QSAR MODEL FOR PREDICTING ANTIOXIDAN CAPACITY OF SOME POLYPHENOLIC ANTIOXIDANTS

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Abstract: Quantitative structure–activity relationship model (QSAR models) is useful method for predicting antioxidant capacity of a molecule based on some chemical-physics properties. In our development of QSAR model are included 21 structural similar antioxidants. It is shown that taking into account some thermodynamical and thermochemical parameters of antioxidant and chemical activity is possible to generate fair antiradical QSAR models.

Key words: QSAR, antioxidant activity, VCEAC, nOHvic, thermodynamical parameters

Introduction

A lot of attention is paid to the investigation of scavenging capacity of natural antioxidants. Their positive effect on the human health and absence of negative influence make them suitable as additives in cosmetic preparates, food, and food supplements. Beside considerable interest on natural sources of antioxidants, there are interests on finding appropriate synthetic antioxidants.

In our QSAR model are included 21 antioxidants. Among them 18 are natural benzoic acids, phenylacetic acids and phenols. The synthetic antioxidants used in foodstuffs to protect fats against oxidative rancidity are phenols: butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), 2-tert-butilhydroquinone (TBHQ).

VCEAC is defined as the antioxidant capacity equivalent to vitamin C concentration (mg/L). The antioxidant capacity of vitamin C was designated at a value of 100 mg/L. VCEAC value greater than 100 indicates that the corresponding compound is a more effective antioxidant than vitamin C. The data set we used for development of QSAR models containing VCEAC values of various polyphenols was taken from Kim and Lee (2004).

Material and methods

There are at last three well described mechanisms through which antioxidant forms appropriate radical (Marković et al., 2016; Leopoldini et al., 2011). The first one is named HAT ("Hydrogen Atom Transfer"), and bond cleavage reaction can be described by Eq. 1.

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Thermodynamical propitiatory of this reaction in appropriate environmental conditions can be established by calculating bond dissociation enthalpy (BDE) value (Eq. 1.1).

$$A-OH \rightarrow A-O^{\bullet} + H^{\bullet} \quad (1)$$

$$BDE = H(A-O^{\bullet}) + H(H^{\bullet}) - H(A-OH) \quad (1.1)$$

The second mechanism is two-step mechanism known as SET-PT ("Single-Electron Transfer followed by Proton Transfer") (Eq. 2). Whether the reaction is possible or not can be estimated based on the values of IP (ionization potential) (Eq. 2.1) and PDE (proton dissociation enthalpy) (Eq. 2.2).

$$A-OH \xrightarrow{-e^-} A-OH^{\bullet+} \xrightarrow{-H^+} A-O^{\bullet} \quad (2)$$

$$IP = H(A-OH^{\bullet+}) + H(e^-) + H(A-OH) \quad (2.1)$$

$$PDE = H(A-O^{\bullet}) + H(H^+) - H(A-OH^{\bullet+}) \quad (2.2)$$

The third mechanism is another two-step mechanism known as SPLET ("Sequential Proton Loss Electron Transfer") (Eq. 3). The possibility of radical formation via this mechanism can be estimate on the basis of the PA (proton affinity) (Eq. 3.1) and ETE (electron transfer energy) (Eq. 3.2).

$$A-OH \xrightarrow{-H^+} A-O^- \xrightarrow{-e^-} A-O^{\bullet} \quad (3)$$

$$PA = H(A-O^-) + H(H^+) - H(A-OH) \quad (3.1)$$

$$ETE = H(A-O^{\bullet}) + H(e^-) - H(A-O^-) \quad (3.2)$$

Optimization of all charged and radical species, as the neutral molecules are done using M05-2X functional (Zhao et al., 2006) in conjugation with 6-311++G(d,p) basis set implemented in Gaussian 09 program package (Frisch et al, 2009). All optimized geometries are obtained in water as solvent. To approximate the effect of solvent is used PCM/SMD solvation model. The absence of imaginary frequencies in optimized structure confirmed structure with energy minima. The effect of solvation to the enthalpies of the proton (H^+) and electron (e^-) are taken from the literature (Marković et al., 2013).

Values of hardness (η), softness (σ), electronegativity (χ), chemical potential (μ) and electrophilicity index (ω) are calculated using equations 4 – 8.

$$\eta \approx \frac{1}{2}(\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (4)$$

$$\sigma = \frac{1}{2\eta} \quad (5)$$

$$\mu \approx -\frac{1}{2}(\varepsilon_{LUMO} + \varepsilon_{HOMO}) \quad (6)$$

$$\chi = -\mu \quad (7)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

QSAR models are obtained using linear regression analysis with confidence interval 95%.

