Full Articles

7-Ethyl-2,3,5,6,8-pentahydroxy-1,4-naphthoquinone (echinochrome A): a DFT study of the mechanism of the antioxidant action.

4.* Migration of protons and the Na^+ cation in echinochrome A monosodium salts

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According to B3LYP/6-31G(d,p) and B3LYP/6-31G(d) calculations, intramolecular migrations of H^+ and Na^+ cations in the molecule of 7-ethyl-2,3,5,6,8-pentahydroxy-1,4-naphthoquinone (echinochrome A) monosodium salt in the gas phase and in clusters containing five water molecules can proceed asynchronously through the chain of O—H...O hydrogen bonds by the jump-over mechanism.

Key words: density functional theory, polyhydroxy-1,4-naphthoquinones, echinochrome A, spinochrome D, echinochrome A monosodium salts, spinochrome D monosodium salts, antioxidant, hydroperoxyl radical, cationotropic rearrangement.

Studies[1—3] on the antioxidant properties of 7-ethyl-2,3,5,6,8-pentahydroxy-1,4-naphthoquinone (echinochrome A, **1**), the active principle of a domestic cardiac and ophthalmology drug Histochrome®, revealed a dramatic enhancement of its antioxidant activity (ability to reduce the hydroperoxyl radical $^{\cdot}OOH$ to hydrogen peroxide HOOH) upon transformation of **1** to the anionic form **2** or to sodium salts. It was found that the thermodynamically most favorable isomeric forms of the starting reactants (echinochrome A monosodium salt, **3**) differ from the corresponding forms of reaction products (radicals **4**).

The molecule of echinochrome A bears five hydroxyl groups. Therefore, Histochrome® at $T = 300$ K exists as a mixture of various isomeric forms of echinochrome A as well as its sodium salts and anions. The antioxidant activity of the drug against hydroperoxyl radicals depends strongly on the isomeric (tautomeric-rotameric) form in which it reacts with $^{\cdot}OOH$.

In this connection, studies on the migration ability of the Na^+ cation in sodium salts of hydroxy derivatives of 1,4-naphthoquinones (in particular, in monosodium salts of echinochrome A) are topical.** If such a migration is

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* For Part 3, see Ref. 1.

** Positive charge on the atom being transferred is denoted by K^+, Na^+, and H^+.

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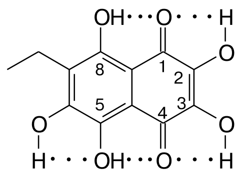

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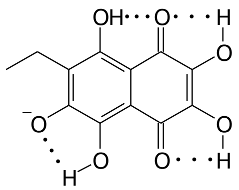

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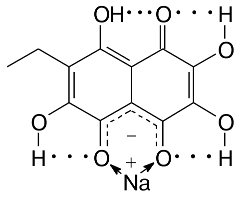

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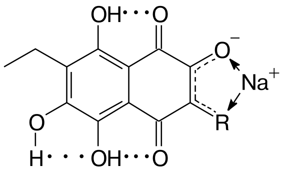


4, 5

R = $O^{\cdot}$ (**4**); OH (**5**)

impossible, the major contribution to the antioxidant activity of echinochrome A monosodium salts comes from the isomeric forms whose content in the reactant mixture is less than 0.1% (taking into account all tautomeric forms due to intramolecular proton transfer in the six-membered chelate rings with intramolecular hydrogen bonds formed by α-OH groups and all rotamers with respect to internal rotation of five hydroxyl groups).[3]

An alternative mechanism involves dissociation of the main isomeric form **3** (its percentage *g* is 98.5%) to the Na^+ cation and the echinochrome A anion. The latter can then be transformed with ease to monoanion **2** having the highest antioxidant activity against $^{\cdot}$OOH (the height of the barrier to this reaction is less than 3.1 kcal mol^{-1}) by one-step intramolecular proton transfer 6β-OH $\rightleftharpoons$ 5α-OH. The limiting step of this process is the dissociation of salt **3** to the Na^+ cation and the echinochrome A anion, which requires an energy expenditure of more than 123 kcal mol^{-1} (this is almost twice as high as the energy needed for homolytic dissociations of O—H bonds in echinochrome A, its monosodium salts, and monoanions).[2,3]

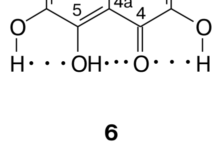
If the cationotropic rearrangement in sodium salts and their radicals is possible, it may serve as a basis for an alternative and, probably, very efficient natural mechanism of optimizing the antioxidant properties of echinochrome A monosodium salts. The heights of the potential barriers to different elementary steps of this rearrangement are about 40.6 kcal mol^{-1},[3] thus being much lower than the homolytic dissociation energies of the O—H bonds in the molecules under study (see above).

