work and it has been described in detail before,[8-14] all computational studies were performed with the Gaussian 09[24] 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.[25,26]

For the calculation of the molecular structure and properties of the studied systems, we have chosen several density functional from the latest Minnesota density functional family, which consistently provide satisfactory results for several structural and thermodynamic properties:[7] M11, which is a is a range-separated hybrid meta-GGA,[27] M11L, which is a dual-range local meta-GGA,[28] MN12L, which is a nonseparable local meta-NGA,[29] MN12SX, which is a range-separated hybrid nonseparable meta-NGA,[30] N12, which is a nonseparable gradient approximation,[31] N12SX, which is a range-separated hybrid nonseparable gradient approximation,[30] SOGGA11, which is a GGA density functional[32] and SOGGA11X, which is a hybrid GGA density functional.[33] In these functional, 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.[34]

Results and discussion

As a first step, the most stable conformers of the reducing disaccharides Cellobiose, Gentiobiose, Isomaltose, Lactose, Laminaribiose, Maltose, Mannobiose and Xylobiose whose structures are shown in Figure 1 were found by means of the Avogadro 1.2.0 program[35,36] through molecular mechanics calculations. The structures of the resulting conformers were then reoptimized with the density functional mentioned in the previous section in connection with the Def2SVP basis set and the SMD solvation model, using water as a solvent.

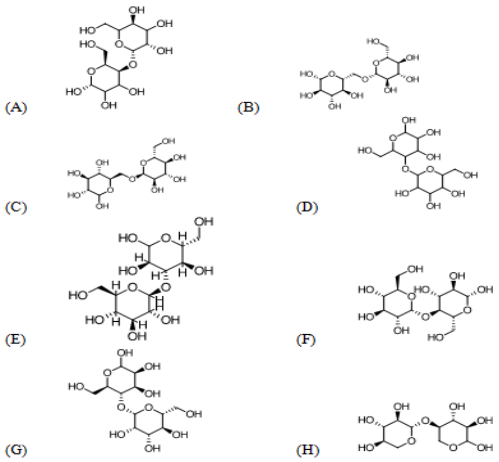

Figure 1 Molecular Structures of A) Cellobiose, B) Gentiobiose, C) Isomaltose, D) Lactose, E) Laminaribiose, F) Maltose, G) Mannobiose and H) Xylobiose.

The next step was to perform single-point energy calculations on the chosen conformers for each reducing disaccharide for the neutral, radical cation and radical anion species, all at the optimized geometry of the neutral molecules, with the M11, M11L, MN12L, MN12SX, N12, N12SX, SOGGA11 and SOGGA11X density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model.

The HOMO and LUMO orbital energies (in eV), ionization potentials I and electron affinities A (in eV), and global electro negativity χ, total hardness η, global electrophilicity ω, electro donating power (ω^-), electro accepting power (ω^+), and net electrophilicity $\Delta\omega^\pm$ of the reducing disaccharides are presented in Tables S1A-S8A of the Electronic Supplementary Information (ESI), showing the results derived assuming the validity of KID procedure (hence the subscript K) and the calculated vertical ΔSCF energies.

With the object of analyzing the behavior of the studied density functional in fulfilling the KID procedure, we have previously designed several accuracy descriptors that relate the results obtained through the HOMO and LUMO calculations with those obtained by means of the vertical I and A with a ΔSCF procedure.[14] The first three descriptors are

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

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

$$J_{HL} = \sqrt{\left(J_I^2 + J_A^2\right)}$$

However, it is convenient to consider next how well the studied density functional are useful for the prediction of the electro negativity χ, the global hardness η and the global electrophilicity ω. Thus another four accuracy descriptors were devised:[14]

$$J_\chi = \left|\chi - \chi_K\right|$$

$$J_\eta = \left|\eta - \eta_K\right|$$

$$J_\omega = \left|\omega - \omega_K\right|$$

$$J_{D1} = \sqrt{\left(J_\chi^2 + J_\eta^2 + J_\omega^2\right)}$$

where D1 stands for the first group of Conceptual DFT descriptors. Moreover, the goodness of the model chemistry considered here in the prediction of the electrodonating power ω^-, the electro accepting power ω^+ and the net electrophilicity $\Delta\omega^\pm$ has been assessed by the following accuracy descriptors:[14]

$$J_{\omega+} = \left|\omega^+ - \omega_K^+\right|$$

$$J_{\omega-} = \left|\omega^- - \omega_K^-\right|$$

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

$$J_{D2} = \sqrt{\left(J_{\omega+}^2 + J_{\omega-}^2 + J_{\Delta\omega\pm}^2\right)}$$