Results and discussion

Here presented development of QSAR model is based on finding correlation between experimental measure of the antioxidant capacity and different thermodynamical and thermochemical parameters of molecule scavenger capacity.

It is widely known that the number of O–H groups influences to the antioxidant capacity of molecule (Kim and Lee, 2004; Filipović et al., 2015). The greatest effect to the antioxidant capacity of molecules has vicinal O–H groups. It is proven that vicinal O–H groups participate in the creation of intramolecular hydrogen bonds, stabilizing neutral molecule, and the appropriate radical form (Marković et al., 2016).

As is shown in the Table 1, the best one-descriptor correlation is obtained with number of vicinal O-H groups ($n\mathrm{OH_{vic}}$) as independent variable (Eq. 9):

$$\mathrm{VCEAC} = 73.0(\pm 10.4) + 80.86(\pm 8.20)n\mathrm{OH_{vic}} \quad (9)$$
$$N = 21,\ r = 0.915,\ s = 40.7,\ F = 97.3$$

In the above and in subsequent equations, N represents the number of compounds, r is the correlation coefficient, s the standard error of estimate, and F is Fisher's F-value. A reliable QSAR model should have high r and F value, and low s value.

The best two-descriptor model was obtained by using $n\mathrm{OH_{vic}}$ and (PA+ETE) as molecular descriptors, Eq. (10):

$$\mathrm{VCEAC} = 896.230(\pm 180.679) + 69.447(\pm 6.258)n\mathrm{OH_{vic}} - 1.515(\pm 0.332)(\mathrm{PA+ETE}) \quad (10)$$
$$N = 21,\ r = 0.961,\ s = 28.5,\ F = 109.8$$

There are more two-descriptor models with high coefficient of correlation obtained using $n\mathrm{OH_{vic}}$ as one independent variable. Therefore, including BDE or (IP+PDE) values as the other independent variable, two-descriptor models with coefficient of correlation 0.957 are obtained. Including electronegativity or chemical potential, QSAR models with coefficient of correlation 0.942 are obtained. If electrophilicity index is used as second independent variable, significant QSAR model with coefficient of correlation 0.940 is obtained.

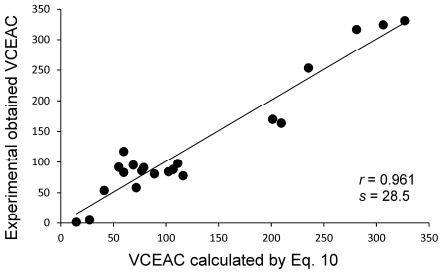
Previous results indicate that antioxidant capacity of molecules can be properly estimated based on some theoretical obtained parameters of their physical-chemistry activity.

Graph 1 shows that there are good correlation between experimental and calculated VCEAC values. It indicates possibility to estimate antioxidative capacity of molecule based on its number of vicinal O–H groups and sum of proton affinity and electron transfer energy.

Tabela 1. Vrednosti eksperimentalnih i nekih teorijskih parametara antioksidativnosti ispitivanih molekula. BDE, (IP+PDE) i (PA+ETE) su vrednosti entalpija u kJ mol^{-1}. Vrednosti η, σ, χ, μ i ω su izračunate iz energija HOMO i LUMO orbital u eV.

Table 1. Values of eksperimental and some theoretical parameters of scavenger activity of investigated molecules. BDE, (IP+PDE) and (PA+ETE) are appropriate enthalpies in kJ mol^{-1}. Values of η, σ, χ, μ and ω are calculated using energies of HOMO and LUMO in eV.

