CrossMark

Experimental and mechanistic study of the inhibitory effects by phenolics on the oscillations of the Orbàn–Epstein Reaction

Rinaldo Cervellati[1] · **Emanuela Greco[1]** · **Slavica M. Blagojević[2]** ·
Stevan N. Blagojević[3] · **Slobodan Anić[4]** · **Željko D. Čupić[5]**

Abstract The system KSCN–H_2O_2–$CuSO_4$–NaOH, also known as the Orbàn–Epstein oscillatory reaction, is exposed to external perturbations by several phenolic compounds: catechol, resorcinol, hydroquinone, 2,5-dihydroxybenzoic acid, 2,6-dihydroxybenzoic acid, 2,3-dihydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid, caffeic acid, and ferulic acid. As a result of the performed perturbation in most examined cases, oscillations have been inhibited for some characteristic time, and resumed afterwards. The evaluated inhibition time is typical for each substance and strongly dependent on its concentration. The chemical mechanism of the interaction between the Orbàn–Epstein system and phenolic compounds is briefly discussed. Numerical simulations are performed using the original Orbàn–Epstein model with 30 reactions, extended by three reactions describing the interaction with inhibitory substances. The rate constants of three added reactions are adjusted to fit experimental inhibition times, and compared among used compounds. The observed effects are discussed further in relation with the bond dissociation enthalpy theory. Unlike other tested compounds, 2,5-dihydroxybenzoic acid remains off from predicted order of activity.

✉ Rinaldo Cervellati
  rinaldo.cervellati@unibo.it

[1] Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi 2, Bologna, Italy

[2] Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, Belgrade, Serbia

[3] Institute of General and Physical Chemistry, University of Belgrade, Studentski trg 12-16, Belgrade, Serbia

[4] Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, Belgrade, Serbia

[5] Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, Belgrade, Serbia

🖄 Springer

Introduction

Alongside the well-known Bray–Liebafsky (BL) [1, 2], Belousov–Zabotinski (BZ) [3–5] and Briggs–Rauscher (BR) [6] reactions, another system that shows chemical oscillations also in batch conditions is the system KSCN–H_2O_2–$CuSO_4$–NaOH, also known as the Orbàn–Epstein reaction (OE) [7, 8]. Following Epstein, these systems belong to different families of chemical oscillators, BL, BZ and BR to the halite-halide family, OE to the sulfur one [9].

However, a common feature of OE, BL, and BR oscillating reactions is hydrogen peroxide as a reagent. The presence of oxygen-centered radicals such as $^{.}$OH and $^{.}$OOH as intermediates has then been postulated in the mechanisms of these reactions [7, 10, 11]. Even if the debate on the effective role of these radicals is still open [12, 13], some experimental evidence of their presence has been recently reported in a subsystem of BL and BR reactions [14, 15].

In a previous investigation on the OE system, we reported a revised study of the effects of component concentration variations on the oscillation parameters over a wide concentration range under batch conditions [16]. We also investigated the effect of the addition of catechol (1,2-benzenediol), resorcinol (1,3-benzenediol) and hydroquinone (1,4-benzenediol) to a suitable high oscillation number, long oscillation time, OE mixture. The effect was similar to that induced by adding polyphenols to an active BR system [17]: an immediate quenching of oscillation followed by an inhibition time after which oscillatory regime resumed, an indirect experimental evidence of oxygen-centered radicals involvement in the mechanism of both reactions. The unperturbed behavior was qualitatively simulated [16] by a mechanistic model using the stoichiometric network analysis (SNA) [18–20].

The aim of the present research is to extend the study of inhibitory effects to other phenolics as di-hydroxybenzoic acids and phenolic acids as caffeic and ferulic acids on the oscillations of the OE reaction, which takes place in the strong alkaline environment (pH 10–12). Another goal is to improve the theoretical model also inserting suitable steps for the main reactions that account for inhibitory effects. The reactivity of phenolics as antioxidants scavengers of free radicals will be interpreted by the bond dissociation enthalpy (BDE) theory.

Experimental

Materials and apparatus

KSCN (Potassium thiocyanate, Merck, reagent grade, 99% min.), hydrogen peroxide (H_2O_2, Sigma Aldrich, reagent grade, 30% w/w) $CuSO_4 \cdot 5H_2O$ (copper(II) sulfate pentahydrate, Merck, reagent grade, 99.0–100.5%), sodium hydroxide (NaOH, Merck, reagent grade, 99% min.) were of analytical grade and used without

further purification. All stock solutions were prepared from the double distilled deionized water. Sodium hydroxide solution was analyzed by titration vs standard HCl 0.1 M (Carlo Erba). H_2O_2 was standardized daily by manganometric analysis. *Phenolics used*: catechol [1,2-dihydroxybenzene, Sigma-Aldrich, reagent grade, $\geq$ 99%), resorcinol (1,3-dihydroxybenzene, Fluka, reagent grade, $\geq$ 98%)], hydroquinone (1,4-dihydroxybenzene, Carlo Erba, reagent grade, 99%), 2,5-DHBA (2,5-dihydroxybenzoic acid, Aldrich, reagent grade, 98%), 2,6-DHBA (2,6-dihydroxybenzoic acid, Aldrich, reagent grade, 98%), 2,3-DHBA (2,3-dihydroxybenzoic acid, Aldrich, reagent grade, 99%), 2,4-DHBA (2,4-dihydroxybenzoic acid, Aldrich, reagent grade, 97%), 3,4-DHBA (3,4-dihydroxybenzoic acid, Aldrich, reagent grade, 97%), 3,5-DHBA (3,5-dihydroxybenzoic acid, Aldrich, reagent grade, 97%), caffeic acid (3-(3,4-dihydroxyphenyl)prop-2-enoic acid, Fluka, reagent grade, 97%), ferulic acid [3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid, Fluka, reagent grade, $\geq$ 99%].