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}, $J_{\omega+}$, $J_{\omega-}$, $J_{\omega\pm}$ and J_{D2} for the reducing disaccharides considered in this work are displayed in Tables S1B-S8B of the Electronic Supplementary Information (ESI). On the basis of the results for the descriptors presented on Tables S1B-S8B of the ESI, we have compiled the average values for each density functional on the whole group of reducing disaccharides and the calculated results are displayed on Table 1.

As can be seen from Table 1, the KID procedure is fulfilled with great accuracy for the MN12SX and N12SX density functional, while the usual GGA (SOGGA11) and hybrid- GGA (SOGGA11X) as well as the M11 and the local functional M11L, MN12L and N12 are not good for the fulfillment of the KID procedure. It is worth to mention that this is the same behavior that we found in our previous studies on simple carbohydrates and reducing carbonyl compounds.

The next step was the calculation of the local reactivity descriptors (LRD) as the condensed Fukui functions, the condensed dual descriptor and the Parr functions. The condensed Fukui functions and condensed dual descriptors have been calculated using the AOMix molecular analysis program.[37,38] The condensed dual descriptors Δf_k and electrophilic Parr functions P_k^+ over the car- bonyl C atoms of the reducing disaccharides calculated with the MN12SX and N12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model are shown in Table 2.

It would be very interesting to find a relationship between the glycation power GP of the reducing disaccharides and the Conceptual DFT descriptors as we have performed in our previous work on simple carbohydrates and carbonyl compounds. Unfortunately, to the best of our knowledge, the experimental rate constants for the reaction of the the disaccharides with the amino group of amino acids and proteins have not been yet reported. Notwithstanding, we believe that it could be possible to apply the previous for simple carbohydrates, that is,

$$GP = a \times \omega + b$$

where a=67.52 and b= -134.33, or

$$GP = a_1 \times \omega + a_2 \times {}_\Delta f_k + b$$

where a_1=94.65, a_2=-29.60 and b=-128.28. In order to do not report negative glycation powers, it is necessary to renormalize both expressions by correcting the parameter b, in both cases, giving b=-125 for the first case and b=-116.60 for the second case.

Using these expressions, the following trend for the glycation power of the reducing disaccharides is found:

Maltose> Mannobiose≈ Xylobiose> Lactose> Cellobiose> Gentiobiose≈ Isomaltose≫ Laminaribiose

Table S1A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a ni-ties A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!*), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the M11 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies.

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^\pm_K$
Cellobiose	-9.859	1.217	4.321	11.076	0.843	4.538	0.217	4.756
Gentiobiose	-10.070	1.274	4.398	11.345	0.853	4.613	0.215	4.828
Isomaltose	-10.070	1.274	4.398	11.344	0.853	4.613	0.215	4.828
Lactose	-9.656	1.155	4.250	10.811	0.835	4.472	0.221	4.693
Laminaribiose	-10.019	1.359	4.330	11.378	0.824	4.524	0.194	4.718
Maltose	-10.039	1.147	4.446	11.186	0.884	4.690	0.243	4.933
Mannobiose	-10.106	1.204	4.451	11.309	0.876	4.684	0.233	4.917
Xylobiose	-10.17	1.231	4.469	11.401	0.876	4.699	0.230	4.929
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
Cellobiose	7.513	1.639	4.576	5.874	1.783	6.22	1.644	7.864
Gentiobiose	7.68	1.583	4.632	6.096	1.759	6.216	1.584	7.800
Isomaltose	7.679	1.584	4.632	6.096	1.760	6.216	1.584	7.800
Lactose	7.328	1.690	4.509	5.638	1.803	6.213	1.704	7.917
Laminaribiose	7.635	1.470	4.553	6.165	1.681	6.024	1.471	7.495
Maltose	7.656	1.613	4.635	6.043	1.777	6.25	1.615	7.865
Mannobiose	7.832	1.646	4.739	6.187	1.815	6.386	1.647	8.033
Xylobiose	7.842	1.616	4.729	6.226	1.796	6.346	1.617	7.963

