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Why naturally occurring quinone redox systems lack amino groups: consideration using 1,4-naphthoquinone derivatives

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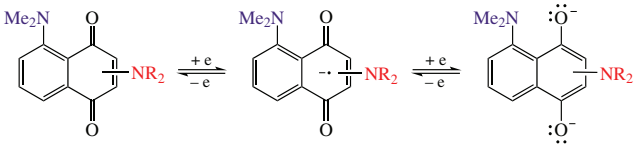
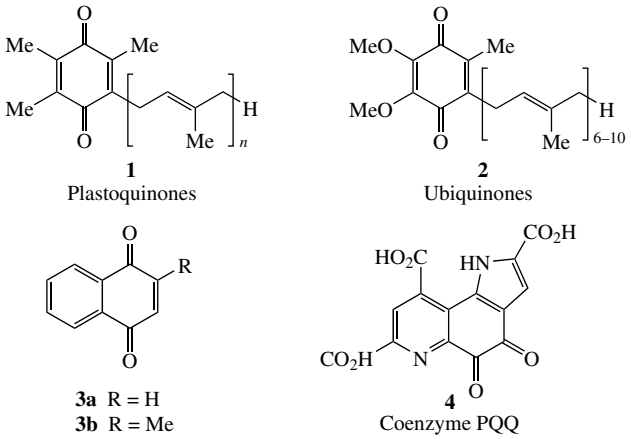
Four representatives of amino derivatives of 1,4-naphthoquinone were examined by combination of cyclic voltammetry, ESR spectroscopy and quantum chemical calculations. The results obtained help to rationalize why natural quinonoid redox systems do not contain amino groups so common in proteins, nucleobases, numerous signal and other biologically important molecules.



High conformational mobility of NR_2 groups can be the main factor inhibiting redox activity of the aminated quinones

Keywords: 1,4-naphthoquinones, amines, oxidation, reduction, radical anions.

It is known that most biochemical reactions are reversible and, depending on the body's needs, the equilibria shift to one side or the other.[1] Apparently, this circumstance, by reducing the amount of substances necessary to support life, in thermodynamic terms, slows down the growth of entropy (the development of chaos), and contributes to more sustainable life. Many hundreds of processes in living organisms are based on electron and proton transfer, which are realized through the so-called redox systems. One of the most common groups of redox systems is based on quinones (Figure 1) susceptible to reversible reduction/oxidation into radical anions (RAs) and then dianions of the corresponding diatomic phenols.[2] Thus, plastoquinones **1** provide electron and proton transfer in the photosynthetic system of plants, ubiquinones **2** (coenzyme Q) are involved in oxidative phosphorylation, a key reaction in the synthesis of ATP, and a large group of vitamins K, in particular vitamin K_3, operates on the basis of 1,4-naphthoquinone **3a** (or **3b**) responsible for many metabolic processes, such as the regulation of blood clotting in animals.[3] Dozens of other quinones of the benzene, naphthalene and anthracene series exist in nature.[2]



1 Plastoquinones

2 Ubiquinones

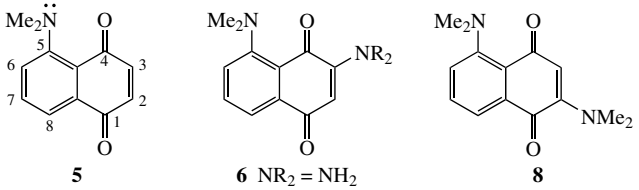
3a R = H
3b R = Me

4 Coenzyme PQQ

Figure 1 Some natural redox systems based on quinones.

Against the backdrop of the enormous role that amino acids, nucleobases and numerous signaling molecules such as dopamine, tryptamine or histamine play in living organisms, it seems surprising that natural quinones practically do not contain nitrogen functions, especially amino groups.[4] Almost the only exception is quinone (PQQ coenzyme) **4** of pyrrolo-[2,3-*f*]quinolone series, which contains an electron-donating pyrrole ring instead of amino groups.[5] Recently, we were able to discover a relatively simple route to the preparation of 5-dimethylamino-1,4-naphthoquinone **5** and its amino derivatives **6**–**8** (Figure 2).[6] In this regard, in the present work we have tried to shed some light on the issue raised above. To do this, the redox potentials of compounds **5**–**8** were measured in comparison with 1,4-naphthoquinone **3a** using cyclic voltammetry (CV). Additionally, RAs of these compounds were generated and characterized by ESR spectra, and quantum chemical calculations of their parameters were carried out. Tetrahydrofuran and dichloromethane which have close polarity (μ = 1.7 and 1.5 D, respectively[7]), were used as solvents for CV. The results obtained are shown in Table 1 and in Figures 3–6.