Oscillations in the OE mixtures were followed potentiometrically by recording the potential of the solution using a couple bright platinum electrode (Hamilton, model P/N 238 945)—reference electrode (double-junction Ag/AgCl electrode, Ingold, model 373-90-WTE-ISE-S7). Electrodes were connected to a pH multimeter (WTW, model pH 540 GLP) controlled by an IBM-compatible PC. The accuracy of the multimeter was $\pm$ 1 mV. The data acquisition program Multi Achat II (WTW) has been used. The multimeter was equipped with a temperature sensor with an accuracy of $\pm$ 0.1 °C. OE mixtures were prepared by mixing the appropriate amounts of stock solutions of reagents using pipets or burettes in a 100 mL beaker to a total volume of 30 mL. The order of addition was: KSCN, NaOH, H_2O_2, and $CuSO_4$. Oscillations start after the addition of $CuSO_4$. All solutions and reaction mixtures were maintained at constant temperature by means of a suitable thermostating system (accuracy $\pm$ 0.1 °C). Inhibitory effects by phenols were studied adding 1.0 mL of a suitable diluted solution of each compound to 30 mL of an active OE mixture after the second or third oscillation.

Results

In our previous paper [16], we found that the mixture of the initial formal composition: $[KSCN]_0 = 0.06$ M; $[NaOH]_0 = 0.050$ M; $[H_2O_2]_0 = 0.20$ M; $[CuSO_4]_0 = 1.8 \times 10^{-4}$ M, oscillations last for 5635 s (ca. 1 h 34 min) and their number is 24, as shown in Fig. 1. The behavior of this unperturbed mixture was then taken as reference.

Inhibitory effects by phenols

Most of the phenolic compounds tested show inhibitory effects similar to those observed in the BR reaction: an immediate quenching of oscillations, an inhibitory time ($t_{inhib.}$) that linearly depends on the concentration of the compound added in a narrow range of concentration, followed by a resumption of oscillations. A typical recording of an inhibited OE mixture is shown in Fig. 2a, while in Fig. 2b, the linear
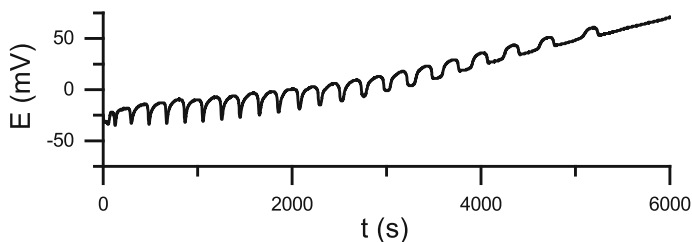
Fig. 1 Long last recording of E(Pt) versus time. Initial composition of mixture, see text. T = 25 °C

Fig. 2 a Recording of the potential of the mixture (initial composition see Fig. 1) versus time when 1.0 mL of a suitably diluted solution of resorcinol was added to 30 mL of the mixture after the second oscillation, the initial concentration of Resorcinol in mix = 2.10 mM. **b** Graph of the inhibition time (t_{inhib} corresponds to the quiescent period between the perturbation and first next oscillation) versus concentration of resorcinol added to the mixture
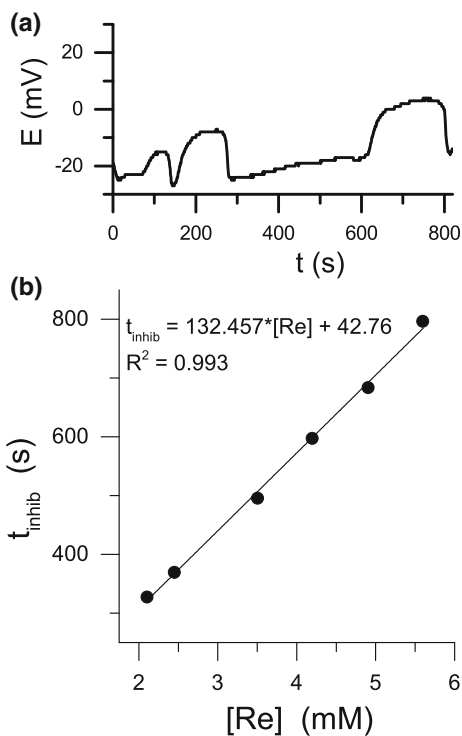
relationship between $t_{inhib.}$ and concentration of inhibitor (resorcinol in this example) is reported.

At low concentrations of substance added (different for each substance), the inhibition times become too low to be measured. There is a threshold under which inhibition time cannot be detected. We believe that under this threshold the straight line curves towards the period of oscillation. At high concentrations of inhibitor added, the amplitude of the resumed oscillations becomes too low, so that at a given concentration value (different for each inhibitor), oscillations do not resume. This means that the oscillating reaction reached its end.

The main results obtained by experiments on all tested phenolics are reported in Table 1.

