LOGISTIC KINETIC MODEL FOR CHLORINATED POLY AROMATIC HYDROCARBONS (CLPAHS) ACTIVITY IN CANCER SIGNALING

Ana-Maria Putz[1,2], Mihai V. Putz[3]

[1]Institute of Chemistry Timisoara of the Romanian Academy, 24 Mihai Viteazul Bld., RO-300223, Timisoara, putzanamaria@yahoo.com

[2]Nicolas Georgescu-Roegen Forming and Research Center of West University of Timişoara, 4th, Oituz Street, Timişoara, RO-300086, Romania

[3]Laboratory of Computational and Structural Physical Chemistry, Chemistry Department, West University of Timişoara, Pestalozzi Street No.16, Timişoara, RO-300115, Romania

ABSTRACT

The logistic kinetics model of quantitative structure-activity relationships was here implemented for modeling the depletion of the ClPAHs in MCF-7 cells; it was found that the best statistical performances are given by polarizability, electronegativity and hydrophobicity within density functional framework, through a mono-linear Spectra-SAR analysis.

Keywords: enzyme kinetics; QSAR; algebraic norm; EROL activity; DFT structure computation; PM3 semiempirical computation

INTODUCTION

The time-evolution binding substrate, of chlorinated polycyclic aromatic hydrocarbons (ClPAHs) with aryl hydrocarbon receptor (AhR) in expressing of the cytochrome P450 (CYP) 1 family, CYP1A1 and 1B1, in human breast cancer MCF-7 cells, is accomplished. This aim is achieved through combining the recent advanced logistic form of substrate-enzyme kinetics with the spectral-structure activity relationships (S-SAR), while semiempirical and density functional structure properties are comparatively considered. The ClPAHs under concern are: 9-chlorophenantrene(9-ClPhe),9,10-dichlorophenantrene(9,10-Cl_2Phe), 3,9,10-trichlorophenantrene (3,9,10-Cl_3 Phe), 1-chloropyrene (1-ClPy) and 6-chlorobenzo[a]pyrene (6-ClBaP).

The Logistic Kinetics [1]

The mechanism of the biological activity produced by a substance usually involve the combination between the molecules of those substance, called effector or ligand (L) with a receptor (R), a protein, a biologically macromolecule, a complex of macromolecules from within of cell. The intensity of the biological action is illustrated in a ordinary way as logarithm of inverse of the concentration C which produce a specify biological answer, that is mean: A=Log (1/C) (1). In many situations C_{50} concentration is used, that mean those molar concentration that produce 50% from the maximum biological activity. It could be shown that the biological activity, A, is proportional with the affinity of the molecule or of the ligand, L_i for the receptor, R, which stay at the basis of explicated biological action. The most rational hypothesis concerning the mode of action of the bioactive substances presumes that the biological activity produce by a ligand L is proportional with the complexation degree of the receptor R from the L. In this situation, the presuming a biological activity of α% (comparing from the maximum of 100%) is produced by a concentration, [L] of ligand. Therefore, we may safety generalize the chemical-biological-kinetics in terms of the general rate of biological uptake β respecting the chemical concentration $[S]$: $\beta = \frac{\beta_{max}[S]}{[S]+EC_{50}}$ (2). Recognizing in equation (2) the temporal link between the