Table S1B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S1A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	2.35	2.86	3.7	0.26	5.2	0.94	5.29	1.68	1.43	3.11	3.81
Gentiobiose	2.39	2.86	3.73	0.23	5.25	0.91	5.33	1.6	1.37	2.97	3.64
Isomaltose	2.39	2.86	3.73	0.23	5.25	0.91	5.33	1.6	1.37	2.97	3.64
Lactose	2.33	2.85	3.68	0.26	5.17	0.97	5.27	1.74	1.48	3.22	3.95
Laminaribiose	2.38	2.83	3.7	0.22	5.21	0.86	5.29	1.5	1.28	2.78	3.41
Maltose	2.38	2.76	3.65	0.19	5.14	0.89	5.22	1.56	1.37	2.93	3.59
Mannobiose	2.27	2.85	3.65	0.29	5.12	0.94	5.22	1.7	1.41	3.12	3.82
Xylobiose	2.33	2.85	3.68	0.26	5.17	0.92	5.26	1.65	1.39	3.03	3.72
Average	2.35	2.84	3.69	0.24	5.19	0.92	5.28	1.63	1.39	3.02	3.7

Citation: Frau J, Mitnik DG. Molecular modeling of the structures, properties and glycating power of some reducing disaccharides. *MOJ Drug Des Develop Ther.* 2017;1(1):12–24. DOI: 10.15406/mojddt.2017.01.00003

Table S2A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a ni-ties A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! Of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the M11L density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^\pm_K$
Cellobiose	-6.385	-1.84	4.112	4.545	1.86	6.06	1.948	8.009
Gentiobiose	-6.557	-1.811	4.184	4.746	1.844	6.077	1.893	7.97
Isomaltose	-6.557	-1.812	4.184	4.745	1.845	6.079	1.894	7.973
Lactose	-6.124	-1.92	4.022	4.204	1.924	6.121	2.099	8.22
Laminaribiose	-6.469	-1.656	4.062	4.813	1.715	5.761	1.699	7.46
Maltose	-6.477	-1.859	4.168	4.618	1.881	6.135	1.967	8.101
Mannobiose	-6.555	-1.854	4.204	4.701	1.88	6.157	1.952	8.109
Xylobiose	-6.599	-1.842	4.22	4.757	1.872	6.151	1.931	8.083
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
Cellobiose	6.595	1.533	4.064	5.061	1.632	5.612	1.548	7.16
Gentiobiose	6.759	1.461	4.11	5.297	1.594	5.575	1.465	7.04
Isomaltose	6.76	1.462	4.111	5.297	1.595	5.576	1.466	7.042
Lactose	6.408	1.592	4	4.816	1.661	5.623	1.623	7.246
Laminaribiose	6.685	1.341	4.013	5.344	1.507	5.355	1.341	6.696
Maltose	6.699	1.544	4.122	5.155	1.647	5.678	1.556	7.234
Mannobiose	6.717	1.537	4.127	5.181	1.644	5.675	1.548	7.224
Xylobiose	6.796	1.528	4.162	5.268	1.644	5.698	1.536	7.235

Table S2B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S2A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.21	0.31	0.37	0.05	0.52	0.23	0.57	0.45	0.4	0.85	1.04
Gentiobiose	0.2	0.35	0.4	0.07	0.55	0.25	0.61	0.5	0.43	0.93	1.14
Isomaltose	0.2	0.35	0.4	0.07	0.55	0.25	0.61	0.5	0.43	0.93	1.14
Lactose	0.28	0.33	0.43	0.02	0.61	0.26	0.67	0.5	0.48	0.97	1.19
Laminaribiose	0.22	0.31	0.38	0.05	0.53	0.21	0.57	0.41	0.36	0.76	0.94
Maltose	0.22	0.32	0.39	0.05	0.54	0.23	0.59	0.46	0.41	0.87	1.06
Mannobiose	0.16	0.32	0.36	0.08	0.48	0.24	0.54	0.48	0.4	0.89	1.09
Xylobiose	0.2	0.31	0.37	0.06	0.51	0.23	0.56	0.45	0.39	0.85	1.04
Average	0.21	0.32	0.39	0.06	0.54	0.24	0.59	0.47	0.41	0.88	1.08