In the last column, the relative antioxidant capacity is quoted. It was found [21] that a way to calculate the relative antioxidant activity is to compare the concentrations of a sample and a chosen standard (resorcinol) that give the same inhibition time, called the relative activity with respect to concentrations (rac), that is, the ratio:

$$rac = [std]/[smp] \tag{1}$$

Here [smp] is the concentration of the sample added to the mixture giving a certain inhibition time and [std] is the concentration of resorcinol that should give the same inhibition time. The latter concentration is obtained from the straight line equation of the substance chosen as standard (Fig. 2b).

The inhibition time for a rac calculation must be in the linear concentration range of the standard and of all of the examined substances. When possible, it is convenient to calculate a mean value of rac in the linear concentration range of the sample and the standard. This mean value, $(rac)_m$, is more significant than the rac value calculated at only one inhibition time.

Even if a comparison between perturbations in OE and BR systems by phenols is arbitrary because the only common feature between the two systems is H_2O_2, the inhibitor concentrations for the first system fall at mM level, for the second at μM level. This could be an indication that the perturbation effects by phenolics are more effective at acidic pH.

Among diphenols, hydroquinone shows the high activity, catechol the less. Three di-hydroxybenzoic acids (2,4-; 2,6- and 3,5-DHBA) do not show inhibitory effects until 5.60 mM, the maximum concentration explored for this series of compounds. On the contrary, 2,5-DHBA shows an unusual potency if compared with 2,3- and

Table 1 Summary of experimental results

Compound	Number of experiments	Concentration range (mM)	Inhibition time range (s)	$(rac)_m \pm$ SE
Resorcinol	6	2.10–5.60	328–796	1 (std)
Catechol	4	4.90–7.00	254–792	0.6 ± 0.1
Hydroquinone	7	0.70–4.90	241–2779	3.5 ± 0.3
2,3-DHBA	6	1.75–3.50	393–707	1.47 ± 0.02
2,4-DHBA	6	No inhibition until 5.60	–	–
2,5-DHBA	5	0.21–0.49	266–2832	28 ± 7
2,6-DHBA	6	No inhibition until 5.60	–	–
3,4-DHBA	5	2.10–3.50	330–680	1.25 ± 0.06
3,5-DHBA	6	No inhibition until 5.60	–	–
Caffeic acid	4	2.10–3.15	328–943	1.6 ± 0.2
Ferulic acid	4	-no inhibition until 5.60	–	–

3,4- isomers. Caffeic acid is an effective inhibitor while the other phenolic acid, ferulic, does not show any activity until 5.60 mM concentration.

Theory

Mechanism for the unperturbed reaction

A detailed mechanism for the OE reaction involving 30 steps and 26 independent variables was first presented in 1989 by Luo et al. [8]; this mechanism was satisfactorily checked comparing some experimental and simulated behaviors both under batch and flow conditions [8]. In this mechanism, HOO· radicals play an important role, but since the pK_a for the couple HOO·/O_2^- is 4.8 [22], and the reaction takes place between about pH 10 and 12, most HOO· would be in the form of O_2^-. Thus, Luo et al. [8] used a rate constant that is appropriate for about pH 10–12 for the disproportionation of HOO·. In a previous paper, Luo et al. [23], reported a strong evidence of the formation of a superoxide–copper(I) complex, formally [HO_2-Cu(I)], in the Cu(II)-catalyzed alkaline decomposition of hydrogen peroxide, so they inserted these species in their mechanism [8]. The same mechanism has been reported in a paper by Orbàn et al. about mechanistic studies on oxidation of several inorganic sulfur compounds by H_2O_2 with the copper ion as a catalyst that induces exotic phenomena as periodic oscillations [24]. More recently, the different potentiometric responses of various inert electrodes were successfully interpreted as a function of the concentrations of a few species. Particularly, the Pt electrode potential was found to be proportional to square root of the product of the concentrations of the most abundant copper ions with oxidation numbers I and II. In a simplified model of the OE reaction involving 12 steps and 9 intermediates, the $Cu(OH)_3^-$ and $Cu(OH)_2^-$ species were used [25].

In our previous paper [16], we further developed the reduced model given by Wisniewski et al. [25] to simulate different dynamic states achievable in the batch reactor, obtaining a reasonable qualitative agreement between simulated and experimental oscillating reaction and for the Arrhenius-type temperature dependence.

However, in order to improve the simulation of the unperturbed system and simulate perturbations by some phenolic compounds, we use here the original model with 30 steps and 26 variables [8]. Few rate constants were slightly adapted to get better fit of our experimental results, and changes are given in Table 2. Since the original values of all these constants were a just rough estimate, small changes in their values may be justified by slightly different experimental conditions in our experiments. In the same way as in the original model, in some reactions given in Table 2, both OH$^-$ and SCN$^-$ are given in square brackets which means they do not enter the rate laws of these reactions. The underlying assumption is that these reactions are not elementary steps. The used rate law corresponds to the rate determining step of the more complex mechanism which yields given stoichiometry.

