Remote stereoelectronic effects in pyrrolidone- and caprolactam-substituted phenols: discrepancies in antioxidant properties evaluated by electrochemical oxidation and H-atom transfer reactivity

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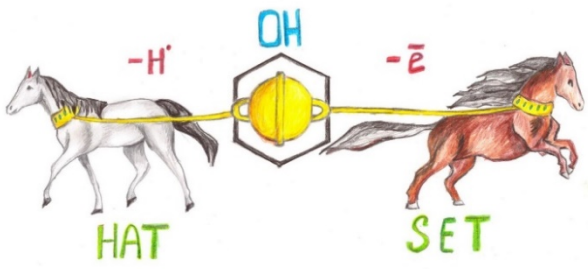


Abstract

New antioxidants are commonly evaluated via two main approaches, i.e., the ability to donate an electron and the ability to intercept free radicals. We compared these approaches by evaluating properties of eleven compounds containing both antioxidant moieties (mono- and polyphenols) and auxiliary pharmacophores (pyrrolidone and caprolactam). Several common antioxidants, such as

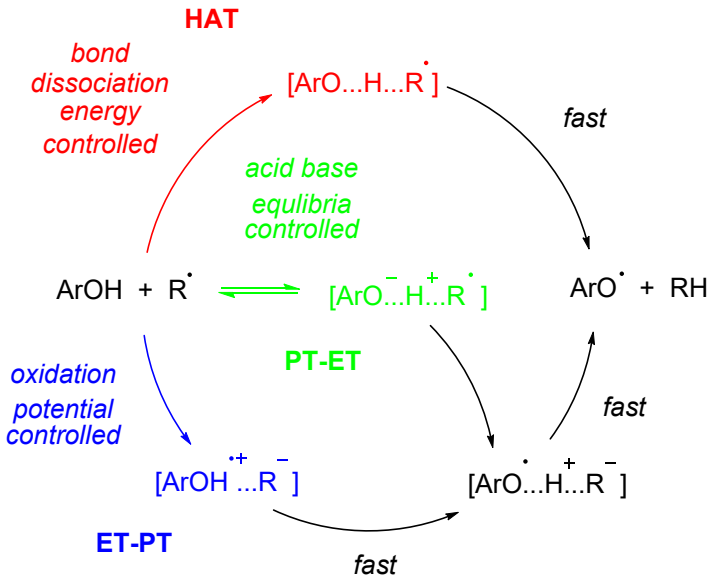
butylated hydroxytoluene (BHT), 2,3,5-trimethylphenol (TMP), quercetin, and dihydroquercetin, were added for comparison. The antioxidant properties of these compounds were determined by their rates of reaction with 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and their oxidation potentials from cyclic voltammetry. Although these methods test different chemical properties, their results correlate reasonably well. However, several exceptions exist where the two methods give opposite predictions! One of them is the different behaviour of mono- and polyphenols: polyphenols can react with DPPH more than an order of magnitude faster than monophenols of a similar oxidation potential. The second exception stems from the size of a "bystander" lactam ring at the benzylic position. Although the phenols with a 7-membered lactam ring are harder to oxidize, the sterically non-hindered compounds react with DPPH about 2x faster than the analogous 5-membered lactams. The limitations of computational methods, especially those based on a single parameter, are also evaluated and discussed.

Keywords: phenolic antioxidants, lactams, cyclic voltammetry, DPPH test, stereoelectronic effects

Introduction

Research on antioxidants draws considerable attention as illustrated by the nearly exponential increase in scientific publications on this topic.[1] To a large extent, this continuing interest can be explained by two reasons: (*i*) the variety of applications (antioxidant systems in living organisms,[2] dietary supplements,[3] preservatives in food [4-5] and other areas [6]), and (*ii*) the breadth of the concept of "antioxidant" itself (i.e. preventing electron removal from a molecular entity, increase in the oxidation number, gain of oxygen, and/or loss of hydrogen [7]). Generally, the ability of antioxidants to stop radical chains by intercepting free radicals is considered to be their most important feature.[8-9] This process can occur through several fundamentally different mechanisms.[10,11,12] The key mechanistic scenarios for phenols, one of the most common type of antioxidants, are presented in Scheme 1.[13] The deceivingly simple process of hydrogen atom transfer can proceed through a variety

of mechanisms: HAT – a process where a hydrogen atom (H•) from the antioxidant (Ar-OH) is transferred to a peroxy radical (ROO•) to give a more stable free radical (ArO•). This process is typically related to the ArO-H BDE (Bond Dissociation Energy).[14,15,16] Both PT-ET – stepwise proton-transfer-electron-transfer, and ET-PT – stepwise electron-transfer-proton-transfer are two-step reactions, where the former is related to ArO-H acidity and ionization potential, and the latter is related to oxidation potential. Even more diverse scenarios exist when multiple H-atoms are removed from one molecule.[17,18,19,20]



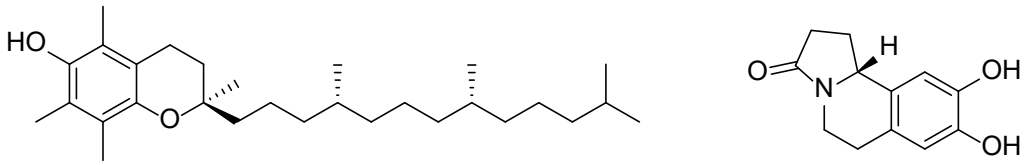
Scheme 1. Various mechanisms of interaction of phenols as antioxidants with free radicals: ET-PT (*blue*, electron transfer followed by proton transfer), PT-ET (*green*, proton transfer followed by electron transfer), and HAT (*red*, hydrogen-atom transfer).

Considering these mechanistic variations, it is interesting to evaluate the main choices of methods used for testing the antioxidant activity. First, one can measure the oxidation potential [21], i.e., the ability of a compound to donate an electron to an oxidant. Equally common is the determination of the kinetics of the reaction between an antioxidant and model free radicals. The most common of

the latter is the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.[22,23,24] This method was also standardized.[25] Even though both approaches provide quantitative data to assess antioxidant activity, the data obtained by only one method is obviously insufficient for the confident comparison of antioxidants that operate via different mechanisms. However, even despite the variety of possible mechanisms and the large conceptual differences between these approaches, it is not common practice to compare antioxidants using the different methods.[26,27,28] Thus, one of the goals of this work was to directly compare the two methods. By evaluating the oxidation potentials and kinetics of reactions with DPPH for the same set of mono- and polyphenols, we planned to determine whether these different approaches give the same answers when comparing the relative activity of two antioxidants.

The additional element in the design of new antioxidants is the effect of auxiliary pharmacophores on the overall physiological activity. This effect can be well illustrated by tocopherol (Scheme 2) – one of the most important physiological antioxidants of the vitamin E group.[29] Tocopherol contains an easily oxidized phenolic moiety and a long alkyl substituent having several stereogenic centers. Although the latter does not affect the redox properties of the compound, it is well recognized by the phospholipid layers in cell membranes. Hence, the chiral form of RRR-α-tocopherol exhibits the greatest antioxidant activity among the eight possible isomers under physiological conditions.[30] Another well-known example is the physiological antioxidant activity of flavonoids. Despite the polyphenolic nature of these compounds, which should render them much more powerful antioxidants than mononuclear phenols in accordance with their redox properties, many flavonoids have relatively low bioavailability.[31,32,33,34] Hence, they are rapidly eliminated from the body, and are relatively inactive as antioxidants. The toxicity of phenols is also an essential point[35] that can be potentially reduced by introducing a suitable pharmacophore.[36] Furthermore, several natural compounds, bearing both phenolic and heterocyclic moieties, when the latter belongs to lactams, are known for their biological activity. Thus, phenolic alkaloid oleracein E (Scheme 2), made via the

fusion of tetrahydroisoquinoline and pyrrolidone fragments, demonstrates neuroprotective activity[37] whereas brominated phenols with lactam substituents, extracted from algae, possess antifungal properties.[38]

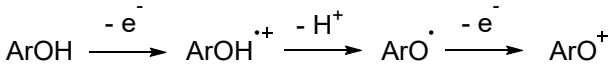


Scheme 2. (*left*) RRR-α-Tocopherol – a physiological phenolic antioxidant from the group of vitamin E compounds, (*right*) oleracein E – natural antioxidant with a lactam moiety.

