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Estimating flavonoid oxidation potentials: mechanisms and charge-related regression models

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In this paper, I tested our quadratic regression models for the estimation of flavonoid oxidation potentials based on spin populations, the differences in the net atomic charges between a cation and a neutral flavonoid, between a radical and an anion of a flavonoid, and between a radical and a neutral flavonoid on a larger set of flavonoids ($N = 35$). By including six new flavonoids (5,6,7-trihydroxyflavone, 3,3',4',7-tetrahydroxyflavone, 3,7-dihydroxyflavone, 4',7-dihydroxyflavone, 4',5,7-trihydroxyisoflavone, and 6-hydroxyflavone), we created a respectable calibration set of 35 flavonoids with their oxidation potentials all measured at the same conditions by the same experimentalist. The best model was based on the mean values of the three variables using differences in the net atomic charges ($R^2 = 0.970$, S.E. = 0.043), which are connected with the three different mechanisms of electrochemical oxidation, SET-PT, SPLET, and HAT.

KEY WORDS: atomic charges; electrochemical oxidation; PM6; polyphenols; QSPR

The 120 000 published studies that can be found in the Web of Science Core Collection (Topic search: "Flavonoid") published after 1992 and the French paradox (1) and the 43,000 published papers since 2019 show that flavonoids are an inexhaustible mine for researchers. Apart from the protective effect of flavonoids on neurodegenerative diseases, diabetes, cardiovascular diseases, cancer, and allergies (2-6), there are also studies about their gastric protective effect (7), ability to protect the heart from diabetic cardiomyopathy (8), antimalarial activities (9), etc. Therefore, the antioxidant activity (AA) of flavonoids and the theoretical models for its prediction, along with mechanisms of flavonoids action, are of particular interest to science. Research papers dealing with these issues frequently attempt to establish a mathematical connection between AA and the first electrochemical oxidation potential, E_{p1}, of the flavonoids, with more or less success (10-17). Our team strives to develop a comprehensive model for the estimation of the E_{p1} based on the electronic structure and its changes during electrochemical oxidation (18-23). A reliable theoretical model, not yet presented in the literature, would enable the fast prediction of oxidation potentials, and consequently antioxidant activity, for any flavonoid of interest. In this way, we could obtain its E_p values without experiments, which is faster and cheaper. Moreover, a flavonoid of interest may be unavailable at the moment or even not synthesized yet. The advantage of dealing with oxidation potentials is that they can be measured very accurately using electrochemistry (21), unlike antioxidant activities for whose determination many methods are in use (DPPH, FCR, FRAP, etc.). They often yield very different results because each has its own limitations (14-16, 24). Thus, our intention was to create a calibration set of flavonoids, as big as possible, with the oxidation potentials all measured in our laboratory at the same conditions. This is of extreme importance for developing a reliable calibration model because the values measured by different laboratories found in the literature may differentiate significantly, e.g. the case of epicatechin (Table 1; 21), and using bad experimental values introduces an error into the model.

In this study, I used the oxidation potentials of six new flavonoids [5,6,7-trihydroxyflavone, 3,3',4',7-tetrahydroxyflavone, 3,7-dihydroxyflavone, 4',7-dihydroxyflavone, 4',5,7-trihydroxyisoflavone, and 6-hydroxyflavone (30-35, Table 1)] measured for our previous paper (17) and added them to our set of 29 flavonoids (18, 19). The aim of this work was to test the stability and predictivity of our quadratic regression models for the estimation of the first oxidation potential (18, 19) on a larger set of flavonoids. Besides the model based on the sum of atomic orbital spin populations over the carbon atoms in the skeleton of a flavonoid radical molecule, $\sum_{s(C)} \mathrm{AOSP}_{Rad}$, we also used quadratic regression models based on the differences in the net atomic charges between a cation and a neutral flavonoid, $\sum_{s(C)} \Delta \mathrm{NAC}_{Cat\text{-}Neut}$, between a radical and an anion of a flavonoid, $\sum_{s(C)} \Delta \mathrm{NAC}_{Rad\text{-}Anion}$, and between a radical and a neutral flavonoid, $\sum_{s(C)} \Delta \mathrm{NAC}_{Rad\text{-}Neut}$, connected to the oxidation mechanisms (or part of the mechanisms): single electron transfer-proton transfer (SET-PT), sequential proton loss electron transfer (SPLET) and hydrogen atom transfer (HAT), respectively:

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Table 1 The values for the first oxidation potential, E_{p1}, for 35 flavonoids at pH 3 and 7, active site (A site), the sum of atomic orbital spin populations over the carbon atoms in the skeleton of a flavonoid radical molecule, $\sum_{s(C)} AOSP_{Rad}$, the sum of differences in the net atomic charges between cation and neutral flavonoid ($\sum_{s(C)} \Delta NAC_{Cat\text{-}Neut}$), radical and anion ($\sum_{s(C)} \Delta NAC_{Rad\text{-}Anion}$) and radical and neutral flavonoid ($\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$) calculated using the PM6 in water method and their mean values, and the number of OH groups in a flavonoid.

No.	Flavonoid	A site	E_{p1}/V (pH=3)	E_{p1}/V (pH=7)	$\sum_{s(C)}$ AOSP$_{Rad}$	$\sum_{s(C)} \Delta NAC_{Cat\text{-}Neut}$ (var. 1)	$\sum_{s(C)} \Delta NAC_{Rad\text{-}Anion}$ (var. 2)	$\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$ (var. 3)	Mean var. 1-3	N_{OH}
1	3,3',4'THF	4'	0.456[b]	0.197[b]	0.527	0.353	0.333	0.249	0.312	3
2	3',4'DHF	4'	0.513[b]	0.283[b]	0.631	0.373	0.387	0.272	0.344	2
3	3HF	3	0.751[b]	0.566[b]	0.697	0.428	0.44	0.239	0.369	1
4	5HF	5	1.164[b]	0.909[b]	0.845	0.516	0.493	0.358	0.456	1
5	7,8DHF	8	0.456[b]	0.225[b]	0.538	0.339	0.361	0.217	0.306	2
6	Apigenin	4'	0.928[c]	0.696[g]	0.792	0.467	0.46	0.335	0.421	3
7	Chrysin	5	1.162[c]	0.956[g]	0.923	0.508	0.493	0.375	0.459	2
8	Galangin	3	0.655[c]	0.430[b]	0.733	0.437	0.444	0.244	0.375	3
9	Luteolin	4'	0.513[b]	0.288[g]	0.631	0.366	0.38	0.266	0.337	4
10	Quercetin	4'	0.435[c]	0.180[g]	0.519	0.350	0.325	0.248	0.308	5
11	Myricetin	4'	0.351[c]	0.089[d]	0.364	0.281	0.253	0.229	0.254	6
12	EGC	4'	0.307[e]	0.028[e]	0.471	0.283	0.293	0.248	0.275	6
13	EC	4'	0.390[f]	0.150[f]	0.621	0.372	0.374	0.28	0.342	5
14	Morin	3	0.458[c]	0.227[g]	0.591	0.380	0.335	0.239	0.318	5
15	EGCG	4'	0.367[c]	0.051[e]	0.472	0.298	0.294	0.248	0.28	5
16	ECG	4'	0.477[c]	0.162[f]	0.622	0.362	0.374	0.276	0.337	4
17	Naringenin	4'	0.929[c]	0.704[h]	0.790	0.480	0.462	0.356	0.433	3
18	Kaempferid	3	0.584[c]	0.369[h]	0.654	0.414	0.407	0.233	0.351	3
19	Dyhidromyricetin	4'	0.354[d]	0.098[d]	0.470	0.305	0.302	0.245	0.284	6
20	Rutin	4'	0.504[c]	0.267[h]	0.610	0.361	0.367	0.271	0.333	4
21	Hesperetin	3’	0.737[i]	0.510[i]	0.751	0.423	0.429	0.322	0.391	3
22	Daidzein	4’	0.795[i]	0.592[i]	0.772	0.451	0.432	0.328	0.404	2
23	Kaempferol	3	0.498[i]	0.235[i]	0.659	0.419	0.409	0.234	0.354	4
24	Acacetin	5	1.174[i]	0.952[i]	0.925	0.509	0.491	0.374	0.458	2
25	Naringin	4’	0.959[i]	0.732[i]	0.791	0.466	0.463	0.348	0.426	2
26	Neohesperidin	3’	0.766[i]	0.549[i]	0.750	0.424	0.424	0.322	0.39	2
27	Hesperidin	3’	0.739[i]	0.542[i]	0.750	0.424	0.424	0.322	0.39	2
28	Quercitrin	4’	0.500[i]	0.270[i]	0.610	0.361	0.367	0.271	0.333	4
29	Gossypin	4’	0.416[i]	0.132[i]	0.515	0.349	0.328	0.244	0.307	5
30	567THF	6	0.411[a]	0.162[a]	0.409	0.304	0.293	0.233	0.277	3
31	Fisetin	4’	0.435[a]	0.183[a]	0.524	0.355	0.331	0.252	0.313	4
32	37DHF	3	0.643[a]	0.474[a]	0.726	0.436	0.448	0.246	0.377	2
33	4'7DHF	4’	0.948[a]	0.692[a]	0.793	0.474	0.466	0.339	0.426	2
34	Genistein	4’	0.809[a]	0.613[a]	0.773	0.450	0.433	0.328	0.404	3
35	6HF	6	0.975[a]	0.751[a]	0.742	0.449	0.467	0.322	0.413	1