Table S3A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a nities A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the MN12L density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^\pm_K$
Cellobiose	-6.254	-1.463	3.858	4.791	1.553	5.335	1.477	6.813
Gentiobiose	-6.489	-1.481	3.985	5.008	1.585	5.476	1.491	6.967
Isomaltose	-6.494	-1.455	3.975	5.039	1.568	5.438	1.463	6.901
Lactose	-6.192	-1.573	3.882	4.619	1.632	5.493	1.611	7.104
Laminaribiose	-6.354	-1.322	3.838	5.032	1.464	5.161	1.323	6.484
Maltose	-6.333	-1.509	3.921	4.825	1.593	5.449	1.528	6.977
Mannobiose	-6.425	-1.5	3.963	4.924	1.594	5.478	1.515	6.993
Xylobiose	-6.488	-1.479	3.984	5.008	1.584	5.473	1.49	6.963
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
Cellobiose	6.458	1.219	3.839	5.24	1.406	5.059	1.22	6.279
Gentiobiose	6.685	1.193	3.939	5.492	1.412	5.138	1.199	6.336
Isomaltose	6.651	1.16	3.906	5.491	1.389	5.074	1.169	6.243
Lactose	6.454	1.296	3.875	5.158	1.455	5.171	1.296	6.467
Laminaribiose	6.577	1.059	3.818	5.518	1.321	4.896	1.078	5.973
Maltose	6.728	1.207	3.968	5.52	1.426	5.181	1.213	6.393
Mannobiose	6.58	1.243	3.911	5.336	1.433	5.156	1.245	6.401
Xylobiose	6.667	1.224	3.946	5.443	1.43	5.173	1.228	6.401

Table S3B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S3A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.2	0.24	0.32	0.02	0.45	0.15	0.47	0.28	0.26	0.53	0.65
Gentiobiose	0.2	0.29	0.35	0.05	0.48	0.17	0.52	0.34	0.29	0.63	0.77
Isomaltose	0.16	0.29	0.33	0.07	0.45	0.18	0.49	0.36	0.29	0.66	0.81
Lactose	0.26	0.28	0.38	0.01	0.54	0.18	0.57	0.32	0.31	0.64	0.78
Laminaribiose	0.22	0.26	0.35	0.02	0.49	0.14	0.51	0.27	0.25	0.51	0.63
Maltose	0.39	0.3	0.5	0.05	0.7	0.17	0.72	0.27	0.32	0.58	0.72
Mannobiose	0.16	0.26	0.3	0.05	0.41	0.16	0.45	0.32	0.27	0.59	0.73
Xylobiose	0.18	0.26	0.31	0.04	0.43	0.15	0.46	0.3	0.26	0.56	0.69
Average	0.22	0.27	0.35	0.04	0.49	0.16	0.52	0.31	0.28	0.59	0.72

Table S4A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a nities A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the MN12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^\pm_K$
Cellobiose	-7.064	-1.262	4.163	5.802	1.494	5.431	1.268	6.7
Gentiobiose	-7.337	-1.197	4.267	6.14	1.483	5.483	1.216	6.698
Isomaltose	-7.337	-1.197	4.267	6.14	1.483	5.482	1.215	6.698
Lactose	-6.819	-1.319	4.069	5.499	1.505	5.389	1.32	6.709
Laminaribiose	-7.153	-1.126	4.139	6.027	1.421	5.289	1.15	6.439
Maltose	-7.163	-1.32	4.241	5.843	1.539	5.565	1.323	6.888
Mannobiose	-7.255	-1.281	4.268	5.973	1.525	5.557	1.289	6.845
Xylobiose	-7.317	-1.266	4.291	6.051	1.522	5.567	1.276	6.843
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
Cellobiose	7.036	1.46	4.248	5.576	1.618	5.709	1.461	7.171
Gentiobiose	7.297	1.39	4.343	5.906	1.597	5.735	1.392	7.126
Isomaltose	7.296	1.39	4.343	5.906	1.597	5.734	1.391	7.126
Lactose	6.787	1.515	4.151	5.272	1.634	5.673	1.522	7.195
Laminaribiose	7.109	1.307	4.208	5.802	1.526	5.519	1.311	6.83
Maltose	7.137	1.483	4.31	5.654	1.643	5.794	1.484	7.277
Mannobiose	7.237	1.473	4.355	5.764	1.646	5.829	1.474	7.303
Xylobiose	7.282	1.457	4.369	5.826	1.639	5.826	1.457	7.283