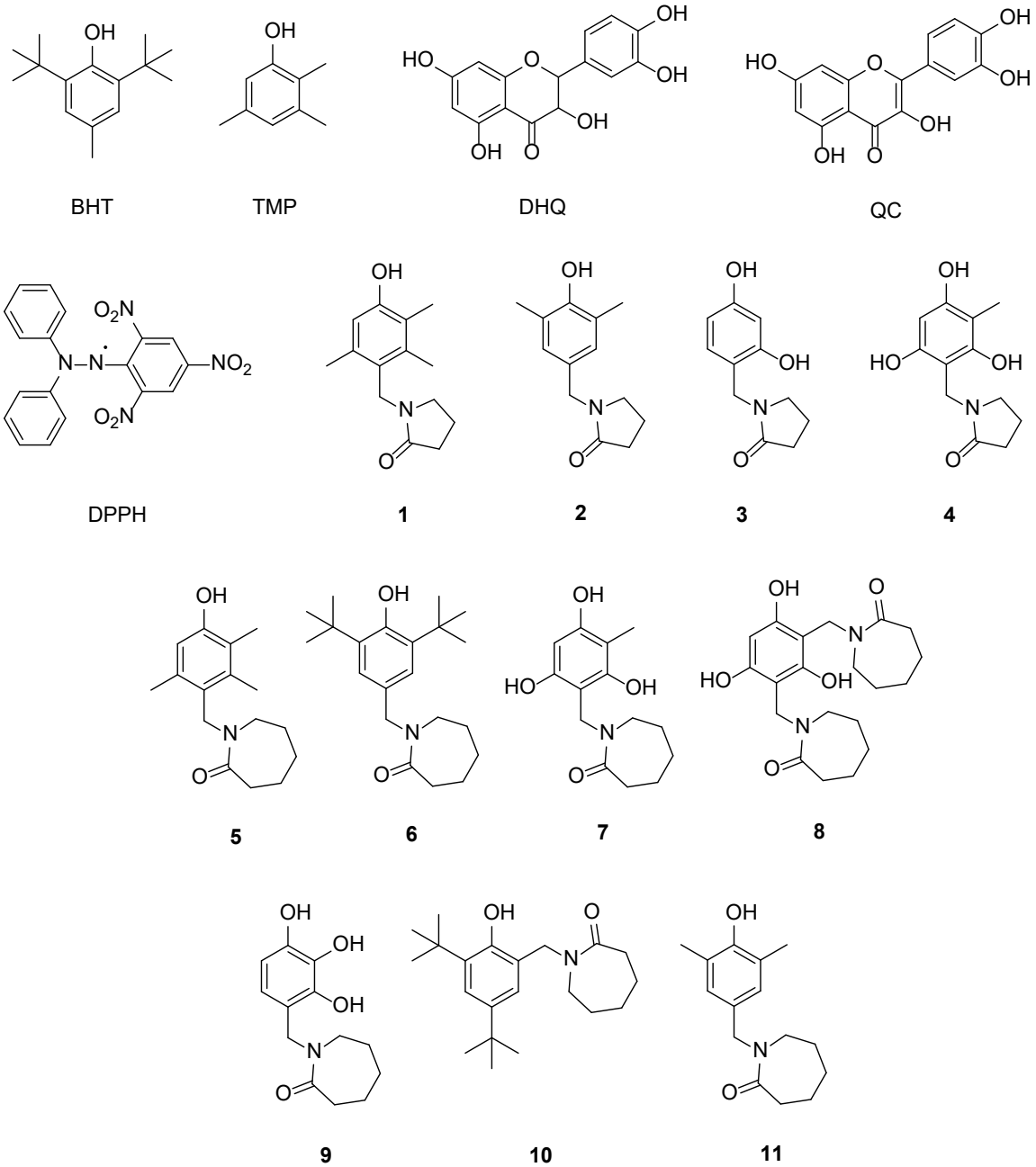
It is interesting to investigate the modulation of antioxidant properties via the introduction of pharmacophore moieties into phenols. Thus, the second aim of this work was to evaluate the antioxidant activity for mono- and polyphenols containing the pharmaceutically relevant heterocyclic moieties such as pyrrolidones **1-4** and caprolactams **5-11** (Scheme 3). The results were compared with the data for widely used synthetic (2,3,5-trimethylphenol, TMP and butylated hydroxytoluene, BHT) and natural (quercetin, QC and dihydroquercetin, DHQ) antioxidants.

Results and Discussions

For all compounds shown in Scheme 3, the voltammetry curves were recorded in 0.1 M Bu_4NBF_4/MeCN supporting electrolyte and the oxidation peak potentials were determined. As an example, the typical curves for caprolactam-substituted monophenol **5** and polyphenol **8** are presented in Figure 1. All compounds are oxidized irreversibly[39],[40] by the electron transfer–chemical reaction–electron transfer (ECE) mechanism. Due to the high acidity of phenol radical cations (i.e., more than 10 orders of magnitude increase relative to the phenol [41]), the primary oxidation products easily eject a proton and can be oxidized further:



With the exception of **1**, **2** and **6**, whose oxidation currents are complicated by subsequent peaks, the peak currents of all compounds correspond to two-electron transfer when referenced to the oxidation peak current of ferrocene (the standard for one-electron oxidation) under the same conditions. Examples (for phenols **5** and **8**) of the series of spectra used for kinetic measurements are presented in Figure 1.



Scheme 3. Structures of the studied compounds.

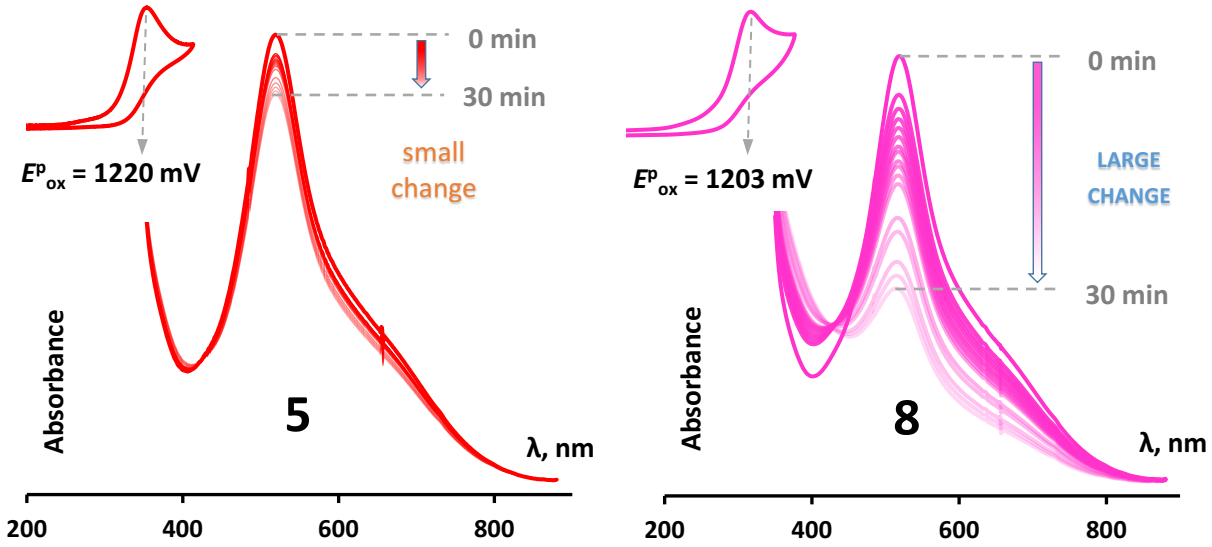


Figure 1. Voltammetry curves of oxidation for $5 \cdot 10^{-3}$ M solutions of **5** and **8** in 0.1 M Bu_4NBF_4/MeCN (with addition of 25 vol.% DMF in case of **8** for complete dissolution) recorded on a glassy carbon electrode (d = 1.7 mm) vs. Ag/AgCl at a scan rate of 100 mV s^{-1}, and UV spectra of the mixtures containing $1 \cdot 10^{-4}$ M **5** or **8** and $1 \cdot 10^{-4}$ M DPPH in acetonitrile taken in 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 10, 15, 20, 25 and 30 min after mixing. *Note that the cv curves are similar whereas the rate of reactions with DPPH is drastically different.*

In addition, the reaction kinetics of all the presented compounds with the stable free radical DPPH was investigated spectrophotometrically by the rate of disappearance of the 520 nm band related to π-π*-transition in DPPH. The spectrum obtained for DPPH solution without phenol was used as zero-time point. The obtained electrochemical and spectrophotometric results are summarized in Table 1. The percentage of DPPH reacted in 20 min is also given for clarity. The obtained data are also presented graphically in Figure 2.[42]

Table 1. Oxidation peak potentials obtained for $5 \cdot 10^{-3}$ M solutions of the studied compounds in 0.1 M Bu_4NBF_4/MeCN on a glassy carbon electrode vs. Ag/AgCl at a scan rate of 100 mV s^{-1} (E_{ox}^{p}), a number of electrons transferred at the first stage of oxidation estimated from the peak current relative to the ferrocene oxidation current under the same conditions (n_{ox}^{p}), a rate constant of reaction of $1 \cdot 10^{-4}$ M solutions of the compounds with DPPH in acetonitrile according to spectrophotometry data (k_{DPPH}^{298}) and mole % of reacted DPPH in 20 min of interaction ($\chi_{DPPH}^{20\,min}$). T = 298 K.

Compound	E_{ox}^{p}, *mV*	n_{ox}^{p}	k_{DPPH}^{298}, *L mol^{-1} s^{-1}*	$\chi_{DPPH}^{20\,min}$, *%*
BHT	1305	2	1.18 ± 0.02	8
TMP	1363	2	1.10 ± 0.07	7
DHQ	1228	2	22.3 ± 0.3	76
QC	1020	2	194.7 ± 0.8	80
1	1185	n/a [1]	1.8 ± 0.1	9
2	1180	n/a [1]	2.42 ± 0.05	15
3	1545	2	0.55 ± 0.04	4
4	1268	2	7.2 ± 0.2	45
5	1220	2	3.27 ± 0.07	16
5 [2]	1145	2	6.02 ± 0.02	29
5 [3]	1138	2	5.91 ± 0.01	25
6	1390	n/a [1]	0.72 ± 0.02	7
7	1297	2	13.3 ± 0.9	55
8	1203 [4]	2	37.0 ± 1.5	70
9	1012	2	1500 [5]	100
10	972 [6]	1	2.92 ± 0.01	16
11	1205	2	1.95 ± 0.04	13

[1] The first stage of oxidation is superimposed on the subsequent ones, which makes it difficult to reliably determine. [2] DMF (15 vol.%) was added to the solution. [3] DMF (25 vol.%) was added to the solution. [4] DMF (25 vol.%) was added to the solution to completely dissolve the substrate. [5] The reaction is too fast for a reliable determination of the rate constant error. [6] DMF (15 vol.%) was added to the solution to completely dissolve the substrate.