The classic foxlike profile[8] for amines **5**–**8** lies in the region of negative potentials (–0.5 to –2.6 V). Its close similarity to the CV of 1,4-naphthoquinone **3a** indicates that amines **5**–**8** undergo sequential reversible one-electron reduction in two stages to RA and a dianion, respectively, $E_{1/2}^{red\text{-}1}$ and $E_{1/2}^{red\text{-}2}$ [Scheme 1(*a*)]. Based on the ease of one-electron reduction in THF (see $E_{1/2}^{red\text{-}1}$ values), the studied compounds are arranged in the following sequence: **3a** > **5** > **6** > **8** > **7**. It nicely corresponds to that we



5

6 $NR_2 = NH_2$
7 $NR_2 = NMe_2$

8

Figure 2 Amino derivatives of 1,4-naphthoquinone studied in this work.

Table 1 Redox CV potentials (*vs.* Fc^+/Fc) of 1,4-naphthoquinone and its amino derivatives.

Quinone	$E^{p}_{1/2}{}^{ox}$/V		$E^{red\text{-}1}_{1/2}$/V		$E^{red*}_{1/2}$/V[a]		$E^{red\text{-}2}_{1/2}$/V	
	THF	CH_2Cl_2	THF	CH_2Cl_2	THF	CH_2Cl_2	THF	CH_2Cl_2
5	0.74	0.75	–1.47	–1.32	–	–1.70	–2.27	–2.03
6	0.68	0.65	–1.59	–1.35	–	–1.65	–2.33	–1.98
7	0.65	0.67	–1.77	–1.31	–	–1.68	–2.21	–1.95
8	0.55	0.58	–1.68	–1.35	–	–1.57	–2.19	–1.91
3a	–	1.30	–1.30	–1.19	–	–1.64	–2.04	–1.90

[a] $E^{red*}_{1/2}$ is additional reduction which is characterized by the influence of the solvent.

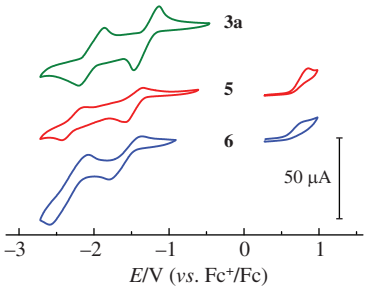


Figure 3 Cyclic voltammograms of 1,4-naphthoquinone **3a** and its amino derivatives **5** and **6** (THF, c = 5 mM, 300 K, scan rate 50 mV s^{-1}).

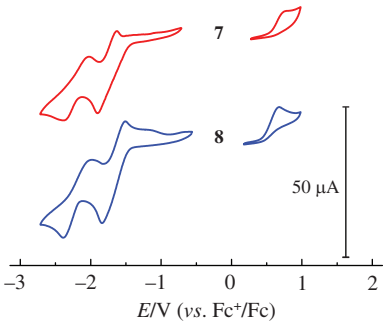


Figure 4 Cyclic voltammograms of compounds **7** and **8** (THF, c = 5 mM, 300 K, scan rate 50 mV s^{-1}).

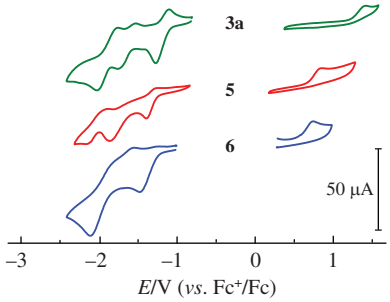


Figure 5 Cyclic voltammograms of 1,4-naphthoquinone **3a** and its amino derivatives **5** and **6** (CH_2Cl_2, c = 5 mM, 300 K, scan rate 50 mVs^{-1}).