The aim of the present work is to investigate in detail the energy characteristics of intramolecular metallotropic (cationotropic) rearrangement of the most stable isomeric form **3** to the isomeric form **5** having the best antioxidant properties in the reaction with the $^{\cdot}$OOH radical. We assumed that transformation **3** → **5** proceeds smoothly on the ground-state potential energy surface (PES) because the echinochrome A monosodium salt has an outer "acceptor framework" comprising oxygen atoms of the hydroxyl and carbonyl groups. Rotation of the Na^+ cation about the C(4)—O bond was chosen as the initial reaction step.

Initially, calculations of gas-phase intramolecular cationotropic rearrangement were carried out. Then, clusters (aquacomplexes) of echinochrome A monosodium salt with five water molecules were modeled using pentahydroxy-1,4-naphthoquinone, or spinochrome D* (**6**), as an analog of compound **1**.

The first coordination sphere of the sodium cation may include up to six water molecules.[4] In such a cluster, the sodium cation forms six coordination bonds with equidistant oxygen atoms of water molecules (R(Na—O) = 2.452 Å). In turn, a hydrogen atom in each of the six water molecules forms an intermolecular hydrogen bond with an oxygen atom of the adjacent water molecule because the distance between the oxygen atoms of the specified water molecule and two its nearest neighbors is about 2.84 Å (see Ref. 5).

In the echinochrome A monosodium salt, the coordination number of the sodium cation is two;[3] therefore, it is sufficient to include four water molecules in the first coordination sphere. As will be shown below, the formation of the first solvation shell of the sodium cation in the transition state (step **7** → **9** for echinochrome A and spinochrome D monosodium salts) involves at least one additional water molecule. Therefore, the barrier heights for clusters formed by salts and their radicals were estimated assuming the same stoichiometry (five water molecules).



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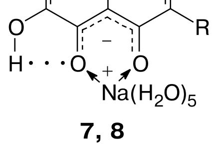
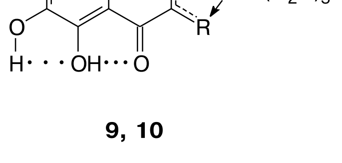


7, 8



9, 10

R = OH (**7, 9**); $O^{\cdot}$ (**8, 10**)

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* The homolytic dissociation energies of the O—H bond in β-OH groups of spinochrome D and echinochrome A are very close.[2]

Calculation Procedure

Gas-phase quantum chemical calculations were performed by the B3LYP/6-31G(d,p) method using the PC GAMESS/Firefly software.[6,7] Clusters of echinochrome A and spinochrome D monosodium salts and their radicals were calculated by the (U)B3LYP method[8] with the 6-31G(d) basis set using the GAUSSIAN-03 program.[9]

The ground-state electronic energies E of the molecules under study were determined after full geometry optimization. The zero-point energy (ZPE) corrections and the thermal corrections (G_T and H_T) were calculated in the "rigid rotator—harmonic oscillator" approximation. The Gibbs free energies G and the enthalpies H were calculated for $T = 298.15$ K taking into account all electronic, translational, rotational, and vibrational degrees of freedom.