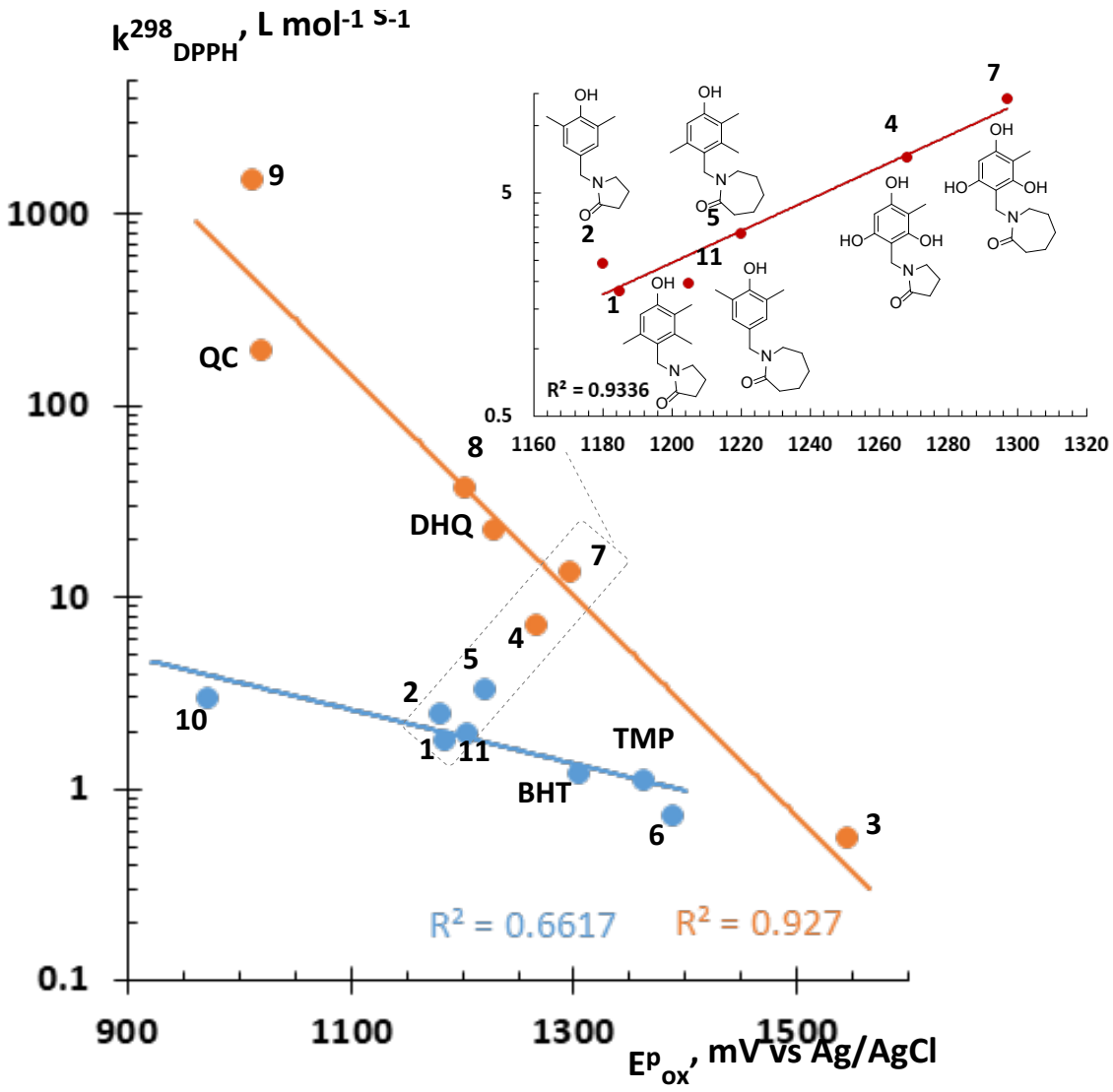


Figure 2. Correlation between the oxidation peak potentials obtained for $5 \cdot 10^{-3}$ M solutions of the studied compounds in 0.1 M Bu_4NBF_4/MeCN on a glassy carbon electrode vs. Ag/AgCl at a scan rate of 100 mV s^{-1} and the rate constants of interaction between $1 \cdot 10^{-4}$ M solutions of the compounds and DPPH in acetonitrile determined from the spectrophotometry data. Orange line – poly-, blue line – monophenols.

Importantly, despite the overall good correlation, there are pairs of molecules where the two methods give opposite predictions regarding the relative antioxidant ability, i.e., **7** vs. **4**, **5** vs. **1** and

11 vs. **2** (Figure 2). In fact, if the oxidation potentials are plotted vs. the DPPH rates, these six compounds show a seemingly paradoxical trend, i.e., an excellent correlation but with the slope opposite of that in Figure 2 (Figure 2, top box). *In this set, the molecules that are harder to oxidize react **faster** via H-atom transfer with DPPH.* Of course, a part of this paradox comes from the systematic differences between mono- and tri-phenols (**1**, **2**, **5** vs. **4**, **7, 11**) but there is also a very interesting trend associated with the "bystander" lactam ring size. Although the 7-membered lactams are harder to oxidize, the sterically non-hindered compounds react with DPPH about 2 times faster than the analogous 5-membered lactams. This ring size effect is observed for both the mono- and tri-phenols. There is one set of compounds (**2** and **11**) which deviate slightly from the trend. While the 7-membered lactam is still harder to oxidize, the rate of H-atom transfer with DPPH for **2** and **11** is nearly equivalent. This discrepancy from the general trend can be attributed to steric hindrance (due to o,o-substitution) minimizing the difference in the rate of reaction with DPPH.

The effect of the remote 'bystander' lactam substituent on the antioxidative ability

The addition of the 'bystander' lactam ring leads to a paradoxical relation between oxidation potentials and reactivity where compounds, that are harder to oxidize, are also more reactive towards DPPH (see the insert to Figure 2). Furthermore, the introduction of either of the two lactams leads to an increase in antioxidant activity relative to the respective phenol unsubstituted at the same position. Not only do these observations suggest that the benzylic lactam substituents are not innocent bystanders but this behavior is noteworthy considering that a σ-acceptor behavior can be expected from the benzylic C-N bond. In general, the σ-acceptor behavior should not facilitate but rather impede the oxidation of the derivative. This assumption is confirmed by quantum chemical calculation data showing that both mono- and polyphenols with both the 5- and 7-membered lactams draw electron density from the aromatic ring to σ*(C-N) orbital. Scheme 4 illustrates that by providing the respective hyperconjugative orbital donation energies (7.8 kcal/mol for **1** and 8.0 kcal/mol for **5**). Along the same

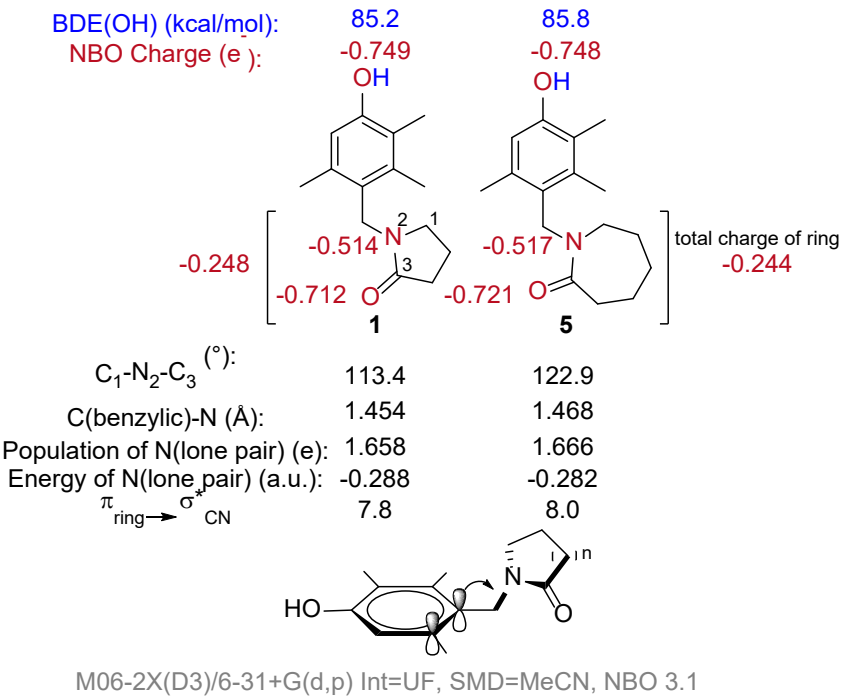
lines, the sum of the NBO atomic charges for all atoms in the lactam rings indicates that about 0.25 electrons are transferred to the heterocyclic moiety from the rest of the molecule.