Table S4B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, J$\Delta\omega$+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S4A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.03	0.2	0.2	0.08	0.23	0.12	0.27	0.28	0.19	0.47	0.58
Gentiobiose	0.04	0.19	0.2	0.08	0.23	0.11	0.27	0.25	0.18	0.43	0.53
Isomaltose	0.04	0.19	0.2	0.08	0.23	0.11	0.27	0.25	0.18	0.43	0.53
Lactose	0.03	0.2	0.2	0.08	0.23	0.13	0.27	0.28	0.2	0.49	0.6
Laminaribiose	0.04	0.18	0.19	0.07	0.23	0.1	0.26	0.23	0.16	0.39	0.48
Maltose	0.03	0.16	0.16	0.07	0.19	0.1	0.23	0.23	0.16	0.39	0.48
Mannobiose	0.02	0.19	0.19	0.09	0.21	0.12	0.26	0.27	0.18	0.46	0.56
Xylobiose	0.03	0.19	0.19	0.08	0.23	0.12	0.27	0.26	0.18	0.44	0.54
Average	0.03	0.19	0.19	0.08	0.22	0.12	0.26	0.26	0.18	0.44	0.54

Table S5A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a nities A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! Of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the N12 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^\pm_K$
Cellobiose	-5.611	-2.038	3.824	3.574	2.046	6.228	2.404	8.632
Gentiobiose	-5.918	-2.031	3.975	3.887	2.032	6.295	2.32	8.615
Isomaltose	-5.918	-2.031	3.975	3.887	2.032	6.295	2.32	8.615
Lactose	-5.523	-1.901	3.712	3.623	1.902	5.886	2.174	8.06
Laminaribiose	-5.734	-1.822	3.778	3.912	1.824	5.782	2.004	7.785
Maltose	-5.654	-1.983	3.819	3.671	1.986	6.111	2.292	8.403
Mannobiose	-5.921	-2.014	3.967	3.907	2.014	6.256	2.289	8.545
Xylobiose	-5.93	-1.977	3.954	3.954	1.977	6.178	2.224	8.402
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^\pm$
Cellobiose	5.922	1.348	3.635	4.574	1.444	4.991	1.357	6.348
Gentiobiose	6.178	1.319	3.749	4.859	1.446	5.07	1.321	6.391
Isomaltose	6.178	1.319	3.749	4.859	1.446	5.07	1.321	6.391
Lactose	5.804	1.212	3.508	4.592	1.34	4.72	1.213	5.933
Laminaribiose	5.964	1.155	3.56	4.809	1.317	4.715	1.156	5.871
Maltose	5.88	1.281	3.58	4.599	1.394	4.865	1.285	6.149
Mannobiose	6.111	1.321	3.716	4.79	1.441	5.04	1.324	6.364
Xylobiose	6.185	1.289	3.737	4.895	1.426	5.027	1.29	6.317

Table S5B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S5A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.31	0.69	0.76	0.19	1	0.6	1.18	1.24	1.05	2.28	2.8
Gentiobiose	0.26	0.71	0.76	0.23	0.97	0.59	1.16	1.22	1	2.22	2.73
Isomaltose	0.26	0.71	0.76	0.23	0.97	0.59	1.16	1.22	1	2.22	2.73
Lactose	0.28	0.69	0.74	0.2	0.97	0.56	1.14	1.17	0.96	2.13	2.61
Laminaribiose	0.23	0.67	0.71	0.22	0.9	0.51	1.05	1.07	0.85	1.91	2.35
Maltose	0.23	0.7	0.74	0.24	0.93	0.59	1.13	1.25	1.01	2.25	2.77
Mannobiose	0.19	0.69	0.72	0.25	0.88	0.57	1.08	1.22	0.96	2.18	2.68
Xylobiose	0.25	0.69	0.73	0.22	0.94	0.55	1.11	1.15	0.93	2.08	2.56
Average	0.25	0.69	0.74	0.22	0.95	0.57	1.13	1.19	0.97	2.16	2.65