Results and Discussion

Figure 1 presents the PES section along the reaction pathway (S) constructed using the results of calculations of the IRC trajectories passing through energy minima and transition states of the reaction under study. The highest barrier ($V^{\neq} \approx 38.0$ kcal mol^{-1}) was found for the first reaction step (see Fig. 1). As the Na$^+$ cation rotates about the C(4)—O bond, the potential energy monotonically increases up to a point ($S_{\mathrm{I,fin}} = -41$ (a.m.u.)$^{1/2} \cdot a_0$) corresponding to a dihedral angle Na$^+$—O—C(4)—C(5) of about 83°. At this point, the character of the rearrangement abruptly changes (a magnified region II of the PES of the transformation **3** → **5** is shown in Fig. 2, *a*) and now the largest contributions to the reaction vector (up to the point $S_{\mathrm{I,fin}} = -37$ (a.m.u.)$^{1/2} \cdot a_0$) come from the rearrangement of the chelate rings and proton migration from the O(3)* to the O(4) atom.

Near the top of the barrier, rotation of the Na$^+$ cation about the C(4)—O bond again contributes largely to the reaction vector. The final point of region II corresponds to the top of the potential barrier. At this point, the Na$^+$ and H$^+$ cations are bound to the same atom O(4). Such a "behavior" of the particles being transferred is probably due to the fact that, at the point $S_{\mathrm{I,fin}}$, there exists a multicenter bond between the Na$^+$ cation and the O(4), C(4), C(3), and O(3) atoms, which leads to weakening of the O(3)—H bond.

In region III (see Fig. 1), the Na$^+$ cation moves parallel to the molecular plane at a distance of about 2 Å, while the proton transferred lies in the molecular plane. The final point of region III corresponds to a dihedral angle Na$^+$—O—C(3)—C(4) of about 90°. At this point, the existing multicenter bond breaks and a new multicenter bond

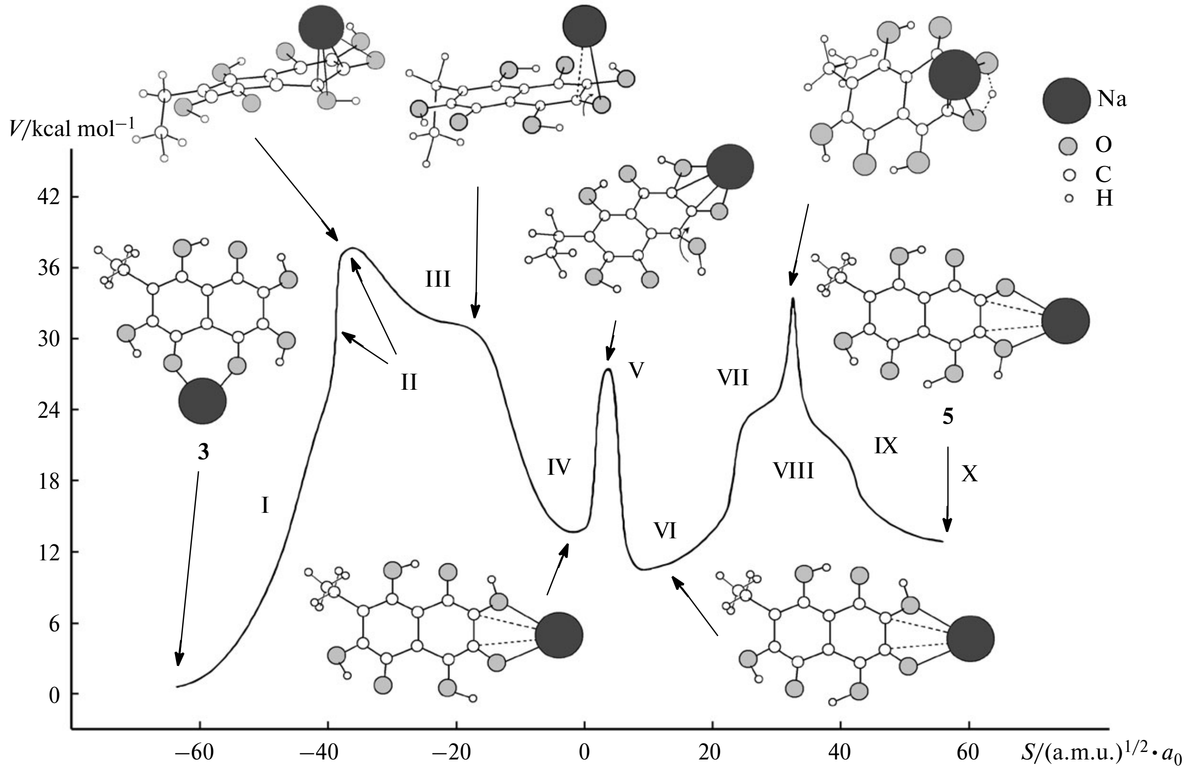

Fig. 1. PES section along the reaction pathway of transition **3** → **5** for asynchronous migration of the Na$^+$ and H$^+$ cations in the molecule of echinochrome A monosodium salt.