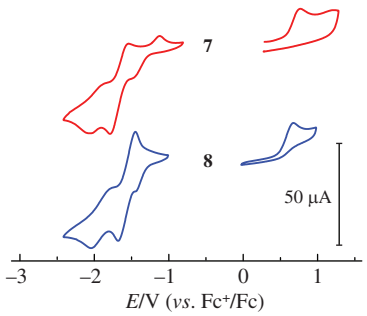
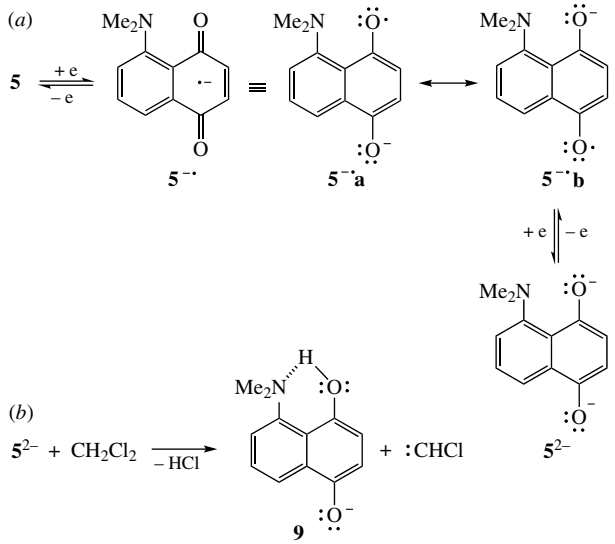


Figure 6 Cyclic voltammograms of compounds **7** and **8** (CH_2Cl_2, c = 5 mM, 300 K, scan rate 50 mV s^{-1}).



Scheme 1 (*a*) Two-step electrochemical reduction of quinones **5–8** exemplified by **5**; (*b*) the proposed nature of the third reduction wave when using CH_2Cl_2.

calculated for the gas phase (Table 2, for details and references see Online Supplementary Materials, Tables S1, S2), and in both series the dominance of unsubstituted quinone **3a** is observed. It is obvious that the strong electron-donating effect of NH_2 and especially NMe_2 groups makes the reduction of the quinonoid system more difficult. This is especially pronounced when the amino groups are located in the quinone ring rather than in the benzene one. Based on this, it seems reasonable to assume that the presence of amino groups in redox systems might complicate electron–proton transfer in living cells, where it occurs in mitochondria with the assistance of an additional NADH/NAD^+ redox system (standard redox potential of the last pair (–0.32 V).[9] In CH_2Cl_2 as in THF, 1,4-naphthoquinone is reduced much more easily than amines **5–8**, but the differences between the latter become minimal.

It was previously noted that the electroreduction in solvents containing geminal halogen atoms (CCl_4, $CHCl_3$, CH_2Cl_2, *etc.*) can sometimes be accompanied by side cathodic processes.[11] They were classified as reactions of the E1 elimination type leading to nucleophilic substitution of chlorine and formation of the corresponding carbenes, which may be caused by the action of substrate or the cathode itself [see Scheme 1(*b*) and review[12] on the reactions of dichloromethane with amines]. Apparently, something similar can occur in our case. Indeed, when working in CH_2Cl_2, in contrast to THF, three rather than two waves of reduction are observed, and the third, which we designated $E^{red*}_{1/2}$, appears between the first and second waves (see Table 1). Presumably its origin is due to the dehydrochlorination of dichloromethane and the formation of chlorocarbene and anion **9**, which is then oxidized to the parent quinone [see Scheme 1(*b*)].

Table 2 The electron affinity (EA) values of the studied compounds calculated as the difference between the energies of the neutral and radical anion structures and according to the Koopmans theorem.[10]

Compound	EA = E(Q) – E($Q^{\bullet-}$) /kcal mol^{-1}	EA (Koopmans theorem) /kcal mol^{-1}
3a	–46.3	–82.2
5	–41.6	–72.8
6	–36.1	–64.6
7	–34.9	–61.5
8	–35.9	–64.6

The oxidation potentials of amines **5–8** fall in the range of positive values ($E_{1/2}^{p,ox} \approx +0.5 - +1.0$ V) and most likely relate to side oxidation processes, the possibility of which we recently demonstrated for amine **5** in an aqueous environment.[6] In terms of ease of oxidation, these amines form the series **8** > **7** ≈ **6** > **5**, and the values of oxidation potentials for all compounds are almost independent of the solvent. According to the CV data for compound **3a**, the reversibility of reduction is more pronounced and the rate of reduction is higher. The value of the oxidation potential of **3a** in THF was not obtained, because the oxidation wave is outside the operating range of the solvent.