Table S6A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a nities A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the N12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^{\pm}_K$
Cellobiose	-6.711	-1.355	4.033	5.356	1.518	5.388	1.355	6.743
Gentiobiose	-7.089	-1.32	4.204	5.769	1.532	5.527	1.323	6.85
Isomaltose	-7.089	-1.32	4.204	5.769	1.532	5.527	1.322	6.849
Lactose	-6.569	-1.401	3.985	5.168	1.536	5.389	1.403	6.792
Laminaribiose	-6.846	-1.203	4.024	5.643	1.435	5.235	1.21	6.445
Maltose	-6.976	-1.35	4.163	5.626	1.54	5.514	1.351	6.865
Mannobiose	-7.043	-1.333	4.188	5.71	1.536	5.523	1.335	6.857
Xylobiose	-7.083	-1.304	4.194	5.779	1.522	5.501	1.307	6.808
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^{\pm}$
Cellobiose	6.708	1.496	4.102	5.212	1.614	5.605	1.503	7.108
Gentiobiose	7.079	1.455	4.267	5.624	1.619	5.723	1.456	7.178
Isomaltose	7.079	1.455	4.267	5.624	1.619	5.722	1.455	7.178
Lactose	6.568	1.538	4.053	5.031	1.633	5.607	1.554	7.16
Laminaribiose	6.836	1.343	4.089	5.493	1.522	5.432	1.343	6.775
Maltose	6.965	1.471	4.218	5.494	1.619	5.691	1.473	7.163
Mannobiose	7.039	1.472	4.256	5.566	1.627	5.729	1.474	7.203
Xylobiose	7.07	1.444	4.257	5.626	1.611	5.702	1.445	7.146

Table S6B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, J$\Delta\omega$+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S6A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0	0.14	0.14	0.07	0.14	0.1	0.19	0.22	0.15	0.37	0.45
Gentiobiose	0.01	0.14	0.14	0.06	0.14	0.09	0.18	0.2	0.13	0.33	0.4
Isomaltose	0.01	0.14	0.14	0.06	0.14	0.09	0.18	0.2	0.13	0.33	0.41
Lactose	0	0.14	0.14	0.07	0.14	0.1	0.18	0.22	0.15	0.37	0.45
Laminaribiose	0.01	0.14	0.14	0.06	0.15	0.09	0.19	0.2	0.13	0.33	0.41
Maltose	0.01	0.12	0.12	0.06	0.13	0.08	0.16	0.18	0.12	0.3	0.37
Mannobiose	0	0.14	0.14	0.07	0.14	0.09	0.18	0.21	0.14	0.35	0.43
Xylobiose	0.01	0.14	0.14	0.06	0.15	0.09	0.19	0.2	0.14	0.34	0.42
Average	0.01	0.14	0.14	0.06	0.14	0.09	0.18	0.2	0.14	0.34	0.42

Table S7A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a ni-ties A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the SOGGA11 density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model. The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^{\pm}_K$
Cellobiose	-5.605	-2.271	3.938	3.334	2.326	6.829	2.891	9.72
Gentiobiose	-5.754	-2.235	3.994	3.519	2.267	6.751	2.757	9.508
Isomaltose	-5.754	-2.235	3.994	3.519	2.267	6.751	2.757	9.508
Lactose	-5.509	-2.173	3.841	3.336	2.211	6.551	2.71	9.261
Laminaribiose	-5.711	-2.032	3.871	3.679	2.037	6.239	2.368	8.606
Maltose	-5.58	-2.095	3.838	3.484	2.113	6.363	2.525	8.888
Mannobiose	-5.812	-2.237	4.024	3.575	2.265	6.765	2.741	9.506
Xylobiose	-5.876	-2.243	4.059	3.632	2.268	6.793	2.734	9.527
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^{\pm}$
Cellobiose	5.874	1.511	3.693	4.363	1.563	5.245	1.552	6.797
Gentiobiose	6.035	1.522	3.778	4.513	1.581	5.334	1.556	6.89
Isomaltose	6.035	1.522	3.778	4.513	1.581	5.334	1.556	6.89
Lactose	5.84	1.571	3.706	4.269	1.608	5.336	1.631	6.967
Laminaribiose	5.969	1.286	3.627	4.683	1.405	4.915	1.288	6.204
Maltose	5.818	1.42	3.619	4.398	1.489	5.063	1.444	6.507
Mannobiose	6.029	1.461	3.745	4.568	1.535	5.228	1.483	6.711
Xylobiose	6.163	1.518	3.84	4.645	1.588	5.386	1.545	6.931