biological activity and chemical concentration stands as: $\beta = -\frac{d}{dt}[S](t)$ (3), the full temporal version of it can be widely formulated as [2-8]: $\boxed{-\frac{d}{dt}[S](t) = \frac{\beta_{\max}[S](t)}{[S](t) + EC_{50}}}$ (4). However, the main problem with the equation (4) is that it accounts only for the velocity of the initial time of the reaction. The information that is outside the first moments of the inherent progress curve is virtually lost or neglected. Instead, a further generalized kinetics may be assumed, which was recently applied to enzymic Michaelis-Menten case too [9-10], namely: $\boxed{-\frac{d}{dt}[S](t) = \beta_{\max}\left(1 - e^{-\frac{[S](t)}{EC_{50}}}\right)}$ (5) that is clearly reduced to the above equation (4) in the first order expansion of the chemical concentration time evolution respecting the 50-effect concentration (EC_{50}) observed. Although the original chemical-biological-kinetics (4) leads with no analytical solution the actual working kinetics (5) provides the so called logistical solution under the form [9]: $\boxed{[S](t) = EC_{50} \ln\left(1 + e^{-\frac{\beta_{\max}}{EC_{50}}\left(e^{\frac{1}{1-\tau}} - e\right)}\left(e^{\frac{[S_0]}{EC_{50}}} - 1\right)\right)}$ (6) where the time τ is of asymptotic nature and is related with the real one by the relationship: $\boxed{t = e^{\frac{1}{1-\tau}} - e \to \begin{cases} 0...\tau \to 0 \\ \infty...\tau \to 1 \end{cases}}$ (7). The reliability of the logistic solution (6) with (7) was previously tested on enzyme kinetics, within various mechanism, with remarkable results [9-10] thus constituting a trusted background for employing it to the envisaged currently ecotoxicological studies. It gives the actual logistic related chemical-biological Cl-PAH evolution amplitude providing the related kinetic parameters are further identified through a specific QSAR study. This will be achieved through employing the Spectral-SAR methodology as next unfolded.

The Logistic-QSAR METHOD

The logistic-spectral analysis the next steps are assumed: for the activities of their vectorial form is achieved through applying of the Spectral-SAR algorithm [1,11]: $\boxed{|Y_i\rangle^{ENDPOINT} = B_0|X_0\rangle + B_1|X_1\rangle + ...,}$ (8) the predicted spectral norm can be draw, $\left\| Y_i \right\rangle\|$, for each envisaged i-set or model of structural parameters;the initial chemical concentration of logistical chemical-biological progress curve equation is identified with the predicted S-SAR activity norms: $\boxed{[S_{0(i)}] \to \left\| Y_i \right\rangle^{ENDPOINT}\|}$ (9); based on idea that the evolution of the chemical concentration producing a biological effect starts evolving from the predicted (computed) activity and diminished in time under the environmental and bio-degrability effects; in the same heuristically line the real maximum biological effect in chemical-biological equation would be seen as the positive reminiscence of the predicted S-SAR activity against the measured activity: $\boxed{\beta_{\max(i)} \to \sqrt{\left(\left\| Y_i \right\rangle^{ENDPOINT}\| - \left\| Y_i \right\rangle^{EXP}\|\right)^2}}$ (10); in these conditions, the computational EC_{50} parameter of chemical-biological equation is as well considered as the positive reminiscence of the of the predicted S-SAR activity against its average activity: $\boxed{EC_{50(i)} \to \sqrt{\left(\left\| Y_i \right\rangle\| - \overline{|Y_i\rangle}^{ENDPOINT}\right)^2}}$ (11).

RESULTS AND DISCUSSIONS

For the concerned molecules the ethoxyresorufin-O-deethylase (EROD) activities according with generic mechanism of AhR-mediated toxicity [12], along the energetic, polarizability and hydrophobic quantum computational structural parameters, are in Table 1 provided. The generic

mechanism of AhR-mediated toxicity is as follow: AhR mediates the signal transduction by dioxin-like ligands, which forms a transcription factor complex with an aryl hydrocarbon nuclear translocator protein (ARNT); this is a heterodimer that recognizes specific DNA sequences, namely dioxin responsive elements (DRE), and leads to the induction of several genes forming the so called Ah gene battery; in this process, the elevated levels of the protein products are assumed to be involved in the toxic action of AhR ligands [12].

Table 1. The structural parameters for the ClPAH as: highest occupied molecular orbital, HOMO, lowest unoccupied molecular orbital, LUMO, electronegativity, EL=-0.5(HOMO+LUMO), chemical hardness, HD=0.5(LUMO-HOMO), polarizability, POL, and hydrophobicity, LogP. Both density functional theory (DFT), single point and large basis (6-31-G**, B3-LYP) and semiempirical PM3 results are respectively presented, while EROD (ethoxyresorufin-O-deethylase) activity is taken from literature as the relative intensity of ClPAH-induced cytochrome P450 (CYP) activity in human breast cancer MCF-7 cells upon a cellular mechanism unfolded in generic mechanism of AhR-mediated toxicity.