In dichloromethane, the $E_{1/2}^{p,ox}$ value for **3a**, as expected, is strongly shifted toward positive values (+1.30 V) compared to amines **5–8**. It is interesting that in CH_2Cl_2 for **3a** (see Figure 5) as for amines **5–8** (see Figures 5, 6), an additional reduction band $E_{1/2}^{red*}$ appears in CV. It locates in the same range (–1.64 V), which is consistent with its attribution to the interference of the solvent in the reduction process.

To make sure that the reduction of the studied compounds proceeds through the stage of formation of RA, we generated three of them **5**$^{\bullet-}$, **7**$^{\bullet-}$ and **8**$^{\bullet-}$ preparatively by keeping each quinone in THF over a potassium mirror under anaerobic conditions. The ESR spectra were recorded for all obtained RAs. For comparison, the same was done for unsubstituted quinone **3a**, since the ESR spectrum for its RA in THF was not previously recorded.[13]

The ESR spectra of RAs **5**$^{\bullet-}$ and **3a**$^{\bullet-}$ are shown in Figures 7 and S1 (Online Supplementary Materials); for two other spectra see Figures S2 and S3. The ESR results confirm the formation of RA corresponding to the first CV reduction band. Upon further reduction, judging by CV, the corresponding dianion of type **5**$^{2-}$ (see Scheme 1) is formed. As can be seen, the experimental and simulated ESR spectra agree well for **5**$^{\bullet-}$ and rather satisfactorily for **3a**$^{\bullet-}$ (possibly due to the interaction of the RA **3a**$^{\bullet-}$ with the starting quinone). Such correspondence is much worse in the case of RAs **7**$^{\bullet-}$ and **8**$^{\bullet-}$. We explain this by the fact that, according to quantum chemical calculations, due to the conformational mobility of NMe_2 groups, these RAs exist in the gas phase and probably in THF in several forms, which differ markedly in the geometry and energy of the SOMO orbital in which the unpaired electron is located (more details on this question discussed below).

Using the DFT method in the B3LYP/6-311++G(d,p) approximation (for details and references, see Online Supplementary Materials), we also calculated some gas-phase parameters of compounds **3a**, **5–8** and their RAs. The parameters included the geometry and energy of optimized structures, bond lengths, charges on atoms, spin densities, energy of frontier orbitals, and several others. As follows from Tables S3 and S4, for neutral molecules the calculations showed no essential differences with the XRD measurement data.[6]

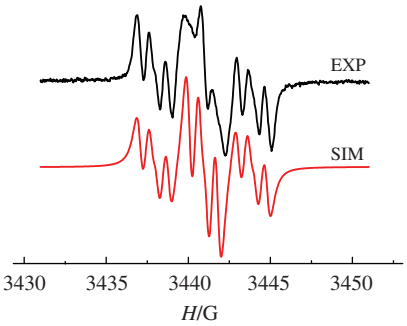


Figure 7 ESR spectra of radical anion **5**$^{\bullet-}$ in THF [experimental (black), calculated (red), $g = 2.001$, $a(H_{2,3}) = 3.27$ G, $a(H_5) = 0.30$ G, $a(H_6) = 1.01$ G, $a(H_8) = 0.67$ G].

Thus, both kinds of estimation demonstrated that the configuration of nitrogen atoms in the amino groups located in both the benzene and quinone rings is close to planar (ΣN = 355–360°). In addition, there is a significant repulsion between the 5-NMe_2 and C^4=O groups, which are *peri*-positioned to each other. It manifests itself in an increase in the distance between them and especially in their strong deviation in different directions from the ring plane (*cf.* values ΔN^5 and ΔO^4). The latter leads to seriate deformation of the naphthalene ring plane: value of θ [torsion angle between bond vectors C(2)–C(3) and C(6)–C(7)] varies between 8–12°.