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* From this point on the digit in parentheses at an O atom denotes the number of the carbon atom bound to the O atom in question.

between the Na^+ cation and the O(3), C(3), C(2), and O(2) atoms forms. At the final point of region IV, the Na^+ and H^+ cations lie in the molecular plane.

Region V (see Fig. 1) exclusively corresponds to rotation of H^+ about the C(4)—O bond. In regions VI—X, the proton bound to the O(2) atom is transferred through the O(2)···O(3) bridge to which the Na^+ cation is bound (this region of the PES section for the transformation **3** → **5** is magnified in Fig. 2, *b*). The trajectory of the proton motion in the region of the O(2)···O(3) bridge passes near the molecular plane and the Na^+ cation again deviates from this plane by about 2 Å. The transition state in the region VI—X corresponds to the structure in which the proton being transferred is almost equidistant from the atoms O(2) and O(3). At the final point of the reaction pathway (see Fig. 1), all the species transferred lie in the molecular plane.

This mechanism of gas-phase rearrangement (especially, in regions II and VI—X) can be treated as asynchronous "jump-over" of the Na^+ and H^+ cations in echinochrome A monosodium salt. Probably, this is a universal mechanism in the case of migration of heavy cations (Na^+, K^+, *etc.*) along the "outer framework" of the molecule, which comprises a chain of intramolecular hydrogen bonds, and an efficient natural method of smooth changes in the antioxidant properties of polyhydroxy-1,4-naphthoquinones.

The mechanism is driven by the ability of heavy cations to form extended multicenter bonds (*e.g.*, the K^+ cation in echinochrome A monopotassium salts can form coordination bonds with eight centers). The larger the number of centers involved in a multicenter bond the easier the migration. Our estimate of the height of the potential barrier to rotation of K^+ cation about the C(4)—O bond in echinochrome A monopotassium salt (steps I and II, see Figs 1 and 2, *a*) is nearly 29 kcal mol^{-1} (*cf.* about 38 kcal mol^{-1} for echinochrome A monosodium salt); the shape of the one-dimensional potential characterizing this rearrangement in echinochrome A monosodium salt remains qualitatively the same. This suggests that the mechanism of gas-phase migration of the heavy cation along the outer perimeter of the molecule described in the present work will always be in operation when a chain of hydrogen bonds (not only O—H...O, but also N—H...O or N—H...N) is bound to the highly conjugated molecular skeleton, thus forming a chain of chelate rings.

Simulation of a similar intramolecular migration of the α-OH proton from the six-membered chelate ring (α-position) to the adjacent five-membered chelate ring (β-position) and an intramolecular "counter"-migration of the β-OH proton from the β-position to the α-position in neutral echinochrome A molecule showed that a proton "jugglery" rather than the "jump-over" mechanism is in operation. An oxygen atom (*e.g.*, O(4)) plays the role of a proton "juggler" while the other atom (*e.g.*, O(3)) acts as a reflecting baffle.

This mechanism includes steps I and II of the "jump-over" mechanism (see above); however, the height of the potential barrier corresponds to a "fork" configuration of the H—O(4)—H group relative to the molecular plane (Fig. 3). In steps III and IV, the α-OH proton moves toward the O(3) atom while the β-OH proton rotates about the C(4)—O bond. The steps I and II are thus repeated in the reverse direction with the participants being permuted. Echinochrome A has the same structure at the starting and final points of the reaction, but with the α-OH and β-OH protons permuted.

Similar calculations for other polyhydroxy compounds showed that the "jugglery" mechanism in the case of intramolecular migration of two protons is common to the molecules having a biphenol and polyphenol moiety (two or more OH groups in adjacent positions).

Spinochrome D clusters with five water molecules. The first solvation shell of the sodium cation includes five or six water molecules.[10,11] This ambiguity is due to the ease of migration of a water molecule between the solvation shells in a large cluster containing up to 19 water molecules.