In this context, it is interesting to compare the effect of H→CH_2NRR' substitution (TMP vs. **1**, **5**) with the effect of CH_3→CH_2NRR' substitution (BHT vs. **6**). From these comparisons, it is clear that CH_3 is a better donor than CH_2NRR' and both of them are better donors than an H atom. Apparently, the two benzylic C-H bonds in the CH_2NRR' moiety can partially compensate for the electron-accepting character of the benzylic σ*CN bond in respect to the phenol ring.

Comparison of the two lactam families shows that the 7-membered lactams are slightly harder to oxidize than the analogous 5-membered lactams for both mono- and polyphenols. A possible explanation for higher oxidation potentials for the caprolactam-substituted phenols is the greater acceptor ability of the C-N bond of the caprolactam. According to NBO analysis, there is a stronger hyperconjugative interaction between the phenolic π-system and the benzylic C-N bond in the caprolactam case. The greater importance of hyperconjugation is further supported by the differences in molecular geometries, e.g., the longer C-N bond connecting the 7-membered lactam to the phenol ring (Scheme 4). Such elongation is expected from the greater population of the respective σ*C-N orbital.

The origin of these differences is complex and seems to be derived from more than one component as it is often observed for stereoelectronic phenomena.[43] Analysis of the geometric and electronic features of the two lactam rings reveals subtle but apparently impactful differences between the 5- and the 7-membered systems. The smaller endocyclic C-N-C angle in the five-membered ring requires greater allocation of p-character to the respective endocyclic N-C bonds from the central nitrogen. As the result, the **exo**-cyclic N-C bond uses a nitrogen hybrid orbital with greater s-character, an electronic modulation that increases the effective electronegativity of nitrogen in this particular bond and is reflected in the shorter exocyclic N-C bond length for the smaller lactam **1**.[44] The

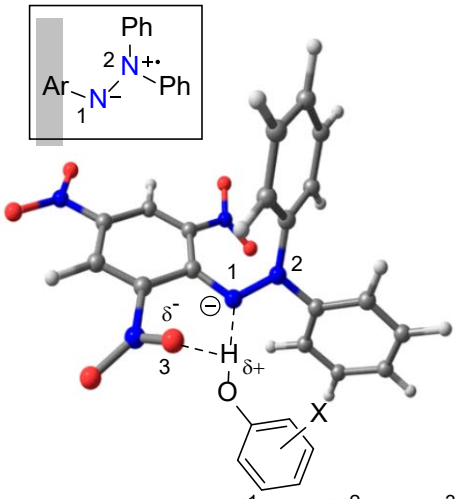
differences between the two rings are also reflected in the greater negative charges at the two heteroatoms (N and O) in the 7-membered lactam ring of **5**. The benzene ring acts like a relay that transmits this information (albeit with some expected dampening) to the phenol moiety as indicated by the slightly less negative charge on the phenolic oxygen of **5**. Clearly, these ground state differences are relatively small but they are likely to be amplified during the reaction path that leads to hydrogen abstraction from the phenolic OH by DPPH.



Scheme 4. The hyperconjugative donation from the phenolic π-system to the benzylic σ*(C-N) is slightly larger for the caprolactam substituent than for the pyrrolidone. This difference could potentially explain the oxidation trends between the five- and seven-membered analogues.

It is also interesting that the computed OH BDE for the two phenols are very close and do not follow the observed experimental trend. However, this is not surprising. The BDE values include

information about only one of the reactants, i.e. the phenol, without considering its interaction with the target DPPH radical.



	N^1	N^2	O^3
Natural Charge (e)	-0.270	-0.129	-0.381
Spin Density	0.39	0.31	0.02

NBO 3.1, uM06-2X(D3)/6-31+G(d,p) Int=UF, SMD=MeCN

Figure 3. Proton moving from the OH group of the phenol to the partial negatively charged N^1 of DPPH.

The observation of reaction with DPPH to be slightly faster for the less donating phenol suggests that phenol may behave as an acceptor in its interaction with DPPH. One could consider a scenario where H-atom transfer is accomplished via the so-called PT-ET mechanism (proton transfer followed by electron transfer), i.e. the green path in Scheme 1.[10,11,12,45,46] This mechanism was suggested to operate when alcohols are used as solvents. However, this path is unlikely in our case because phenols are unlikely to be sufficiently deprotonated in acetonitrile where they are ~13 orders of magnitude less acidic than in ethanol.[47,48] On the other hand, the observed trends can be explained by the features of phenol/DPPH transition state reported by Ingold and coworkers.[49] At the TS geometry, the transferring H-atom interacts with both a radical p-type orbital on N^1 and the lower

energy lone-pair orbital on N^1 (Figure 3). Furthermore, the large negative charge on the nearby O^3 suggests that both atoms (N^1 and O^3) can participate in H-bonding with the phenol, creating a negatively charged 'pocket' for HAT.

The presence of remote substituent effects on the rate of H-abstraction in these phenols by DPPH is another manifestation of polar effects in hydrogen atom transfer.[46,50,51,52,53,54]

The role of H-bonding and steric factors on the reactivity of the OH group in phenols

The antioxidant activity is also affected by the phenolic group environment, including intra- and intermolecular H-bonds. The single crystal structure of **5**, **6** and **10** are presented in Figure 4. In addition, the formation of an intramolecular hydrogen bond in **10** is shown, and Figure 5 shows the formation of intermolecular hydrogen bonds in single crystals of **5** and **6**. The hydrogen bond parameters are shown in Table 2. Crystal data, structure refinement, and more detailed information is provided in SI.

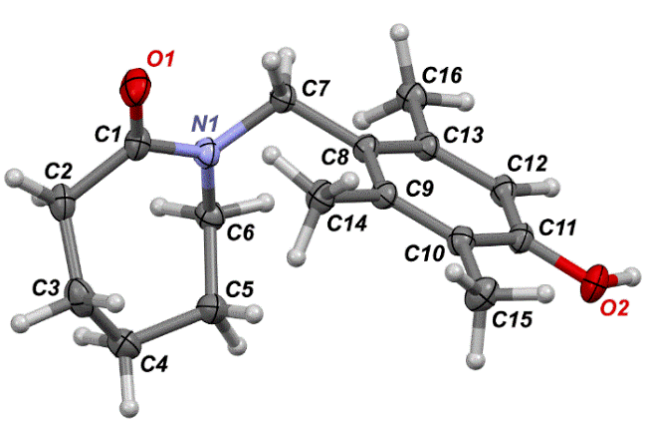
Table 2. Hydrogen bond parameters for **5**, **6** and **10** [Å and °].

Compound	D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
5	O2-H2···O1A	0.99(2)	1.70(2)	2.6798(12)	171.2(19)
6	O2-H2···O3	0.932(13)	1.732(13)	2.6563(8)	170.9(12)
	O4-H4···O1B	0.913(13)	1.800(13)	2.6599(8)	155.8(12)
10	O2-H2···O1	0.924(13)	1.755(13)	2.6577(8)	164.8(11)

Symmetry transformations used to generate equivalent atoms: (A) +x+1, +y, +z; (B) -x+1, -y+1, -z+1.

Thus, the formation of hydrogen bonds is a specific feature for these compounds. The presence of a lactam substituent in the ortho position (**10**) leads to O-H…O intramolecular bonding with the carbonyl oxygen. There are examples in the literature showing that the formation of an intramolecular hydrogen bond with the phenol facilitates oxidation of the phenol.[55,56] Here, the same effect should

facilitate the oxidation of phenol because the O-H…O H-bond is expected to become much stronger in the highly acidic phenol radical-cation in comparison to the moderately acidic phenols. It is known that complete proton abstraction under similar conditions with the formation of phenoxide makes its oxidation easier by as much as ~1.5 V.[57] An intermolecular H-bond may have a similar effect as the intramolecular bond. Therefore, the formation of an intermolecular hydrogen bond between phenolic and carbonyl groups could explain the easier oxidation of **5** in comparison with BHT and TMP, despite the presence of an acceptor substituent in **5**.



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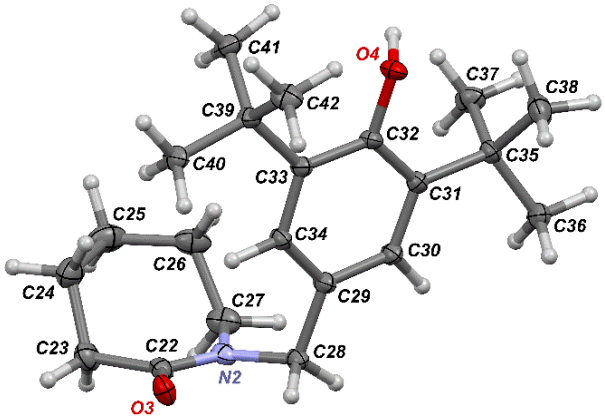

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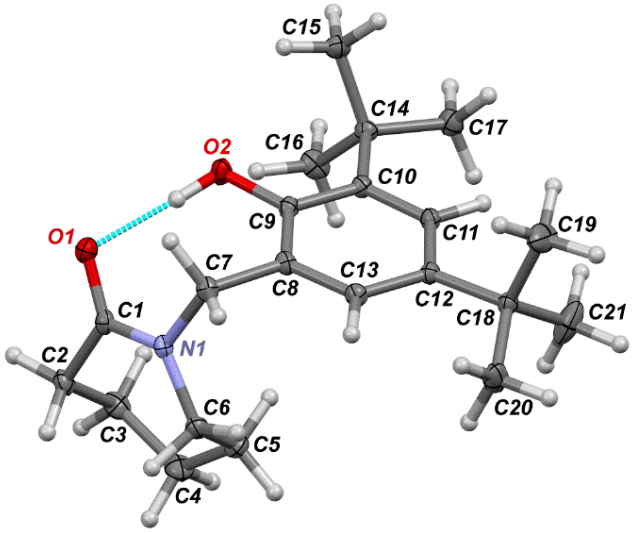


10

Figure 4. Molecular structures of **5**, **6** (only one crystallographically unique molecule is shown) and **10** (p = 50%). For **10** an intramolecular hydrogen bond is shown.