Table 2 List of changed rate constants with respect to the original model

	Reaction	Rate constant	Original value [8]	Value used here
M3	HO_2 - $Cu(I)$ + [$2SCN^-$] → $Cu^+(SCN^-)_2$ + HO_2;	k_3	1×10^{-2} s^{-1}	4×10^{-2} s^{-1}
M4	$2\,HO_2$ → H_2O_2 + O_2	k_4	2×10^1 M^{-1} s^{-1}	4×10^1 M^{-1} s^{-1}
M5	H_2O_2 + SCN^- → $OSCN^-$ + H_2O	k_5	7.5×10^{-4} M^{-1} s^{-1}	1.5×10^{-3} M^{-1} s^{-1}
M18	$OS(O)CN^-$ + $OOS(O)CN^-$ + H_2O → $2\,OS(O)CN^-$ + [$2\,OH^-$]	k_{18}	3×10^3 M^{-1} s^{-1}	9×10^3 M^{-1} s^{-1}
M19	$2\,OS(O)CN$ + [$2\,OH^-$] → $OS(O)CN^-$ + $OOS(O)CN^-$ + H_2O	k_{19}	2×10^6 M^{-1} s^{-1}	2×10^6 M^{-1} s^{-1}
M20	$OS(O)CN^-$ + $Cu^+(SCN^-)_2$ → $OS(O)CN^-$ + Cu^{2+} + [$2\,SCN^-$]	k_{20}	1×10^5 M^{-1} s^{-1}	3×10^5 M^{-1} s^{-1}
M21	$OS(O)CN^-$ + HO_2 → SO_3^- + Cu^{2+} + $HOCN$	k_{21}	2×10^3 M^{-1} s^{-1}	8×10^3 M^{-1} s^{-1}
M22	SO_3^- + $Cu^+(SCN^-)_2$ → SO_3^{2-} + Cu^{2+} + [$2SCN^-$]	k_{22}	1.5×10^5 M^{-1} s^{-1}	4.5×10^5 M^{-1} s^{-1}
M23	$2\,SO_3^-$ + [$2\,OH^-$] + $Cu^+(SCN^-)_2$ → SO_4^{2-} + SO_3^{2-} + H_2O	k_{23}	1×10^8 M^{-1} s^{-1}	1×10^8 M^{-1} s^{-1}

Although their rate constants are unchanged, reactions M19 and M23 are added to this table since they took part in the feedback networks of the original model by Luo et al. [8]

We used the interpretation of the Pt electrode potential given by Wisniewski et al. [25] who gave the extended study dedicated to the interpretation of several inert electrodes in the OE system. They concluded that „…the oscillatory variations of the Pt electrode potential,… are caused mainly by the periodic increase of the exchange current density of the $Cu(OH)_3^-/Cu(OH)_2^-$ couple" and later interpreted this as Cu(II)/Cu(I) couple in general. Since in the model used here, there are no explicit $Cu(OH)_3^-$ and $Cu(OH)_2^-$ species, we used most abundant Cu(II) and Cu(I) species instead, and these are Cu^{2+} and $Cu(SCN)_2^-$. Moreover, Wisniewski et al. [25] concluded: „…that the model oscillatory peak of the "Pt-like" electrode is largely determined by the maximum value of $[Cu(OH)_3^-]^{1/2} \times [Cu(OH)_2^-]^{1/2}$". We accepted their conclusion and used $[Cu^{2+}]^{1/2} \times [Cu(SCN)_2^-]^{1/2}$, not for quantitative comparison with electrode potential, but rather for the identification of peak positions in our simulations, and most importantly for the evaluation of inhibition times. The expression for the mixed potential would be far more complex, essentially logarithmic/exponential dependence on the concentrations, but within the scope of present paper, there is no even need to derive this expression.

All numerical simulations were performed by employing the MATLAB ode15 s solver based on the Gear algorithm for integration of stiff differential equations [26]. Apart from rate constants for reactions M3–M5, M18, and M20–M22, other constants were the same as reported by Luo et al. [8]. Non-zero initial concentrations for simulations are given in Table 3, and all others are taken as zero (HO_2Cu, $Cu(SCN)_2$, $Cu(CN)_2$, $CuCN$, $OSCN^-$, $OOSCN^-$, $OOS(O)CN^-$, $OS(O)CN^-$, $\cdot OS(O)CN$, $\cdot O_2H$, $\cdot OH$, O_2, $HOCN$, OCN^-, $(CN)_2$, HCN, NH_3, NH_4^+, HCO_3^-, H_2CO_3, SO_3^-, SO_3^{2-}).

As reported in Fig. 3, a very satisfactory agreement is achieved between the simulation (Fig. 3) and the experiment reported in Fig. 1.

Oscillations in the simulation are damped with time and disappear after some finite period, typically for a batch reactor. A number of oscillations and characteristic ending time, both well correspond to the experiment.

Mechanism of the reaction perturbed by phenolics

As phenolic compounds exert antioxidant action mainly as free radical scavengers, the following two reactions were inserted in the model:

$$Ar(OH)_2 + HOO^{\cdot} \quad \rightarrow \quad H_2O_2 + \text{Other Unknown Products} \qquad (M31)$$

Table 3 Non-zero initial values of independent species concentrations, used in all simulations