Cl-PAH, (EROD Activity)	Method	HOMO [eV]	LUMO [eV]	EL [eV]	HD[eV]	LogP	POL [Å^3]
9-ClPhe	DFT	-5.782162	-1.124612	3.453387	2.328775	4.57	26.9
(1.2)	PM3	-8.7341	-0.7318015	4.73295075	4.00114925	4.57	26.9
9,10-Cl_2Phe	DFT	-5.85749	-1.304734	3.581112	2.276378	5.09	28.83
(1.4)	PM3	-8.697529	-0.8940602	4.7957946	3.9017344	5.09	28.83
3,9,10-Cl_3Phe	DFT	-5.928534	-1.480939	3.7047365	2.2237975	5.61	30.76
(4.4)	PM3	-8.721235	-1.041793	4.881514	3.839721	5.61	30.76
1-ClPy	DFT	-5.364024	-1.539531	3.4517775	1.9122465	4.89	30.69
(1.3)	PM3	-8.267601	-1.16701	4.7173055	3.5502955	4.89	30.69
6-ClBaP	DFT	-216.9655	-213.0821	215.0238	1.9417	5.89	37.96
(9)	PM3	-8.046288	-1.374431	4.7103595	3.3359285	5.89	37.96

Table 2. Spectral-SAR results in correlating the EROL activity of Cl-PAHs with the structural parameters of Table 1, alongside the Pearson correlation (R) and the kinetic parameters (in arbitrary units) of eqs. (9)-(11).

Variable	Method	Spectral-SAR equation	R	$[S_0]$	β_{max}	EC_{50}
EL	DFT	1.95818+0.0327599 EL	0.912	9.91237	0.356511	6.45237
	PM3	22.085 - 3.90658 EL	0.083	7.75726	2.51162	4.29726
HD	DFT	20.781-8.1069 HD	0.469	8.35904	1.90985	4.89904
	PM3	36.1973-8.78674 HD	0.716	9.12233	1.14655	5.66233
LogP	DFT, PM3	-26.1456+5.68245 LogP	0.902	9.84647	0.422411	6.38647
POL	DFT, PM3	-19.88+0.752223 POL	0.933	9.97643	0.292452	6.51643

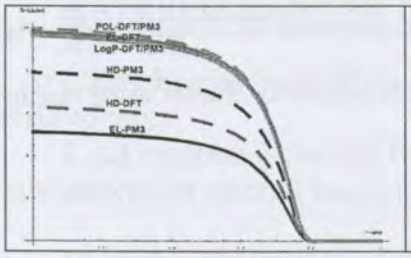

Figure 1. The logistics kinetics of the consumption of the ClPAHs in their interaction with the AhR in providing the cytochrome P450 in MCG-7 cells, for the S-SAR models and data of Table 2 considered in the eqs. (9)-(10).

Table 2 presents all the uni-parametric Spectral-SAR (or QSAR) models along their SSAR quantities according with the eqs. (9)-(11), thereafter used in plotting the associate logistic kinetics for the ClPAH-P450 conversion in Figure 1. The results suggest that: all DFT approaches, except that for chemical hardness (HD) are closely related with the electronegativity (EL) modeling of the interaction; semiempirical treatment of both El and HD does not approach the corresponding behavior of hydrophobicity (LogP) and polarizability (POL).

CONCLUSIONS

In modeling the kinetics of the ClPAH-P450 EROD activity one finds that: polarizability, electronegativity and hydrophobicity provide reliable QSAR models, with high correlations, worthy to be next tested for newly designed PAHs; density functional theory seems to be the most adequate computational framework for these descriptors, since yielding close laying progress curves in concerned logistic kinetics; chemical hardness and semiempirical methods are less adequate for complex chemical-biological interaction, somehow contrarily to the common belief. Future works should address multi-linear correlation to test the inter-parametric synergetics in molcualr mechanism envisaged; yet, for such endeavor having a statistical meaning more ClPAHs with their EROD activities should be available, in accordance with the consecrated Topliss-Costello rule [13].

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