However, the behavior of **6**, which is close to BHT and TMP and sharply differs from other studied monophenols, looks unusual. To explain this, one more structural feature of the studied compounds can be noted. In the crystals, the phenolic groups of **5** and **10** are completely in the plane of the aromatic ring, deviating from it by no more than 0.5°. However, the presence of bulky ortho substituents in **6** causes the OH group to rotate out of the plane of the ring by 90° (Figure 5). The orthogonal second conformation of the OH group in phenols[58] and related OR groups in anisols is known to have quite different stereoelectronic properties.[59,60,61] This stereoelectronic effect may be partially responsible for the specific properties of **6** in addition to the steric hindrance imposed by the two bulky ortho t-Bu substituents on intermolecular reactions at the OH group.

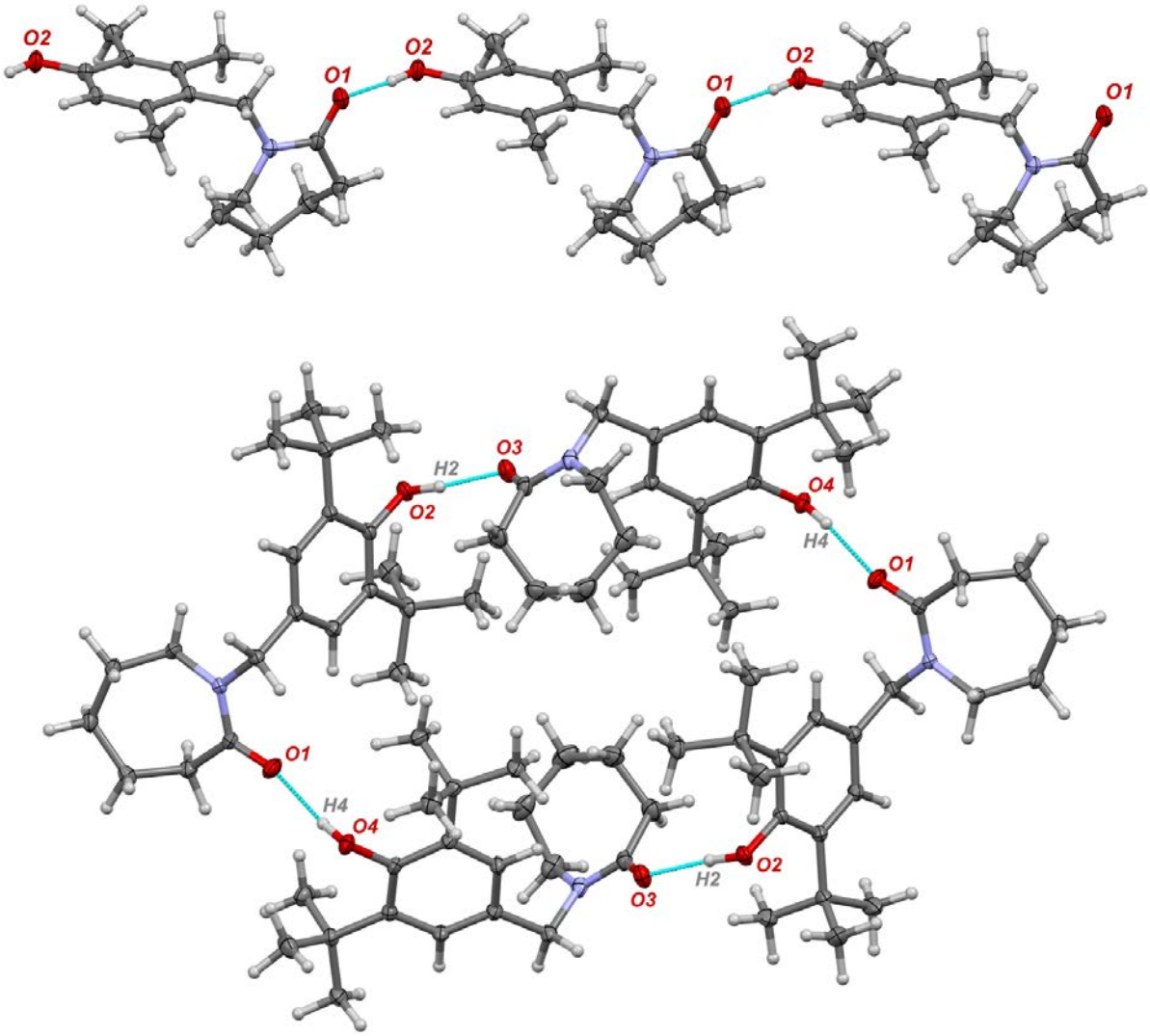


Figure 5. Intermolecular hydrogen bonding in **5** and **6**.

To gain further insights into the role of intramolecular H-bonding, we have also evaluated its effect on BDE and IP of selected phenols from the experimentally studied set (Scheme 5). This data illustrates the contrasting effect of intramolecular H-bonding on BDE and ionization potential. On one hand, the H-bond with an ortho carbonyl group greatly increases the OH BDE and *protects* that phenol group from HAT by a DPPH radical. In contrast, intramolecular H-bonding *facilitates* oxidation of the interacting phenol, by increasing electron density on the oxygen. Scheme 5 illustrates the origin of this difference: while the stabilizing H-bond is lost after the HAT process, the H-bond becomes much stronger after oxidation as illustrated by the shorter O…H-O distance in the radical cation. Furthermore, the OH proton of the phenol is transferred to the carbonyl.

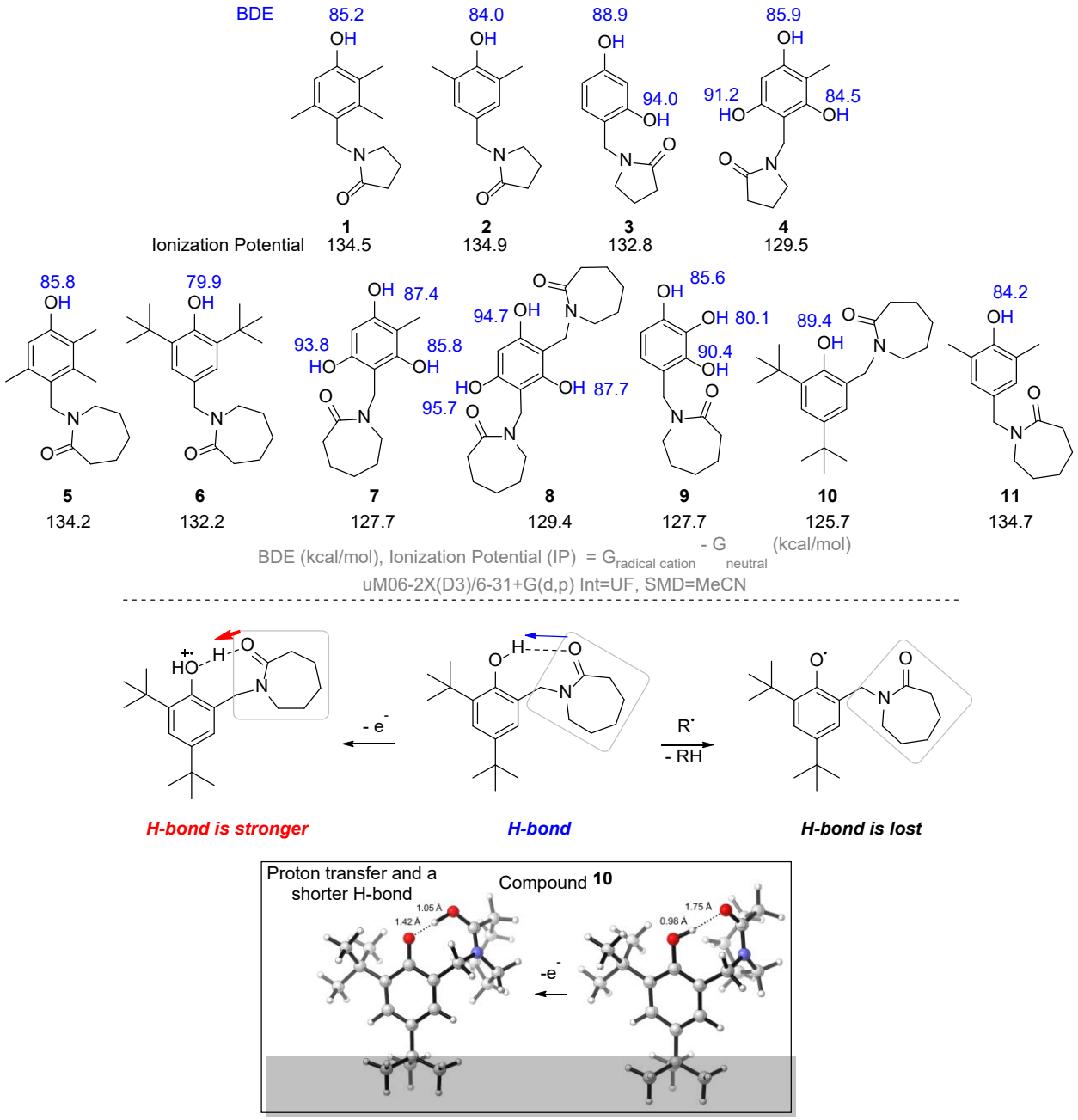
Poly- vs mono-phenols

Compared with monophenols, polyphenols are characterized by a much wider range of rate constants for the reaction with DPPH, while the range of oxidation potentials is comparable (Table 1, Figure 2). The three adjacent phenol groups in compound **9** give the best antioxidant properties.[62] The o-bis-phenols (catechols) DHQ and QC are also relatively easy to oxidize but additional factors are present, as discussed below. Scheme 6 illustrates the unique advantages that the presence of the two adjacent OH groups has on stabilization of the O-centered radical (decrease in the OH BDE) and/or stabilization of phenol radical cation (decrease in the ionization potential).