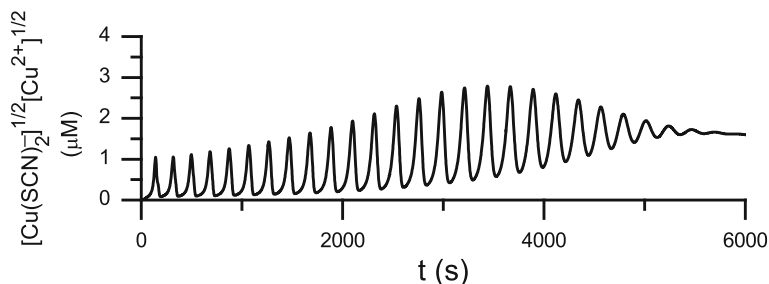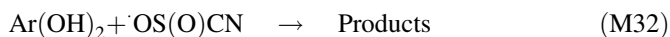| Compound	Initial concentration in M	Compound	Initial concentration in M
Cu^{2+}	0.0003	H_2O_2	0.2
SCN^-	0.06	OH^-	0.05

Fig. 3 Numerical simulation obtained with a model from Ref. [8] with initial concentrations given in Table 3, in accordance to experiment reported in Fig. 1

$$Ar(OH)_2 + \cdot OS(O)CN \quad \rightarrow \quad Products \quad\quad\quad (M32)$$

Since hydrogen peroxide is regarded as a reactive oxygen species, we also added the reaction:

$$Ar(OH)_2 + H_2O_2 \quad \longrightarrow \quad Products \quad\quad\quad (M33)$$

The first two represent the removal of two important radicals in the OE reaction mechanism, $\cdot OS(O)CN$, which in fact mediates the autocatalysis of the intermediate species $^-OS(O)CN$ (reactions M18 + M9 + 2M20, see [8]), and HOO$\cdot$, which is responsible for the negative feedback, limiting the exponential growth of the autocatalytic species (see M21, M22, M23 [8]).

In general, the rates of reactions involving radicals are quite high, so these steps should give a robust contribute to the inhibitory effect.

Reaction M33 was introduced because H_2O_2 in the presence of a metal ion as catalyst can oxidize diphenols via the Fenton reaction [27].

We considered these reactions as a second order step even if surely they are composite reactions eventually giving stable quinones, besides sulfite, cyanate etc.

For the simulation purposes, all the rate constants were kept fixed to the previously given values, allowing k_{31}, k_{32} and k_{33} to vary for the best fit to experimental behaviors. In Figs. 4 and 5, a typical experimental and simulated recordings are reported for two concentrations of 2,3-DHBA and caffeic acid respectively in the OE mixture. The very good agreement between the experimental and calculated inhibition time can be noted. The same agreement was obtained with all initial concentration of these inhibitors as far as with the other four used phenolics, finally obtaining the set of unique rate constants reported in Table 4.

From the values reported in Table 4, it can be seen that rate constants for reaction M32 are somewhat higher than those for reaction M31. In the case of 2,5-DHBA k_{32} is two orders of magnitude higher than k_{31}. On the contrary, the reaction of phenolics with hydrogen peroxide is very slow with rate constants by two to seven orders of magnitude smaller than those of reaction M32, so we can conclude that the main action of the examined compounds is radical scavengers.

The radical scavenging property of polyphenols becomes particularly important in biology to limit cellular oxidative stress due to excess production of oxygen-
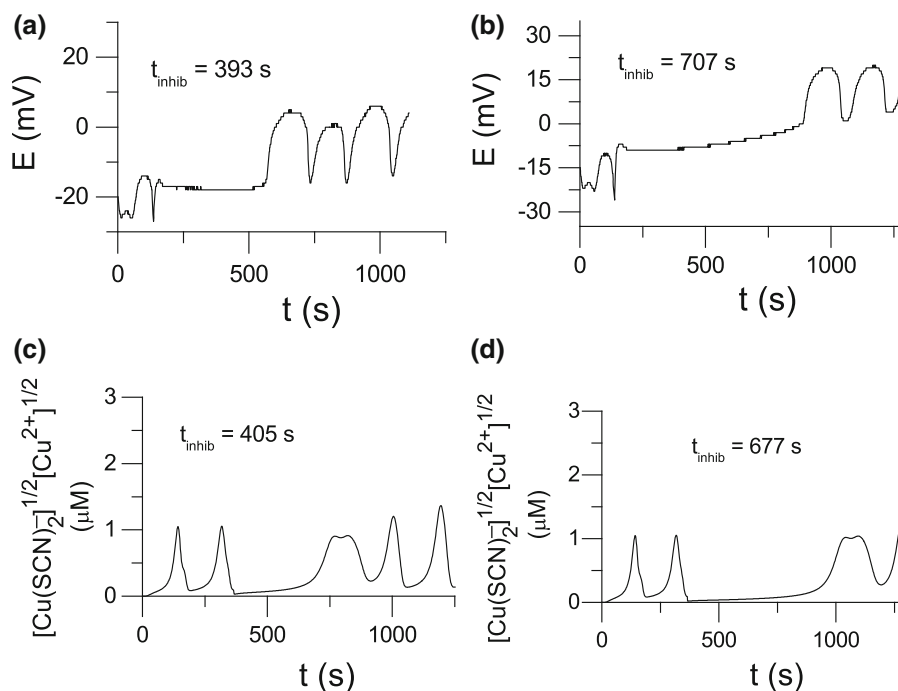
Fig. 4 **a**, **b** Experimental behavior of E(Pt) versus time of an inhibited OE mixture (initial conc. see text) when 1.0 ml of suitably diluted solution of 2,3-DHBA was added after the second oscillation (initial conc. 2,3-DHBA in mixture **a** 1.75 mM and **b** 3.5 mM); **c**, **d**: simulated behavior of the $\sqrt{[Cu(SCN)_2^-][Cu^{2+}]}$ for a mixture of the same composition as in experiments given in parts (**a**) and (**b**), respectively

reactive species, in general hydroxyl and hydroperoxyl radicals such as some neutral molecules as hydrogen peroxide. In fact, oxidative stress is considered to play a role in the onset of many diseases, from cardiovascular disease to some cancers [28]. It is usual to refer polyphenols as phenolic antioxidants.