As expected, large structural changes occur in the RAs (Figure 8). In particular, this manifests itself in a strong elongation of the C=O bonds and in the induction of a significant negative charge on the oxygen atoms, in addition to the spin density (see below). The latter promotes rotation of the neighboring 5-NMe_2 group so that its methyl groups are located closer to the O^4 atom. As a result, short CH···O^4 contacts arise, which probably stabilize RA, since their length (2.2–2.4 Å) is noticeably less than the sum of the van der Waals radii of isolated oxygen and hydrogen atoms (~2.6 Å).[15] Other significant changes in RAs are: (1) a decrease in the alternation of the

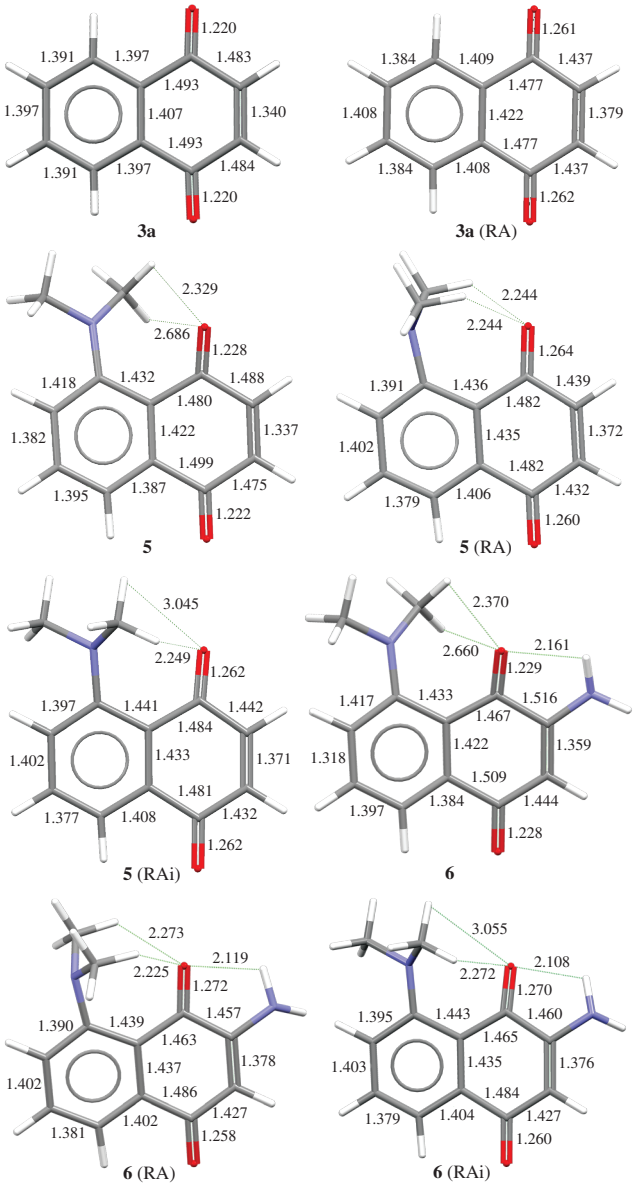


Figure 8 Bond lengths and short CH···O and NH···O contacts (Å) in 1,4-naphthoquinones **3a**, **5** and **6** and their radical anions (according to quantum chemical calculations for gas phase).

lengths of ring C–C bonds, as a result of which the quinone ring largely acquires a benzenoid character; (2) pyramidalization of nitrogen atoms engaged in CH···O contacts (ΣN = 347° *versus* 355–360° in neutral molecules); (3) it is especially interesting that due to these short contacts according to calculations, RAs **5**$^{\bullet-}$ and **6**$^{\bullet-}$ exist in the gas phase in two conformations (see Figure 8) while RAs **7**$^{\bullet-}$ and **8**$^{\bullet-}$ in four ones (Figure S4). All of them lie in potential minima and the difference between their total energies does not exceed 0.6 kcal mol^{-1} for **5**$^{\bullet-}$ and **6**$^{\bullet-}$ and 2.7 kcal mol^{-1} for **7**$^{\bullet-}$ and **8**$^{\bullet-}$ (Table S2 and *ibid* Cartesian coordinates). The difference between the two conformations for **5**$^{\bullet-}$ and **6**$^{\bullet-}$ is as follows. In one of them [**5** (RA) and **6** (RA)], the 5-NMe_2 group turns orthogonal to the naphthalene ring and forms two short CH···O contacts. On the contrary, in the other conformation [**5** (RAi) and **6** (RAi)], the 5-NMe_2 group is approximately coplanar with the ring, which gives an energy gain due to both the n,π-conjugation and one short CH···O contact. The hydrogen bond between oxygen O^4 and the almost planar 3-NH_2 group plays a significant role in stabilizing both conformations of the radical anion **6**$^{\bullet-}$. In RAs **7**$^{\bullet-}$ and **8**$^{\bullet-}$, the 3-NMe_2 and 2-NMe_2 groups are involved in similar conformational changes (Figure S4 and Table S5).