Table S7B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, J$\Delta\omega$+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S7A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.27	0.76	0.81	0.25	1.03	0.76	1.3	1.58	1.34	2.92	3.58
Gentiobiose	0.28	0.71	0.77	0.22	0.99	0.69	1.23	1.42	1.2	2.62	3.21
Isomaltose	0.28	0.71	0.77	0.22	0.99	0.69	1.23	1.42	1.2	2.62	3.21
Lactose	0.33	0.6	0.69	0.14	0.93	0.6	1.12	1.21	1.08	2.29	2.81
Laminaribiose	0.26	0.75	0.79	0.24	1	0.63	1.21	1.32	1.08	2.4	2.95
Maltose	0.24	0.67	0.72	0.22	0.91	0.62	1.13	1.3	1.08	2.38	2.92
Mannobiose	0.22	0.78	0.81	0.28	0.99	0.73	1.26	1.54	1.26	2.79	3.43
Xylobiose	0.29	0.73	0.78	0.22	1.01	0.68	1.24	1.41	1.19	2.6	3.18
Average	0.27	0.71	0.76	0.22	0.98	0.68	1.21	1.4	1.18	2.58	3.16

Table S8A HOMO and LUMO orbital energies (in eV), ionization potentials I and electron a nities A (in eV), and global electro negativity, total chemical hardness, global electrophilicity!, electro donating power (!), electro accepting power (!+), and net electrophilicity ! of cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose calculated with the SOGGA11X density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model.The upper part of the table shows the results derived assuming the validity of the KID procedure and the lower part shows the results derived from the calculated vertical SCF energies

Property	**HOMO**	**LUMO**	χ_K	η_K	ω_K	ω^-_K	ω^+_K	$\Delta\omega^{\pm}_K$
Cellobiose	-8.086	-0.28	4.183	7.806	1.121	4.821	0.638	5.459
Gentiobiose	-8.458	-0.222	4.34	8.237	1.143	4.971	0.632	5.603
Isomaltose	-8.458	-0.221	4.34	8.237	1.143	4.971	0.631	5.602
Lactose	-7.936	-0.32	4.128	7.616	1.119	4.777	0.649	5.427
Laminaribiose	-8.181	-0.142	4.162	8.039	1.077	4.738	0.576	5.314
Maltose	-8.269	-0.306	4.287	7.962	1.154	4.95	0.663	5.613
Mannobiose	-8.389	-0.263	4.326	8.126	1.151	4.974	0.648	5.622
Xylobiose	-8.454	-0.25	4.352	8.204	1.154	4.997	0.645	5.642
Property	**I**	**A**	χ	η	ω	ω^-	ω^+	$\Delta\omega^{\pm}$
Cellobiose	7.188	1.517	4.353	5.672	1.67	5.871	1.518	7.39
Gentiobiose	7.527	1.452	4.489	6.075	1.659	5.942	1.452	7.394
Isomaltose	7.526	1.452	4.489	6.075	1.659	5.941	1.452	7.394
Lactose	7.066	1.546	4.306	5.52	1.679	5.856	1.551	7.407
Laminaribiose	7.389	1.353	4.371	6.036	1.583	5.728	1.357	7.085
Maltose	7.406	1.465	4.436	5.941	1.656	5.901	1.466	7.367
Mannobiose	7.558	1.495	4.526	6.063	1.69	6.021	1.495	7.516
Xylobiose	7.587	1.479	4.533	6.108	1.682	6.012	1.479	7.492

Table S8B Descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose molecules calculated from the results of Table S8A

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega\pm}$	J_{D2}
Cellobiose	0.9	1.24	1.53	0.17	2.13	0.55	2.21	1.05	0.88	1.93	2.37
Gentiobiose	0.93	1.23	1.54	0.15	2.16	0.52	2.23	0.97	0.82	1.79	2.2
Isomaltose	0.93	1.23	1.54	0.15	2.16	0.52	2.23	0.97	0.82	1.79	2.2
Lactose	0.87	1.23	1.5	0.18	2.1	0.56	2.18	1.08	0.9	1.98	2.43
Laminaribiose	0.79	1.21	1.45	0.21	2	0.51	2.08	0.99	0.78	1.77	2.17
Maltose	0.86	1.16	1.44	0.15	2.02	0.5	2.09	0.95	0.8	1.75	2.15
Mannobiose	0.83	1.23	1.49	0.2	2.06	0.54	2.14	1.05	0.85	1.89	2.32
Xylobiose	0.87	1.23	1.5	0.18	2.1	0.53	2.17	1.02	0.83	1.85	2.27
Average	0.87	1.22	1.5	0.17	2.09	0.53	2.16	1.01	0.84	1.85	2.26