In the present work, the solvation shell includes five water molecules because, according to our B3LYP/6-31++G(d,p) calculations,* it is this number of water molecules that a sodium cation can hold in steps II—III**.

The solvation shells of the Na^+ cation in clusters **7** and **9** are structurally different from the solvation shell of the free Na^+ cation. In cluster **7**, the dihedral angle characterizing the deviation of the Na^+ cation from the molecular plane of spinochrome D is small (θ(Na—O—C(4)—C(4a)) ≈ ≈ 21°) and the cation is tightly bound to the atoms O(4) and O(5), namely, R(Na—O(4)) = 2.321 Å and R(Na—O(5)) = 2.347 Å. As a result, in cluster **7** two water molecules (W^4 and W^5)*** are "displaced" to the second solvation shell, *viz.*, R(Na—O(W^4)) = 2.984 Å and R(Na—O(W^5)) = 2.950 Å, whereas R(Na—O(W^1)) = = 2.412 Å, R(Na—O(W^2)) = 2.395 Å, and R(Na—O(W^3)) = = 2.278 Å.

The displaced water molecules are interconnected by a network of three intermolecular hydrogen bonds (IMHBs). The molecule W^4 forms two IMHBs with the adjacent molecules W^2 and W^3 (Fig. 4, *a*) and one IMHB with the O(5) atom of spinochrome D. The molecule W^5 forms two IMHBs with the adjacent water molecules W^1 and W^2 (Fig. 4, *b*) and one IMHB with the O(5) atom of spinochrome D.

In cluster **9b** (Table 1), the Na^+ cation considerably deviates from the molecular plane of spinochrome D. The

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* The energy characteristics of clusters discussed below were calculated by the B3LYP/6-31G(d) method.