As for the spin density distribution (Table 3, Figure S5), according to calculations, in RAs **5**$^{\bullet-}$–**8**$^{\bullet-}$, as in the RA of unsubstituted 1,4-naphthoquinone **3a**, most of it is localized on oxygen atoms, which is typical for semiquinones.[16] There is also a slight increase in the spin density on the carbon atoms of carbonyl groups when an NMe_2 group is located in close proximity to them. In none of the RA structures any noticeable presence of spin density on the nitrogen atoms was noted.

The atomic charges in RAs calculated using the NBO method[17] generally follow the same trends as the spin densities, with the except for the C^1 and C^4 atoms, which carry a significant positive charge (Table 4). The latter indicates that despite the above-mentioned decrease in the alternation of ring bonds in radical anions, the C^1=O and C^4=O bonds in them still retain their carbonyl nature.

It was already mentioned above (see Table 2) about the possibility of using the energy of the frontier orbitals of the studied compounds to assess the relative ease of their reduction and oxidation. Regarding the HOMO and LUMO forms, information on this is contained in Figure S6 and Table S6.

In conclusion, let us draw attention to the fact that almost all natural redox systems have conformational rigidity. Even if functional groups are present in their structure (usually Me, CO_2H, $CONH_2$, MeO or polyalkenyl chains), they cannot significantly affect the geometry of the entire molecular framework due to their reduced steric requirements and low electron donor–acceptor activity. Apparently, these groups are needed to fine-tune the redox potential of the system and molecular recognition of target membrane receptors for fixation on them. The situation changes greatly in the case of amino groups. Their most important feature is their high conformational mobility and sensitivity to steric effects. They easily undergo pyramidal inversion, change the degree of planarity, rotate around the bond connecting them to the backbone of the molecule, and can deviate greatly from it. In addition, amino groups tend to form hydrogen bonds, both as proton acceptors and proton donors. Most of the named characteristics of amino groups are of key importance for nucleic acids, proteins and many other biomolecules, for which skeletal flexibility and ease of conformational transitions serve as the basis for their functioning. On the contrary, in the case of redox systems, as shown by our theoretical calculations and ESR spectra of radical anions, amino groups, increasing the number of possible RA conformations, greatly change the properties of the main functional groups, for example C=O in quinones, and the molecule whole, which should reduce selectivity of the redox process. Finally, the NH_2 group and especially NMe_2 are among the strongest electron donors. By entering conjugation with the

Table 3 Spin densities in radical anions (Q$^{\bullet-}$) of studied quinones (according to quantum chemical calculations for gas phase).

RA Q$^{\bullet-}$ precursor	Atoms[a]								
	$O^1(O^4)$	$C^1(C^4)$	$C^2(C^3)$	$C^{4a}(C^{8a})$	$C^5(C^8)$	$C^6(C^7)$	N^2	N^3	N^5
3a	0.248	0.066	0.127	0.027	0.023	0.024	–	–	–
5	0.243	0.050	0.117	0.049	0.028	0.011	–	–	0.005
	0.249	0.066	0.103	0.055	0.019	0.039			
6	0.192	0.011	0.057	0.024	0.074	–0.020	–	0.022	0.007
	0.255	0.154	0.045	0.126	–0.021	0.090			
7	0.211	0.052	0.050	0.089	0.049	–0.005	–	0.011	0.005
	0.256	0.151	0.072	0.020	–0.013	0.070			
8	0.249	0.116	0.068	0.023	–0.006	0.060	0.008	–	0.001
	0.222	0.045	0.049	0.085	0.057	0.029			

[a] Numbering of atoms in Tables 3 and 4 corresponds to that indicated on structure **5** in Figure 2.