[a]ref(17), [b]ref20), [c]ref(21), [d]ref(25) [e]ref(26), [f]ref(27), [g](22), [h](23), [i](18)

$$\text{R-OH} \rightarrow \text{R-OH}^{\cdot +} + e^- \qquad \text{(Eq. 1)}$$

$$\text{R-O}^- \rightarrow \text{R-O}^{\cdot} + e^- \qquad \text{(Eq. 2)}$$

$$\text{R-OH} \rightarrow \text{R-O}^{\cdot} + \text{H} \qquad \text{(Eq. 3)}$$

To reproduce the E_{p1} using the theory, one would need to know the mechanism of electrochemical oxidation. Thus, we calculated the differences in the net atomic charges on the basis of three possible mechanisms to see which would give the best correlation with the experiment.

THEORETICAL METHODS

MOPAC calculations

The geometries of six new flavonoids, their cations, anions and radicals, were optimised using the MOPAC2016™ PM6 method (28), using the same procedure as in our previous works (18, 20, 23) for the remaining 29 flavonoids. This means that optimization was performed in water (electric permittivity of the solvent = 78.39), the initial structures were taken as planar, and the eigenvector following (EF) optimisation procedure was carried out with a final gradient norm under 0.01 kcal/mol/Å. PM6 calculations, which were much less time-demanding, yielded even better results than the density functional theory (DFT) (22, 23). Thus, we employed PM6 for all of the calculations in this work.

Regression calculations

For multivariate regression calculations, including the leave-one-out procedure (LOO) of cross validation, we used the CROMRsel program (29). The standard error of the cross-validation estimate was defined as:

$$\text{SE}_{\text{cv}} = \sqrt{\sum_i \frac{\Delta X_i^{\,2}}{N}} \qquad \text{(Eq. 4)}$$

where ΔX and N denote cv residuals and the number of reference points, respectively.