** The reaction steps are enumerated in Fig. 1 for the gas phase conditions.

*** Enumeration of water molecules (W^1—W^5).

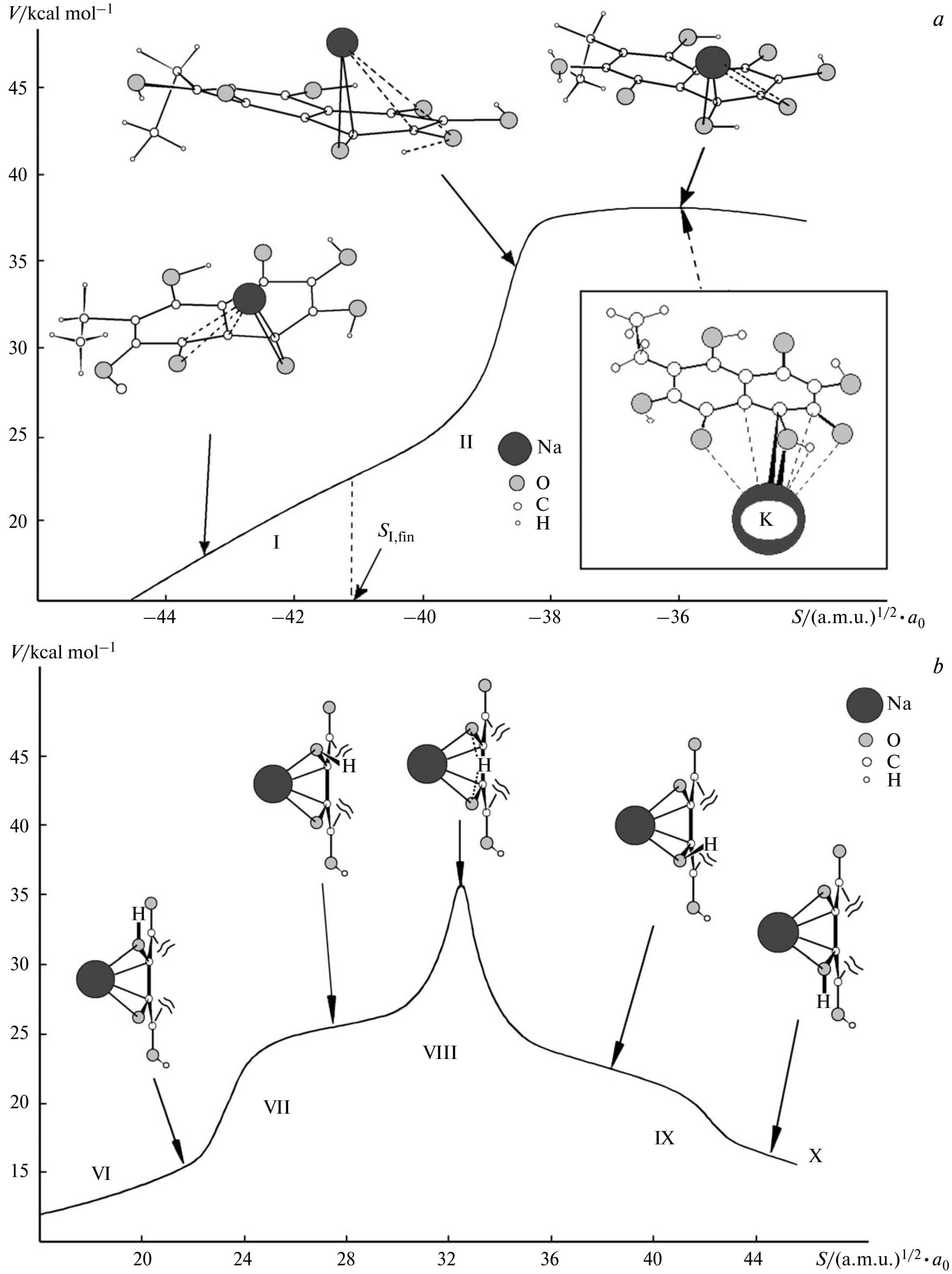


Fig. 2. Regions II (*a*) and VI—IX (*b*) characterized by the largest contribution of proton migration to the reaction vector (the structure shown in Fig. 2, *a* corresponds to the transition state of rotation of the K^+ cation about the C(4)—O bond; Fig. 2, *b* shows only fragments of the echinochrome A molecule).

dihedral angle θ(Na—O—C(2)—C(1)) is nearly 65° and the bond angle φ(Na—O—C(2)) is about 133°. The cation forms strong bonds only with the O(2) atom, *viz.*, *R*(Na—O(2)) = 2.230 Å and *R*(Na—O(1)) = 3.630 Å. In