Jedinjenje *Compound*	VCEAC	nOH$_{vic}$	BDE	(IP+PDE)	(PA+ETE)	η	σ	χ	μ	ω
Salicilna kiselina *Salicylic acid*	1.4	0	400.7	581.8	581.8	3.69	0.14	-4.46	4.46	2.69
4-Hidroksibenzoeva k. *4-Hydroxybenzoic acid*	4.8	0	392.4	573.4	573.5	3.85	0.13	-4.37	4.37	2.48
3-Hidroksibenzoeva k. *3-Hydroxybenzoic acid*	53.7	0	383.2	564.3	564.3	3.69	0.14	-4.46	4.46	2.69
Karvakrol *Carvacrol*	58	0	363.1	544.2	544.2	4.14	0.12	-3.48	3.48	1.46
Butilovani hidroksitoluen *Butylated hydroxytoluene*	77.4	0	333.7	514.8	514.8	4.03	0.12	-3.31	3.31	1.36
Siringinska kiselina *Syringic acid*	80.4	0	351.7	532.8	532.8	3.57	0.14	-4.16	4.16	2.43
4-Hidroksifenilsirćetna k. *4-Hydroxyphenylacetic acid*	82.8	0	371	552.1	552.1	4.09	0.12	-3.73	3.73	1.70
2-*terc*-butilhidrohinon *2-tert-butylhydroquinone*	83.9	0	338.2	519.3	523.9	3.90	0.13	-3.37	3.37	1.46
Timol *Thymol*	85.3	0	359.6	540.7	540.7	4.11	0.12	-3.50	3.50	1.49
Homogentisinska kiselina *Homogentisic acid*	87.8	0	340	521.1	521.1	3.86	0.13	-3.63	3.63	1.71
Gentisinska kiselina *Gentisic acid*	90.8	0	358.5	539.6	539.5	3.39	0.15	-4.23	4.23	2.64
3-Hidroksifenilsirćetna k. *3-Hydroxyphenylacetic acid*	91.6	0	374.1	555.2	555.2	4.05	0.12	-3.87	3.87	1.85
2-Hidroksifenilsirćetna k. *2-Hydroxyphenylacetic acid*	95.1	0	364.9	546.1	546.1	4.14	0.12	-3.82	3.82	1.76
Butilovani hidroksianizol *Butylated hydroxyanisole*	97.6	0	337	518.1	518.1	3.88	0.13	-3.34	3.34	1.44
Vanilinska kiselina *Vanillic acid*	117.2	0	371	552.1	552.1	3.64	0.14	-4.19	4.19	2.41
Protokatehinska kiselina *Protocatechuic acid*	163.2	2	361	542.1	544.9	3.67	0.14	-4.24	4.24	2.45
2,3-Dihidroksibenzoeva k. *2,3-Dihydroxybenzoic acid*	169.6	2	362.1	543.2	550.3	3.52	0.14	-4.29	4.29	2.62
Katehol *Catechol*	253.1	2	346.7	527.8	527.8	4.13	0.12	-3.50	3.50	1.48
Homoprotokatehinska k. *Homoprotocatechuic acid*	316.7	2	316.5	497.6	497.6	4.05	0.12	-3.55	3.55	1.55
Galna kiselina *Gallic acid*	324.3	3	345.7	526.8	526.8	3.67	0.14	-4.26	4.26	2.47
Pirogalol *Pyrogallol*	331.2	3	332.1	513.2	513.2	4.28	0.12	-3.40	3.40	1.35
VCEAC (r)		**0.915**	**-0.641**	**-0.641**	**-0.637**	**0.206**	**-0.189**	**0.221**	**-0.221**	**-0.218**



Graf. 1. Zavisnost eksperimentalnih VCEAC vrednosti i VCEAC vrednosti izračunatih pomoću jednačine 10.
Graph. 1. Experimental VCEAC values versus VCEAC values calculated by Eq. 10.

Developing our QSAR model, we tried to find correct three-descriptor model. We obtained models with high values of coefficient of correlation. However, at all of them the influence of one of coefficients was not statistically significant. Those models therefore were not acceptable.

Conclusion

Developing of QSAR model for predicting antioxidative capacity of selected polyphenolic antioxidants, we obtained one and two-descriptor models with very high value of coefficient of correlation. The best one-descriptor model is obtained using $n\mathrm{OH}_{\mathrm{vic}}$ as independent variable. It indicates that the number of vicinal hydroxyl groups has great influence to the scavenger potency of molecule.

The best two-descriptor model is obtained involving $n\mathrm{OH}_{\mathrm{vic}}$ and (PA+ETE) values as independent variables. There are more acceptable and applicable models with $n\mathrm{OH}_{\mathrm{vic}}$ as one independent variable and some thermodynamilac and thermochemical parameters. It indicates that parameters as are BDE, sum of IP and PDE, electronegativity, chemical potential and electrophilicity index has important influence to the chemical behavior of compounds. Those parameters can be used for predicting antioxidant capacity of molecule.

Obtained QSAR models can be applied in estimation scavenger potency of molecule, but also in the process of designing new antioxidants.

Our results indicate that there is no significant antiradical model with three independent variables.

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