RESULTS AND DISCUSSION

On this enlarged set of flavonoids ($N = 35$, Table 1) our standard model (18, 20, 22, 23) for the estimation of oxidation potentials, based on $\sum_{\text{s(C)}} \text{AOSP}_{\text{Rad}}$ (the sum of atomic orbital spin populations over the carbon atoms in A, B and C rings of the radical molecule):

$$E_{p1} = a_1 \sum_{\text{s(C)}} \text{AOSP}_{\text{Rad}} + a_2 \left(\sum_{\text{s(C)}} \text{AOSP}_{\text{Rad}}\right)^2 + b \qquad \text{(Eq. 5)}$$

yielded $R^2 = 0.920$, S.E. = 0.071, and S.E.$_{\text{cv}}$ = 0.080 (Model 1 in Table 2, Figure 1). The statistics were slightly worse, but similar to the statistics from our earlier work (18) on the smaller sets of flavonoids ($N = 29$).

It is also worth reminding ourselves (20) that the E_{p1} and $\sum_{\text{s(C)}}$ AOSP$_{\text{Rad}}$ values (Table 1, Figure 1, Scheme 1) will be lower if a *o*-trihydroxy group (pyrogallol) instead of only two vicinal OH groups (catechol) is present in a flavonoid (e.g. **11** vs. **10**). If there are no vicinal OH groups in a flavonoid, but rather the OH groups are on positions 3-OH and 4'-OH (e.g. **23**), the E_{p1} will be higher, although significantly lower than when 3-OH or 4'-OH are missing (e.g. **8**), and especially lower compared to the flavonoids without both the 3-OH and the 4'-OH groups, which have the highest E_{p1} and $\sum_{\text{s(C)}}$ AOSP$_{\text{Rad}}$ values (**4**, **7**, and **24**).

The quadratic regression model using the sum of differences in the net atomic charges, over the carbon atoms in the skeleton,

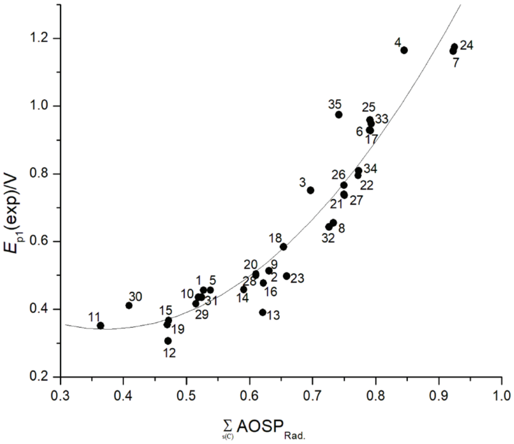


Figure 1 The dependence of experimental E_{p1} (pH = 3) on $\sum_{\text{s(C)}}$ AOSP$_{\text{Rad}}$ for the set of 35 flavonoids. Quadratic regression yielded $R^2 = 0.920$, S.E. = 0.071, and S.E.$_{\text{cv}}$ = 0.080 (Model 1 in Table 2)

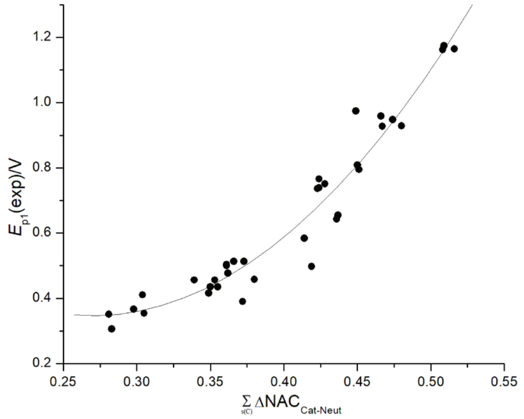
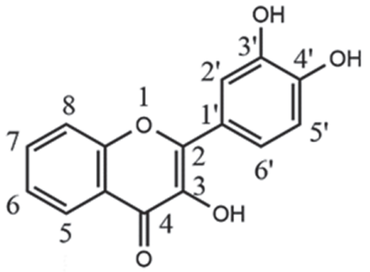