In the case presented here, it can be concluded that diphenols and diphenolic acids are more effective versus the ·OS(O)CN than HOO· radical species. It should be noticed, however, that also cyanosulfite is an oxygen-centered species that play an important role in the positive feedback (onset of oscillation) of the OE reaction mechanism [8], as stated above.

Discussion and conclusions

Recently, a theoretical method to calculate the bond dissociation enthalpies (BDE) for molecules belonging to the class of phenolic antioxidants and to correlate them with their free radical scavenging activities has been reported by Wright et al. [29]. It was found that the number of phenolic OH groups is largely irrelevant and that it is the strategic placing of such groups that determine the antioxidant activity. These authors also proposed empirical additivity rules that take into account the electronic,
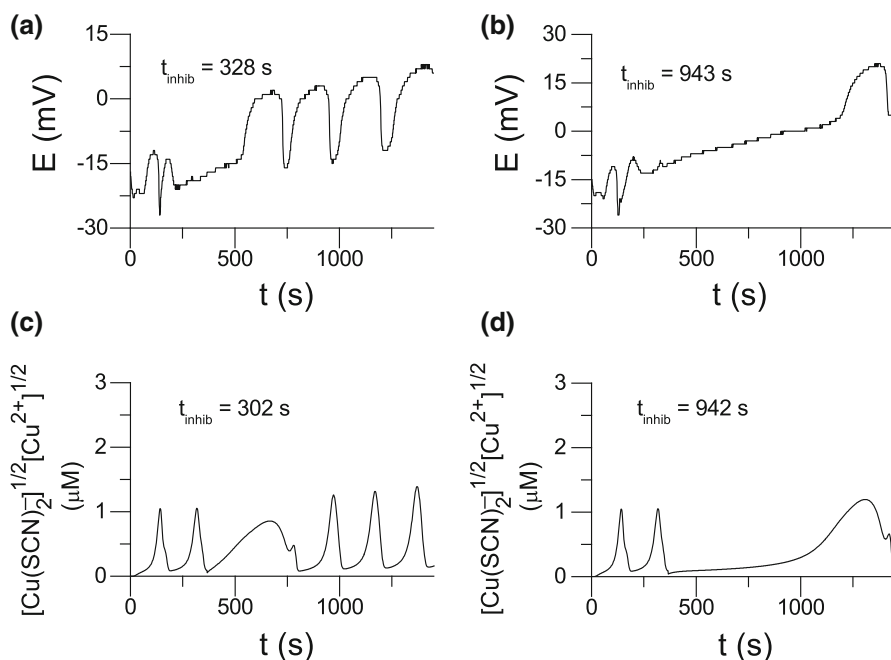
Fig. 5 **a**, **b** Experimental behaviour of E(Pt) versus time of an inhibited OE mixture (initial conc. see text) when 1.0 ml of suitably diluted solution of caffeic acid was added after the second oscillation (initial conc. caffeic acid in mixture **a** 2.10 mM and **b** 3.15 mM); **c**, **d**: simulated behavior of the $\sqrt{[Cu(SCN)_2^-][Cu^{2+}]}$ for a mixture of the same composition as in experiments given in parts (**a**) and (**b**), respectively

Table 4 Calculated rate constants from simulations with regression coefficients R^2 for the simulated inhibition times dependence on inhibitor concentration

Compound	k_{31} $10^4 \times M^{-1} s^{-1}$	k_{32} $10^4 \times M^{-1} s^{-1}$	k_{33} $10^{-3} \times M^{-1} s^{-1}$	R^2
Resorcinol	3.21	4.80	15.5	0.9832
Catechol	7.67	1.06	5.35	0.9999
Hydroquinone	2.39	6.13	5.32	0.9913
2,3-DHBA	0.0397	9.59	18.9	0.9884
2,5-DHBA	0.222	198	4.75	0.9950
3,4-DHBA	1.04	3.94	10.3	0.9957
Caffeic acid	0.704	2.90	4.06	0.9999

H-bond, and conjugation of substituents in the phenol parent molecule to evaluate the antioxidant power and the structure–activity relations. In this way, a value of BDE of a phenolic compound or ΔBDE = (BDEcomp − BDEφ − OH) can easily be calculated from the data reported in Table 4 of Ref. [29].