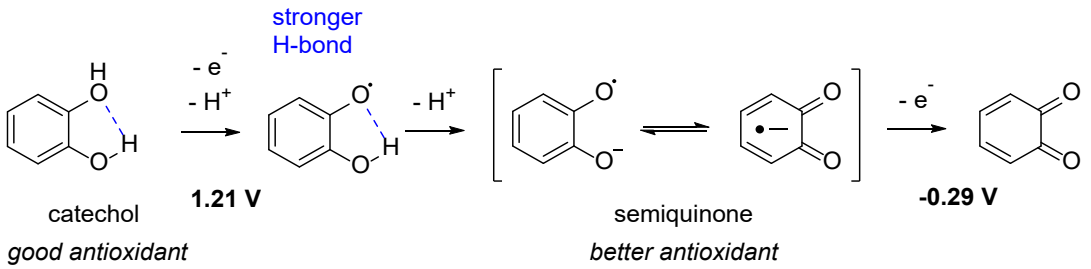
On the other hand, the 1,3,5-trihydroxy benzenes **4**, **7**, **8** have oxidation potentials comparable with those of monophenols **1**, **2**, **5**. The meta bis-phenol **3**, in fact, the hardest to oxidize, indicating that the meta-OR group is an acceptor substituent.[63]

Analysis of the individual relationships between specific pairs of substrates reveals additional interesting features. For example, the oxidation potential of DHQ is close to that of monophenols **5**, **1** and **2**, but DHQ reacts with DPPH an order of magnitude faster than the monophenols, a difference

which cannot be explained by the greater number of hydroxyl groups. In short, the measured oxidation potentials of mono- and polyphenols are comparable but polyphenols react much faster with DPPH.



Scheme 5. Top: Calculated BDEs and ionization potential for each compound. Bottom: Intramolecular H-bonding facilitates oxidation but hinders HAT.



Scheme 6. Origin of increased antioxidant activity in ortho-dihydroxyaromatic compounds: the formation of semi-quinones (potentials from [64] and [65]) and the formation of an intramolecular hydrogen bond.[68]

QC differs from DHQ by the presence of a double bond, which fundamentally affects the redox properties of the compound due to the existing conjugation. As a result, it is oxidized much easier than the above examples and the rate constant of its interaction with DPPH exceeds that of DHQ by an order of magnitude (and those of monophenols by two orders of magnitude).

It is also interesting to compare the meta bis-phenol **3** with the para-pyrrolidone substituted monophenols **1** and **2**. Replacement of an H-atom or a Me-group by a hydroxyl group in the meta position of a phenol does not increase the antioxidant properties of the compound, but, on the contrary, greatly decreases them (Table 1, Figure 2). The m-OR group is a sigma-acceptor and cannot stabilize the oxidized intermediates (radical or radical-cation) by resonance.[9]

The situation changes in an interesting way when going from **3** to **4** and from **7** to **8**. In both cases the addition of an acceptor (the replacement of a methyl group by the methylcaprolactam substituent (**7** → **8**) or introduction of a meta-OH group (**3** → **4**)) makes the oxidation easier. This paradox can be explained by the formation of -OH···O=C- hydrogen bonds discussed in the previous section.

Finally, compound **9** is the most easily oxidizable from the list. It also reacts with DPPH by almost an order of magnitude faster than QC, and more than three orders of magnitude faster than

BHT and TMP. This difference is likely to originate from the synergy of two effects – the high reactivity of 1,2,3-substituted trihydroxyaromatic compounds[66,67,68] and presence of the lactam/OH hydrogen bond discussed above.

Global trends: comparison of computed BDEs and IPs with the experimental HAT rates and oxidation potentials

Finally, it is interesting to compare the computational BDEs and ionization potentials with the observed experimental values. According to quantum chemical calculations, the poly and mono-phenol data can be separated into two trends (Figure 6). The polyphenols show a moderate correlation with bond dissociation enthalpy (BDE). Here, as expected, the weaker O-H bonds show higher reactivity towards the DPPH radical. Paradoxically, the monophenols show the opposite trend, where the weaker O-H bonds react slower. Although it is generally accepted that phenolic O-H BDE is a good indicator of antioxidant activity,[69] this reversed trend clearly suggests that there is an additional factor, perhaps the involvement of intermolecular H-bonds in solution or special features of the HAT transition states that overshadow the BDE contribution to reactivity.

The calculated ionization potentials (IP) of the phenols do show correlations in the right directions, i.e., phenols that are easier to oxidize react faster. However, the overall correlation with the H-abstraction rate is fair for polyphenols, but weak for monophenols.

Overall, the data shows that neither the atom-transfer ($ArOH \rightarrow ArO^{\bullet}$) nor electron transfer ($ArOH \rightarrow ArOH^{+}$) mechanisms fully explain the HAT ability of this family of phenols. In other words, individually neither ionization potential nor BDE seem to be able to accurately predict antioxidant activity.

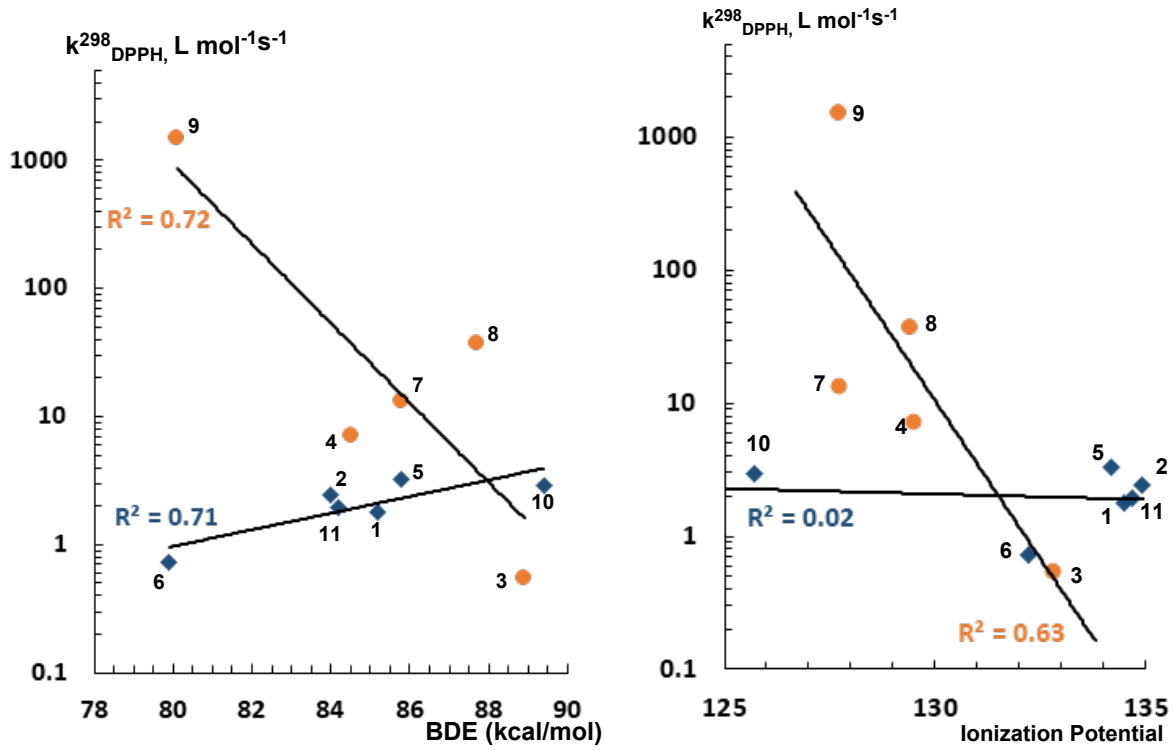


Figure 6. Orange dots are for polyphenols, blue for monophenols. Left: Bond dissociation energy versus rate of DPPH consumption, for polyphenols the lowest O-H BDE was used. Right: Ionization potential versus rate of DPPH consumption.