Figure 2 The dependence of experimental E_{p1} (pH = 3) on $\sum_{\text{s(C)}} \Delta\text{NAC}_{\text{Cat-Neut}}$ for the set of 35 flavonoids. Quadratic regression yielded $R^2 = 0.943$, S.E. = 0.060, and S.E.$_{\text{cv}}$ = 0.065 (Model 2 in Table 2)

Table 2 Quadratic regression models ($E_{p1} = ax^2 + bx + c$) for the estimation of E_{p1} based on $\sum_{s(C)} \mathrm{AOSP}_{Rad}$, $\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$ (var. 1), $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ (var. 2), $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ (var. 3) and the mean of variables 1, 2, and 3.

Model No.	Independent variable (x)	a(S.E.)	b(S.E.)	Intercept c(S.E.)	R^2	S.E.	$\mathrm{S.E.}_{cv}$
1	$\sum_{s(C)} \mathrm{AOSP}_{Rad}$	3.04(58)	–2.27(76)	0.76(24)	0.920	0.071	0.080
2	$\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$ (1)	14.3(24)	–7.7(19)	1.39(38)	0.943	0.060	0.065
3	$\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ (2)	20.1(26)	–11.9(20)	2.14(38)	0.942	0.061	0.066
4	$\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ (3)	37(11)	–17.3(63)	2.47(90)	0.844	0.100	0.108
5	Mean (var. 1, 2 and 3)	17.2(24)	–8.2(18)	1.30(31)	0.970	0.043	0.046



Scheme 1 As an example, the structure of 3,3',4'-tryhydroxyflavone (3,3',4'THF) is given with the numbering of atoms in the skeleton

between a cation and a neutral flavonoid, $\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$ (variable 1, Table 1), introduced in (18), again yielded better statistics than $\sum_{s(C)} \mathrm{AOSP}_{Rad}$: $R^2 = 0.943$, S.E. = 0.060, and $\mathrm{S.E.}_{cv} = 0.065$ (Model 2 in Table 2, Figure 2).

In my previous paper (19), I also introduced the quadratic regression models based on the differences in the net atomic charges between a radical and an anion of a flavonoid, $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ (variable 2, Table 1) and between a radical and a neutral flavonoid, $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ (variable 3, Table 1). The models yielded $R^2 = 0.942$, S.E. = 0.061 and $\mathrm{S.E.}_{cv} = 0.066$ (Model 3 in Table 2, Figure 3), and $R^2 = 0.844$, S.E. = 0.100 and $\mathrm{S.E.}_{cv} = 0.108$ (Model 4 in Table 2, Figure 4), respectively. The model based on $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ was the worst among the presented models as I have shown before (19).

The model using the mean of the variables $\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$, $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ and $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ when correlated to the E_{p1} of the 35 flavonoids yielded a significantly better regression ($R^2 = 0.970$, S.E. = 0.043 and $\mathrm{S.E.}_{cv} = 0.046$, Model 5 in Table 2, Figure 5) and was again (19) shown to be the best among the presented models. The result was better than using any of these variables alone and better than any regression using an averaging of pairs of variables 1, 2 and 3; the mean of $\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$ and $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$, the mean of $\sum_{s(C)} \Delta\mathrm{NAC}_{Cat\text{-}Neut}$ and $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$, and the mean of $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ and $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Neut}$ yielded S.E. = 0.57, 0.55, and 0.50, respectively.

The addition of the number of OH groups in a flavonoid (N_{OH}, Table 1) as a variable (18-20, 22, 23) improved all of the models. The best statistics was determined for the model based on the mean of variables 1, 2, and 3, yielding $R^2 = 0.992$, S.E. = 0.033, and $\mathrm{S.E.}_{cv} = 0.037$ ($N = 35$). The same model that included pH as a variable (18-20, 22, 23) allowed for an estimation of E_{p1} values at both a pH of 3 and a pH of 7 ($N = 70$) and yielded $R^2 = 0.991$, S.E. = 0.039, and $\mathrm{S.E.}_{cv} = 0.042$ (Figure 6).