Table 4 NBO atomic charges in radical anions (Q$^{\bullet-}$) of studied quinones (according to quantum chemical calculations for gas phase).

RA Q$^{\bullet-}$ precursor	Atoms[a]								
	$O^1(O^4)$	$C^1(C^4)$	$C^2(C^3)$	$C^{4a}(C^{8a})$	$C^5(C^8)$	$C^6(C^7)$	N^2	N^3	N^5
3a	–0.682	+0.382	–0.269	–0.109	–0.181	–0.233	–	–	–
5	–0.680	+0.387	–0.270	–0.101	+0.167	–0.157	–	–	–0.586
	+0.690	+0.379	–0.257	–0.123	–0.181	–0.256			–0.349
6	–0.695	+0.430	–0.352	–0.146	+0.147	–0.228	–	–0.810	–0.582
	–0.722	+0.322	+0.136	–0.011	–0.188	–0.221			–0.349
7	–0.702	+0.406	–0.344	–0.141	+0.151	–0.221	–	–0.510	–0.579
	–0.256	+0.343	+0.133	–0.009	–0.179	–0.235		–0.352	–0.347
8	–0.698	+0.375	+0.125	–0.023	+0.171	–0.284	–0.513	–	–0.512
	–0.684	+0.369	–0.328	–0.132	–0.202	–0.216	–0.354		–0.340
									–0.352

[a] The top values in the last three columns refer to the nitrogen atom, and the bottom to the carbon atoms of the NCH_3 groups.

π-system of the molecule, they increase the energy of molecular orbitals, including HOMO and LUMO. This significantly complicates the reduction process and facilitates oxidation, which can become irreversible.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.028.

References

1 D. L. Nelson and M. M. Cox, *Lehninger Principles of Biochemistry*, 4th edn., Worth Publishers, New York, 2004.
2 *The Chemistry of the Quinonoid Compounds*, eds. S. Patai and Z. Rappoport, Wiley, New York, 1988, vol. 2.
3 J. W. Suttie, in *Handbook of Vitamins*, 5th edn., eds. J. Zempleni, J. W. Suttie, J. F. Gregory III and P. J. Stover, CRC Press, London, 2013, ch. 3, pp. 89–124.
4 A. F. Pozharskii, O. V. Dyablo, V. A. Ozeryanskii and O. G. Pogosova, *Russ. Chem. Rev.*, 2022, **91**, RCR5047.
5 A. F. Pozharskii. A. T. Soldatenkov and A. R. Katritzky, *Heterocycles in Life and Society*, Wiley, 2011.
6 M. P. Vlasenko, A. F. Pozharskii, O. P. Demidov, V. A. Ozeryanskii and G. S. Borodkin, *Mendeleev Commun.*, 2023, **33**, 197.
7 V. I. Minkin, O. A. Osipov and Yu. A. Zhdanov, *Dipole Moments in Organic Chemistry*, Plenum Press, New York, 1970.
8 N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenharth and J. L. Dempsey, *J. Chem. Educ*., 2018, **95**, 197.
9 G. Unden and J. Bongaerts, *Biochim. Biophys*. *Acta*, 1997, **1320**, 217.
10 T. Koopmans, *Physica*, 1934, **1**, 104.
11 *Progress in Physical Organic Chemistry*, eds. S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Wiley, New York, 1965, vol. 3.
12 J. E. Mills, C. A. Maryanoff, R. M. Cosgrove, L. Scott and D. F. McComsey, *Org. Prep. Proced. Int.*, 1984, **16**, 97.
13 J. A. Pedersen, *Spectrochim. Acta, Part A*, 2002, **58**, 1257.
14 J. Karpinska, A. Erxleben and P. McArdle, *Cryst. Growth Des.*, 2013, **13**, 1122.
15 S. Alvarez, *Dalton Trans.*, 2013, **42**, 8617.
16 B. S. Prabhananda, *J. Chem. Phys.*, 1983, **79**, 5752.
17 (*a*) A. J. Stone, *J. Phys. Chem. A*, 2017, **121**, 1531; (*b*) P. Foster and F. Weinhold, *J. Am. Chem. Soc.*, 1980, **102**, 7211.

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