A traditional way to improve prediction accuracy is to include additional parameters. For example, a 2010 study[70] attempted to predict antioxidant activity using four parameters: BDE, IP, LogP (lipophilicity) and LogD (relative lipophilicity). It was determined that antioxidant activity could be predicted with a higher degree of accuracy when both BDE and IP were included as parameters. This study indicates that there is a complex relation between BDE and IP and neither are individually capable of accurately predicting a phenol's inhibitory ability. Considering the above, we attempted to fit our data to the two-parameter correlation from the literature (Figure 7):[70]

$$\rho IC_{50} = 6.682 - 0.023(\text{BDE} - \text{OH}) - 0.0036(\text{IP})$$

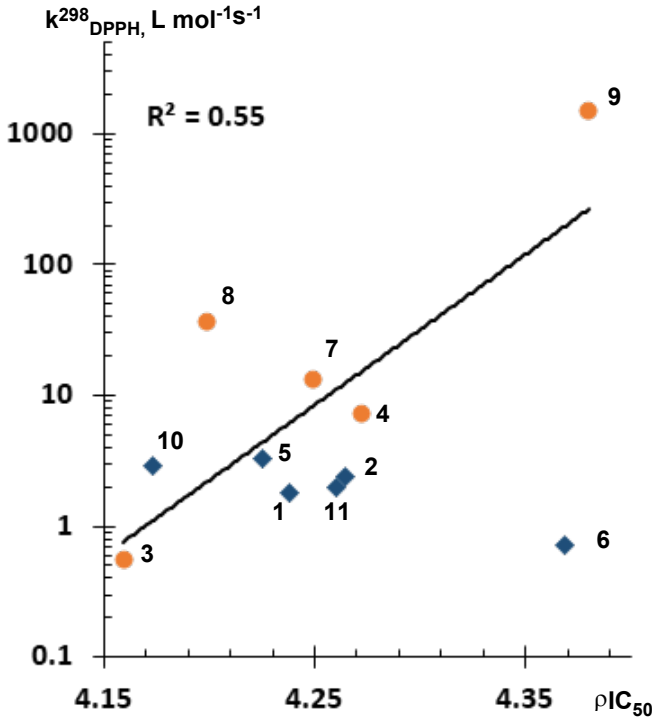


Figure 7. Predicted inhibition ability versus experimentally determined antioxidant ability. Both mono- and polyphenols fit a single trendline. Compound **6** is excluded from the trendline.

Interestingly, as long as the sterically hindered phenol **6** is excluded, all studied compounds do show a fair correlation between the predicted inhibition ability and the experimental antioxidant activity. This correlation suggests that although the addition of the lactam pharmacophore has a noticeable effect on the antioxidant activity, it doesn't cause a significant deviation from the general trends observed for the phenols used in the earlier QSAR study.

It was also interesting to compare the experimental kinetic data and calculated BDEs with a broad selection of the literature data (Figure 8).[49,71] Despite the caveat that the measurements were performed in different solvents which is likely to have some impact on the observed values, one can still draw several conclusions from this general correlation. First, the data obtained in this work are in good agreement with the literature. Secondly, although the rate of interaction of phenols with DPPH is related to BDE, deviations exist. Thirdly, the deviation of compound **6** from the correlation (slow

kinetics at a low BDE value) agrees with the literature data for the similar, sterically hindered phenols with two tert-butyl substituents at the ortho-positions. Interestingly, some of the largest deviations of the correlation in the opposite direction (fast reaction with DPPH despite high BDE values) are observed for phenols **8** and **10** containing an intramolecular hydrogen bond with the auxiliary lactam moiety.

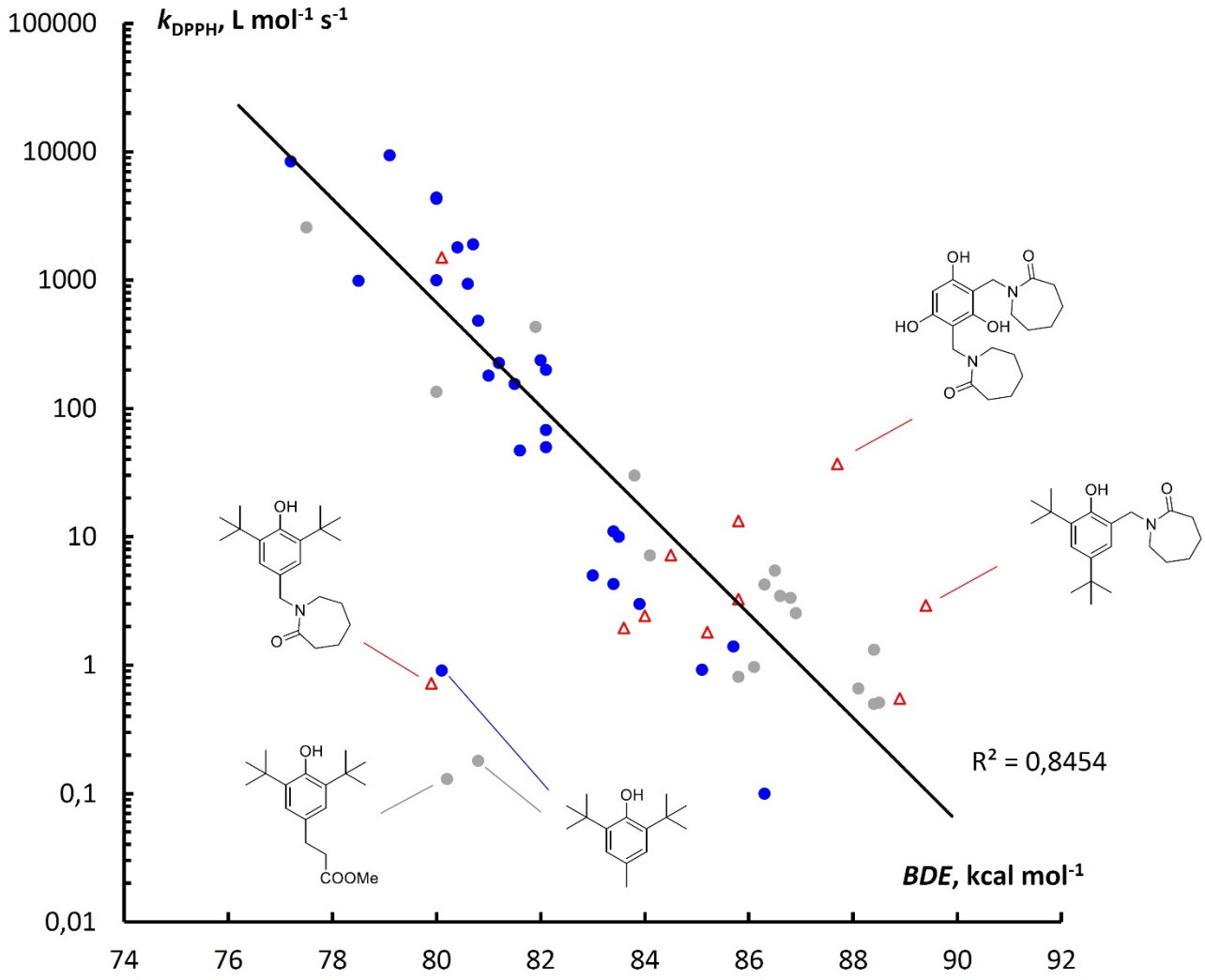


Figure 8. Combined correlation between the DPPH/phenols rate constants and calculated BDE obtained in this work (*red*), and from the literature (*blue* [49] and *gray* [71]). Conditions: this work – MeCN, 298 K,[49] – an alkane solvent, 298 K,[71] – *m*-xylene, 293 K.

Conclusion

Traditionally, the antioxidant activity of phenols can be quantitatively assessed by two approaches: by their ability to donate an electron (oxidation potential) and by their ability to intercept free radicals (the rate constant of the reaction with DPPH). Although the data obtained by the two methods generally correlate with each other, exceptions do exist and a better electron donor is not always a better free radical scavenger. Despite the overall good correlation, there are pairs of molecules where the two methods give opposite predictions regarding the relative antioxidant ability. The second point is that mono- and polyphenols form two independent correlation series for both BDE and ionization potential. Additionally, for mono- and polyphenols with close oxidation potentials, the rate of interaction with the DPPH radical is much higher for the polyphenols. Finally, although the phenols with a 7-membered lactam ring at the *para* position are harder to oxidize, the sterically non-hindered compounds react with DPPH about two times faster than the analogous 5-membered lactams. These observations suggest that there is a complex balance between the ability to donate an electron and the ability to intercept DPPH radicals and that neither approach is able to accurately predict antioxidant ability.

Antioxidants can quench DPPH by either electron or hydrogen atom transfer.[72] The interplay between the ability to donate an electron and ability to intercept a free radical could be different for DPPH and important O-centered radicals, depending on the mixture of potentially competing mechanisms. The relatively significant steric hindrance at the radical center as well as H-bonds with auxiliary functionalities present in DPPH may further complicate the picture. Overall, these observations illustrate the limitations in using DPPH as a probe for antioxidant activity, especially as a mimic for peroxide radicals.