Diphenols

For diphenols, we obtained:

$$1,2\text{-(catechol)} \, \Delta BDE \; = -9.2 \; \text{Kcal/mol}$$

$$1,3\text{-(resorcinol)} \, \Delta BDE \; = -0.4 \; \text{Kcal/mol}$$

$$1,4\text{-(hydroquinone)} \, \Delta BDE \; = -5.9 \; \text{Kcal/mol}$$

This shows that O–H bonds are easily broken in catechol than in hydroquinone than in resorcinol. Zazo et al. [27], in a detailed study of phenol oxidation by H_2O_2 via the Fenton reagent, found that in the first stage of the reaction some amount of catechol, hydroquinone, and a negligible amount of resorcinol were formed, then they observed the formation of 1,4-benzoquinone. They conclude that the –*o* position of phenol is favored in the phenol hydroxylation, but they were unable to detect 1,2-benzoquinone because of *o*-quinones are very unstable compounds, Zazo et al. also explored the behavior of catechol and hydroquinone reactions with the Fenton reagent finding that this latter quickly reacts than the former compound. They did not explore the behavior of resorcinol also because *m*-quinones do not exist. There is a general consensus that the first step of the reaction between diphenols and radicals as HO˙ or HOO˙ is an H atom transfer from a phenolic OH group to the radical. Hydroquinone then initially leads to 1,4-semiquinone radical that in alkaline medium is eventually quickly transformed in the stable 1,4-benzoquinone. On the contrary, catechol initially gives 1,2-semiquinone that slowly could lead to the unstable 1,2-benzoquinone [30]. Then it can be concluded that hydroquinone is a better inhibitor of OE reaction than catechol.

Resorcinol was chosen as a reference for the "antioxidant relative capacity" of phenolics and the experimental results showed it is in some way a better inhibitor than catechol. Even if it cannot form a quinone, it is able to transfer an H atom forming a semiquinone radical that later can rapidly react together leading to peroxy compounds. This could justify the observed order of activity among diphenols, in agreement with the calculated k_{32} constants (see Table 4).

Di-hydroxybenzoic acids

In these compounds, the BDE of the phenolic O–H groups is strongly influenced by their relative positions with respect to the –COOH group. Using the data reported in Table 4 of Ref. [29] the following values of ΔBDE can be calculated:

$$2,3\text{-DHBA} \; \Delta BDE(\text{O}-\text{H in 2}) \; = -1.1 \; \text{Kcal/mol}; \; \Delta BDE(\text{O}-\text{H in 3})$$
$$= -6.7 \; \text{Kcal/mol}$$

$$2,4\text{-DHBA} \; \Delta BDE(\text{O}-\text{H in 2}) \; = +2.2 \; \text{Kcal/mol}; \; \Delta BDE(\text{O}-\text{H in 4})$$
$$= +7.7 \; \text{Kcal/mol}$$

2, 5-DHBA ΔBDE(O−H in 2) $= +2.2$ Kcal/mol; ΔBDE(O−H in 5)
$ = -3.4$ Kcal/mol

2, 6-DHBA ΔBDE(O−H in 2) $= +7.7$ Kcal/mol; ΔBDE(O−H in 6)
$ = +7.7$ Kcal/mol

3, 4-DHBA ΔBDE(O−H in 3) $= -6.6$ Kcal/mol; ΔBDE(O−H in 4)
$ = -6.6$ Kcal/mol

3, 5-DHBA ΔBDE(O−H in 3) $= +2.1$ Kcal/mol; ΔBDE(O−H in 5)
$ = +2.1$ Kcal/mol

From these calculations, it can be seen that the breaking of both O–H bonds is highly unfavored in the 2,4-; 2,6- and 3,5-isomers. These isomers all have the two OH groups in *m*-position and cannot form the quinone reacting with radicals or with hydrogen peroxide. Moreover, for compound 2,4- and especially for 2,6-, the steric hindrance of the –COOH group must also be taken into account. These considerations can account for the absence of inhibitory effects on the OE reaction (almost until a concentration of 5.60 mM), confirmed by mechanistic calculations.

The break of O–H bond is favored for both OH groups in 2,3- and 3,4-DHBA but the reactions with radicals or H_2O_2 lead to unstable *o*-quinones, so they can act as inhibitors with some potency.

The order of activity is 2,3- $>$ 3,4 in agreement with the recent theoretical calculations reported by Milenkovic et al. [31].

The behavior of 2,5-DHBA

This compound shows an unexpected higher activity with respect to other DHBAs isomers. ΔBDE calculations showed that the O–H bond break is favored for only the OH group in *p*-position. We believe that the only possible explanation should be that 2,5 DHBA leads to some unusual stabilization of the radical species. This species could then give the stable 1-carboxy 2,5-benzoquinone either by reaction with radicals or with H_2O_2 justifying at least in part, the unusual activity of this compound as inhibitor of oscillations in the OE reaction

Hydroxycinnamic acids

Similar considerations can be made for caffeic and ferulic acids, the first has two phenolic OH groups highly favored from the BDE point of view and can also react with radicals and H_2O_2 to give an unstable *o*-quinone, while the second doesn't show antioxidant activity almost up to 5.60 mM.