Citation: Frau J, Mitnik DG. Molecular modeling of the structures, properties and glycating power of some reducing disaccharides. *MOJ Drug Des Develop Ther.* 2017;1(1):12–24. DOI: 10.15406/mojddt.2017.01.00003

Table 1 Average descriptors JI, JA, JHL, Jχ, Jη, Jω, JD1, Jω-, Jω+, JΔω+ and JD2 for the reducing disaccharides calculated with the eight density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parameterization of the IEF-PCM model

	J_I	J_A	J_{HL}	J_χ	J_η	J_ω	J_{D1}	$J_{\omega-}$	$J_{\omega+}$	$J_{\Delta\omega+}$	J_{D2}
M11	2.35	2.84	3.69	0.24	5.19	0.92	5.28	1.63	1.39	3.02	3.70
M11L	0.21	0.32	0.39	0.06	0.54	0.24	0.59	0.47	0.41	0.88	1.08
MN12L	0.22	0.27	0.35	0.04	0.49	0.16	0.52	0.31	0.28	0.59	0.72
MN12SX	0.03	0.19	0.19	0.08	0.22	0.12	0.26	0.26	0.18	0.44	0.54
N12	0.25	0.69	0.74	0.22	0.95	0.57	1.13	1.19	0.97	2.16	2.65
N12SX	0.01	0.14	0.14	0.06	0.14	0.09	0.18	0.2	0.14	0.34	0.42
SOGGA11	0.27	0.71	0.76	0.22	0.98	0.58	1.21	1.4	1.18	2.58	3.16
SOGGA11X	0.87	1.22	1.5	0.17	2.09	0.63	2.16	1.01	0.84	1.85	2.26

Table 2 Condensed dual descriptors ΔfK and electrophilic Parr functions P_k^+ for cellobiose, gentiobiose, isomaltose, lactose, laminaribiose, maltose, mannobiose and xylobiose 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		
	Δf_K	P^+_K(MPA)	P^+_K(HPA)	Δf_K	P^+_K(MPA)	P^+_K(HPA)
Cellobiose	0.637	0.739	0.548	0.635	0.691	0.558
Gentiobiose	0.640	0.756	0.560	0.635	0.697	0.564
Isomaltose	0.640	0.756	0.560	0.637	0.697	0.564
Lactose	0.630	0.732	0.548	0.626	0.686	0.558
Laminaribiose	0.606	0.711	0.566	0.603	0.681	0.568
Maltose	0.612	0.744	0.531	0.626	0.692	0.554
Mannobiose	0.618	0.747	0.548	0.613	0.696	0.559
Xylobiose	0.616	0.75	0.547	0.625	0.697	0.558

Conclusion

The main conclusion from our work is that the quality of the model chemistry employed in the study of the chemical reactivity of reducing disaccharides that are susceptible to go into the Maillard reaction could be determined by resorting to some previously designed accuracy descriptors. With the object in mind of fulfilling the KID procedure, it has been established 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. Thus, it has been demonstrated that the tuning of the behavior of a density functional through a gap-fitting procedure can be avoided by selecting any of these density functional that represent a good prospect for their usefulness in the description of the chemical reactivity of molecular systems of large size.

Moreover, on the basis of previous studies, a trend for the glycating power GP of the reducing disaccharides has been found, being maltose the most powerful, with lactose in an intermediate level and laminaribiose with almost non GP. It is expected that these conclusions could be extended to larger glycating molecular systems.

This knowledge could be helpful in the design and development of new drugs useful as inhibitors of the formation of AGEs by interfering with the glycation process. Although only a few reducing disaccharides have been considered in this work, the ideas presented here could be extended to other potential similar molecules which mode of action is unknown leading to the design and development of specific drugs for every case under study.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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