CONCLUSION

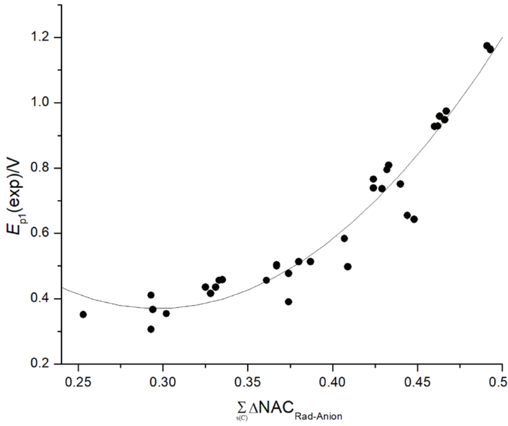


Figure 3 The dependence of experimental E_{p1} (pH 3) on $\sum_{s(C)} \Delta\mathrm{NAC}_{Rad\text{-}Anion}$ for the set of 35 flavonoids. Quadratic regression yielded $R^2 = 0.942$, S.E. = 0.061, and $\mathrm{S.E.}_{cv} = 0.066$ (Model 3 in Table 2)

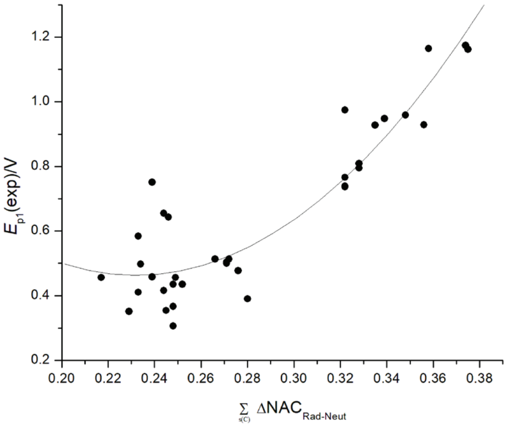


Figure 4 The dependence of experimental E_{p1} (pH 3) on $\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$ for the set of 35 flavonoids. Quadratic regression yielded $R^2 = 0.844$, S.E. = 0.100, and S.E.$_{cv}$ = 0.108 (Model 4 in Table 2)

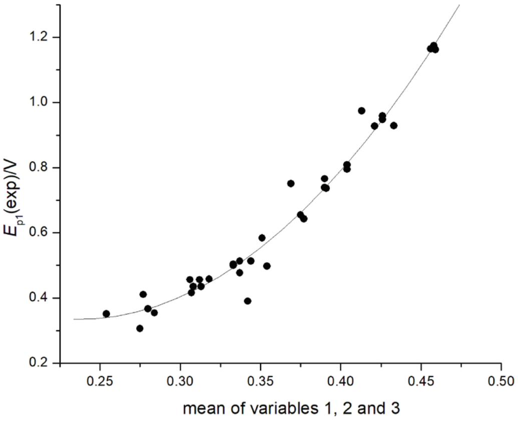


Figure 5 The dependence of experimental E_{p1} (pH 3) on the mean values of $\sum_{s(C)} \Delta NAC_{Cat\text{-}Neut}$, $\sum_{s(C)} \Delta NAC_{Rad\text{-}Anion}$ and $\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$ (variables 1, 2, and 3, Table 1) for the set of 35 flavonoids. Quadratic regression yielded $R^2 = 0.970$, S.E. = 0.043, and S.E.$_{cv}$ = 0.046 (Model 5 in Table 2)