However, DPPH still remains a useful probe because it is not easy to find an oxygen-centered radical that is more appropriate and convenient for investigating antioxidant ability. The most

common and widely available stable oxygen-centered radicals are nitroxyls, such as TEMPO. They differ from DPPH (as well as, for example, molecular oxygen) by a greater than 1 V more negative reduction potential, making them much weaker (~20 orders of magnitude) oxidizers. For example, the reduction potential of DPPH, TEMPO, and molecular oxygen can be estimated as +0.23 V,[73] -0.835 V,[74] and -0.87 V[75] (in MeCN or DMF), respectively. The latter reduction potentials are much more negative than the potentials for the primary oxidants, such as peroxyl $HO_2^{\bullet}$ and hydroxyl $HO^{\bullet}$. Although the direct comparison is complicated by the fact that the published data for these two oxidants mainly refer to the aqueous medium, which is inaccessible for DPPH and many phenolic antioxidants due to their insolubility in water, the difference is so significant that one can draw qualitative conclusions. The potential value for the $O_2/O_2^{\bullet-}$ pair is -0.32 V, for $HO_2^{\bullet}/HO_2^-$ is +0.79 V, and for $HO^{\bullet}/HO^-$ is +1.90 V (in aqueous solution).[76] Extrapolating the ~+0.5 V shift (from the $O_2/O_2^{\bullet-}$ pair) to the potentials of TEMPO and DPPH in a non-aqueous medium leads to the conclusion that DPPH is a reasonable model for the properties of $HO_2^{\bullet}$. Although DPPH is ~1 V less oxidizing than $HO^{\bullet}$, it is still a better model for the oxidative potential of a hydroxyl radical than TEMPO and O_2.

In addition, TEMPO, as well as molecular oxygen, are known to be very poor H-atom abstractors[77] whereas HAT of $HO_2^{\bullet}$ with aromatic alcohols proceeds at a high rate (10^8 M^{-1} s^{-1} and more).[78] At the same time, TEMPO and its analogues are very easily oxidized, often even easier than phenols. This makes them oxidation inhibitors rather than antioxidant oxidizers. These features explain why nitroxyls, the common stable oxygen-centered radicals, are not used as a test for antioxidant activity.

As in the case of DPPH, other common spectrophotometric methods for quantitative estimation of antioxidant activity (such as ORAC, HORAC, TRAP, CUPRAC, FRAP, PFRAP, ABTS-tests, etc. [79]) can also be expected to have their own limitations,. However, results obtained in this work illustrate that limitations in a single method do not create insurmountable obstacles in

constructing a qualitative ranking of a series of antioxidants. The combination of conceptually different and, therefore, complementary methods, both experimental and theoretical, is currently the best approach in the search for better antioxidants.

Experimental Section/Computational Methods

Materials

Acetonitrile (99.8%), dimethylformamide (DMF, 99.8%), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4, 99%), 2,2-diphenyl-1-picrylhydrazyl (DPPH), butylated hydroxytoluene (BHT, ≥ 99%), 2,3,5-trimethylphenol (TMP, 99%), quercetin hydrate (QC, ≥ 95%), dihydroquercetin hydrate (DHQ, ≥ 90%) were purchased from Sigma-Aldrich. The synthesis of the target compounds **1**-**11** was accomplished by the reported procedures. The data are the following: **1**, 1-(4-hydroxy-2,3,6-trimethylbenzyl)pyrrolidin-2-one, 1.44 g (62%) of white powder;[80] **2**, 1-(4-hydroxy-3,5-dimethylbenzyl)pyrrolidin-2-one, 1.53 g (70%) of white powder;[81] **3**, 1-(2,4-dihydroxybenzyl)pyrrolidin-2-one, 1.66 g (80%) of white powder;[82] **4**, 1-(2,4,6-trihydroxy-3-methylbenzyl)pyrrolidin-2-one, 2.32 g (98%) of light brown powder;[82] **5**, 1-(4-hydroxy-2,3,6-trimethylbenzyl)azepan-2-one, 1.77 g (68%) of yellow powder;[80] **6**, 1-(3,5-di-tert-butyl-4-hydroxybenzyl)azepan-2-one, 2.32 g (70%) of white powder;[81] **7**, 1-(2,4,6-trihydroxy-3-methylbenzyl)azepan-2-one, 2.52 g (95%) of light brown powder;[82] **8**, 1,1'-[(2,4,6-trihydroxy-1,3-phenylene)di(methylene)]diazepan-2-one, 2.89 g (77%) of pale yellow powder;[82] **9**, 1-(2,3,4-trihydroxybenzyl)azepan-2-one, 1.98 g (79%) of white powder;[82] **10**, 1-(3,5-di-tert-butyl-2-hydroxybenzyl)azepan-2-one, 2.02 g (61%) of colorless crystals;[83] **11**, 1-(4-hydroxy-3,5-dimethylbenzyl)azepan-2-one, 1.78 g (72%) of pale yellow powder.[81] The structures of the obtained compounds were supported by FT-IR, ^1H and ^{13}C NMR. The absence of impurities was estimated by TLC, NMR-spectroscopy and elemental analysis. Single crystal of compound **5** was obtained by the

recrystallization from ethanol, crystal of compound **10** was isolated directly from the reaction after a prolonged standing. In case of compound **6**, the residue after solvent's evaporation was allowed to crystallize in hexane.

Cyclic voltammetry

The oxidation potentials of phenols were studied by cyclic voltammetry using the potentiostat IPC-Pro MF (Econix). The measurements were carried out in a standard three-electrode glass cell having additional inlet and outlet for purging argon through a phenol solution in a supporting electrolyte, which is necessary to remove dissolved oxygen. The supporting electrolyte was a 0.1 M solution of Bu_4NBF_4 in acetonitrile. In case of **8**, 25 vol.%, and in case of **10**, 15 vol.% DMF was added to completely dissolve the compound. A glassy carbon disc electrode with a diameter of 1.7 mm was used as the working electrode. Its surface was polished with abrasive paper and then GOI paste to a mirror finish before each use. The counter electrode was a Pt wire preannealed in a gas burner flame to remove oxides and other possible contaminations. The oxidation potentials were measured versus the commercial Ag/AgCl electrode separated from the bulk electrolyte solution by an electrolytic bridge filled with the supporting electrolyte. Voltammograms were recorded at a scan rate of 100 mV s^{-1}.

Kinetic measurements by UV spectroscopy

Kinetics of the reaction between phenols and a stable free radical DPPH was measured spectrophotometrically using an UV-vis spectrometer Agilent 8453. The rate of reaction was determined by the rate of disappearance in the spectrum of the band at 520 nm related to π-π*-transition in DPPH. First of all, the spectrum of DPPH solution in acetonitrile was recorded and considered as zero-time point. After that, an equimolar amount of phenol was added to the DPPH solution, and the spectra of the mixture were taken in different time intervals: more frequently at the

beginning of the reaction than later. The DPPH concentration at each measurement point was evaluated as the ratio of intensities of the band maxima at a given and zero point in time multiplied by the initial DPPH concentration ($1 \cdot 10^{-4}$ M). The reaction rate constant was determined from the slope of a linear fit to the plot of reverse DPPH concentration versus time.

X-ray crystallographic data and refinement details

X-ray diffraction data were collected at 100K on a Rigaku Synergy S diffractometer equipped with a HyPix600HE area-detector (kappa geometry, shutterless ω-scan technique), using monochromatized Cu Kα-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.[84] The structure was solved by direct methods using SHELXT [85] and refined on F^2 using SHELXL-2018[86] in the OLEX2 program.[87] Positions of all atoms were found from the electron density-difference map. Atoms were refined with individual anisotropic (non-hydrogen atoms) or isotropic (hydrogen atoms) displacement parameters. Aspherical scattering factors[88] were applied at the final steps of the refinement.

Computational details

Calculations were performed with Gaussian 09[89] using the (u)M06-2X[90] functional with Grimme's dispersion[91] and solvation effects with SMD=MeCN at the (u)M06-2X/6-31+G(d,p) level. Molecules were visualized with CYLView.[92]

Supporting Information. The Supporting Information is available free of charge at https://pubs.acs.org/doi/...

The X-ray crystallographic data and refinement details for CCDC 2112928, 2119411 and 2119412†. Cyclic voltammetry and UV spectroscopy data for **1**-**11**. Calculated Cartesian coordinates of the structures **1**-**11**.

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42. It should be noted that all the studied compounds are sufficiently soluble in acetonitrile for recording UV-vis spectra, and all kinetic measurements were performed in this solvent. However, electrochemical measurements require concentrations an order of magnitude higher. Due to the low solubility of **8** and **10**, in order to reliably determine their oxidation potentials and achieve the required concentration, it was necessary to add 25 and 15% DMF, respectively. It should be noted that DMF is a very strong hydrogen bond acceptor and it can potentially engage in intermolecular hydrogen bonding with the phenolic OH group of **8** and **10**. In order to determine the effect of DMF on the parameters under study, we performed an experiment on compound **5** in acetonitrile in 0%, 15%, and 25% DMF. The results are presented in Table 1. It can be seen that the presence of DMF leads to a decrease of the oxidation potential by approximately 80 mV and almost doubles the rate of the reaction with DPPH. Thus, for points **8** and **10** in Figure 2 in the case of recording the CV curves in the absence of DMF, one can expect some shift to the right. While the addition of DMF does seem to impact the measure oxidation potential and rate of reaction, based off of the experiments with **5**, we would expect **8** and **10** to have a larger oxidation potential and a smaller rate or reaction which is in agreement with the overall trends we observe for both the mono- and polyphenol compounds.

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