References

1. Bray WC (1921) A periodic reaction in homogeneous solution and its relation to catalysis. J Am Chem Soc 43:1262–1267
2. Bray WC, Liebhafsky HA (1931) Reactions involving hydrogen peroxide, iodine and iodate ion. I. Introduction. J Am Chem Soc 53:38–44
3. Belousov BP (1959) in: Sbornik Referatov po Radiatsinnoi Meditsine (1958, Medgiz, Moscow), pp 145–147 (in Russian). English translation in: Field RJ, Burger M (1985) (ed) Oscillations and travelling waves in chemical systems, Wiley, New York, pp 605–613
4. Zhabotinsky AM (1964) Periodic course of oxidation of malonic acid solution. An investigation of the kinetics of the reaction of Belousov. Biofizica 9:329–335 **(in Russian)**
5. Zhabotinsky AM (1964) Periodic liquid-phase oxidation reactions. Doklady Akademii Nauk SSR 157:392–395 **(in Russian)**
6. Briggs TS, Rauscher WC (1973) An oscillating iodine clock. J Chem Educ 50:496–496
7. Orbán M (1986) Oscillations and bistability in the Cu(II)-catalyzed reaction between H_2O_2 and KSCN. J Am Chem Soc 108:6893–6898
8. Luo Y, Orbán M, Kustin K, Epstein IR (1989) Mechanistic study of oscillations and bistability in the Cu(II)-catalyzed reaction between H_2O_2 and KSCN. J Am Chem Soc 111:4541–4548
9. Epstein IR (1987) Patterns in time and space—generated by chemistry. Chem Eng News 65:24–36
10. Sharma KR, Noyes RM (1976) Oscillations in chemical systems. 13. A detailed molecular mechanism for the Bray-Liebhafsky reaction of iodate and hydrogen peroxide. J Am Chem Soc 98:4345–4361
11. Furrow SD, Cervellati R, Amadori G (2002) New substrates for the oscillating Briggs-Rauscher reaction. J Phys Chem A 106:5841–5850
12. Olexova A, Marakavova M, Melichercik M, Triendl L (2010) Oscillatory system I –, H_2O_2, $HClO_4$: the modified form of the Bray-Liebhafsky reaction. J Phys Chem A 114:7026–7029
13. Schmitz G (2010) Iodine oxidation by hydrogen peroxide in acidic solutions, Bray-Liebhafsky reaction and other related reactions. Phys Chem Chem Phys 12:6605–6615
14. Stanisavljev DR, Milenković MC, Mojović MD, Popovic-Bijelic AD (2011) Oxygen-centered radicals in iodine chemical oscillators. J Phys Chem A 115:7955–7958
15. Milenković MC, Stanisavljev DR (2012) Role of free radicals in modeling the iodide-peroxide reaction mechanism. J Phys Chem A 116:5541–5548
16. Čupić ZD, Greco E, Cervellati R (2015) New Experimental and Mechanistic Investigation on the KSCN-H_2O_2-NaOH-Cu(II)-catalyzed oscillating system (Orbàn–Epstein reaction): inhibitory effects by diphenols. Int J Chem Kinet 47:82–92
17. Cervellati R, Furrow SD (2013) Effects of additives on the oscillations of the Briggs-Rauscher reaction. Russ J Phys Chem 87:2121–2126
18. Clarke BL (1980) Stability of complex reaction networks. In: Prigogine I, Rice SA (eds) Advances in chemical physics, vol 43. Wiley, New York, NY, pp 1–216
19. Clarke BL (1998) Stoichiometric network analysis. Cell Biophys 12:237–253
20. Čupić Ž, Marković V, Ivanović A, Lj Kolar-Anić (2011) Modeling of the complex nonlinear processes: determination of the instability region by the stoichiometric network analysis. In: Brennan CR (ed) Mathematical modelling. Nova Science Publishers Inc., New York, pp 111–178
21. Cervellati R, Hoener K, Furrow SD, Neddens C, Costa S (2001) The Briggs-Rauscher reaction as a test to measure the activity of antioxidants. Helv Chim Acta 84:3533–3547
22. Bielsky BHJ, Cabelli DE, Arudi RL, Ross AB (1985) Reactivity of HO_2/O_2^- radicals in aqueous solution. J Phys Chem Ref Data 14:1041–1100
23. Luo Y, Kustin K, Epstein IR (1988) Kinetics and mechanism of H_2O_2 decomposition catalyzed by Cu^{2+} in alkaline solution. Inorg Chem 27:2489–2496
24. Orbán M, Kurin-Csorgei K, Ràbai G, Epstein IR (2000) Mechanistic studies of oscillatory copper(II) catalyzed oxidation reactions of sulfur compounds. Chem Eng Sci 55:267–273
25. Wisniewski A, Pekala K, Orlik M (2010) Kinetic model of the $H_2O_2 - SCN^- - OH^- - Cu^{2+}$ oscillator and its application to the interpretation of the potentiometric responses of various inert electrodes monitoring the reaction course. J Phys Chem A 114:183–190
26. Gear CW (1971) Numerical initial value problems in ordinary differential equations. Englewood Cliffs Prentice-Hall Inc, New Jersey

27. Zazo JA, Casas JA, Mohedano AF, Gilarranz MA, Rodriäguez JJ (2005) Chemical pathway and kinetics of phenol oxidation by Fenton's reagent. Environ Sci Technol 39:9295–9302
28. Pham-Huy LA, Hua H, Pham-Huy C (2008) Free radicals antioxidants in disease and health. Int J Biomed Sci 4:89–96
29. Wright JS, Johnson ER, Di Labio GA (2001) Predicting the activity of phenolic antioxidants: theoretical method, analysis of substituent effects and application to major families of antioxidants. J Am Chem Soc 123:1173–1183
30. Eckschlager K, Horsak I, Veprek Siska J (1974) Oxidation of metol, resorcinol and pyrocatechol with hydrogen peroxide, catalyzed by Cu^{2+} ions. Collect Czech Chem Commun 39:2353–2362
31. Milenkovic D, Jorovic J, Jeremic S, Dimitric Markovic J, Avdovic EH, Markovic Z (2017) Free radical scavenging potency of dihydroxybenzoic acids. J Chem. https://doi.org/10.1155/2017/5936239