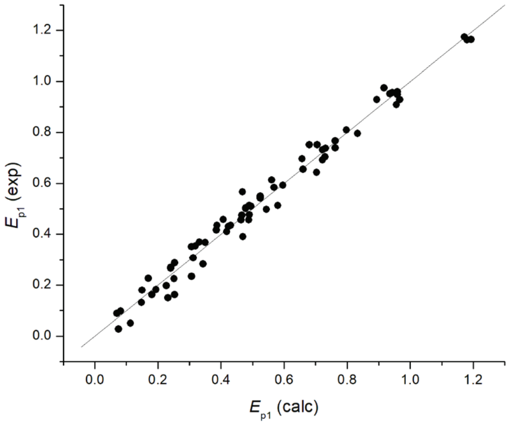


Figure 6 Correlation of experimental *vs.* theoretical E_{p1} values for the set of 35 flavonoids at pH 3 and 7 ($N = 70$). Theoretical values were calculated by the model: $E_{p1} = a_1$ (mean of variables 1, 2, and 3) + a_2 (mean of variables 1, 2, and 3)^2 + a_3 N_{OH} + a_4 pH + b; $r = 0.991$, S.E. = 0.039, and S.E.$_{cv}$ = 0.042

The results obtained on the set of 35 flavonoids showed that the best among the presented quadratic models for the estimation of the first oxidation potential is the model that uses the mean values of $\sum_{s(C)} \Delta NAC_{Cat\text{-}Neut}$, $\sum_{s(C)} \Delta NAC_{Rad\text{-}Anion}$ and $\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$ as the variable, yielding $R^2 = 0.970$, S.E. = 0.043, and S.E.$_{cv}$ = 0.046 (Figure 5). This was the same finding and practically the same statistics as in my last paper (19) on the 29 flavonoids ($R^2 = 0.974$, S.E. = 0.042, and S.E.$_{cv}$ = 0.045). It proved the stability of the model regarding the size of the set used and its great predictivity, as the oxidation potentials were estimated by an error of 5% of the E_{p1} range [(S.E./range E_{p1})100 %]. By inclusion of the N_{OH} into the model, the error became even lower, 3.8 %.

According to the model using the mean values of variables 1, 2, and 3 (Table 2), all of the mechanisms (SET-PT, SPLET, and HAT) equally contributed to the electrochemical oxidation of all of the flavonoids. However, there is a possibility that for some flavonoids, one or two mechanisms were dominant, which was especially highlighted by the model based on $\sum_{s(C)} \Delta NAC_{Rad\text{-}Neut}$ (Figure 4), also discussed previously (19). Exploring that possibility will be the subject of my upcoming research.

Acknowledgements

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Procjena oksidacijskih potencijala flavonoida: mehanizmi i regresijski modeli povezani s nabojima atoma

U ovom radu testirao sam naše kvadratne regresijske modele za procjenu oksidacijskih potencijala flavonoida, temeljene na spinskim populacijama, razlici atomskih naboja u kationu i neutralnoj formi flavonoida, radikala i aniona te između radikala i neutralnog flavonoida, na većem skupu flavonoida (*N* = 35). Uključenjem šest novih flavonoida (5,6,7-trihidroksiflavon,3,3’,4’,7-tetrahidroksiflavon, 3,7-dihidroksiflavon, 4’,7-dihidroksiflavon, 4’,5,7-trihidroksiizoflavon i 6-hidroksiflavon) stvorili smo respektabilan skup od 35 flavonoida s oksidacijskim potencijalima mjerenima od strane istog eksperimentalista pri istim uvjetima. Najbolji model temeljen je na srednjim vrijednostima triju varijabli koje su izvedene iz razlika atomskih naboja, a koje su povezane s tri moguća mehanizma elektrokemijske oksidacije flavonoida: SET-PT, SPLET i HAT.

KLJUČNE RIJEČI: atomski naboji; elektrokemijska oksidacija; PM6; polifenoli; QSPR