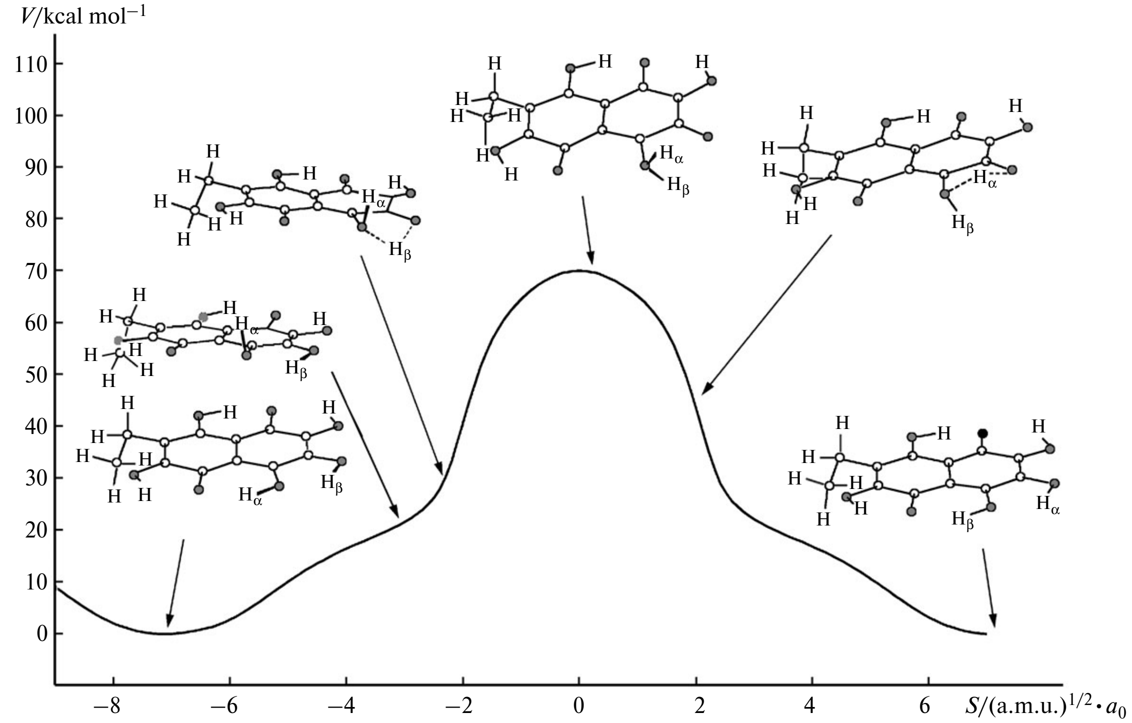


Fig. 3. PES section along the reaction pathway for asynchronous migration of protons of adjacent α- and β-OH groups in the echinochrome A molecule.

this cluster, the molecules W^4 and W^5 are displaced to the second solvation shell, namely, $R(Na—O(W^4)) = 2.940$ Å and $R(Na—O(W^5)) = 3.113$ Å. The displaced water molecule W^4 forms strong hydrogen bonds with the molecules W^2 and W^3 ($R(O(W^4)...O(W^2)) = 2.849$ Å, $R(O(W^4)...O(W^3)) = 2.696$ Å), while molecule W^5 is bound to the molecules W^1, W^2, and the O(3) atom of spinochrome D ($R(O(W^5)...O(W^1)) = 2.848$ Å, $R(O(W^5)...O(W^2)) = 2.651$ Å and $R(O(W^5)...O(3)) = 2.743$ Å).

The solvation shell predetermines the appearance of a variety of channels for migration of the sodium cation. For instance, asymmetry (with respect to the number of water molecules conditionally located "above" and "under" the molecular plane of spinochrome D) leads to efficient stabilization of structures of the types **7a** and **9a** in which the Na^+ cation deviates from the molecular plane (see Table 1).

An important role in providing this mechanism is played by the extension of the first solvation shell. Its

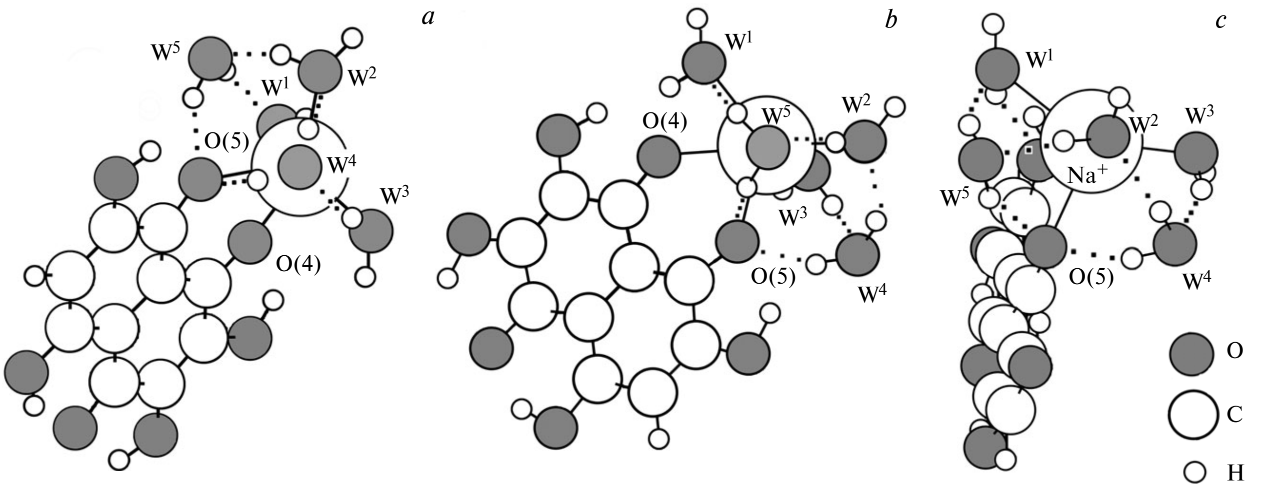
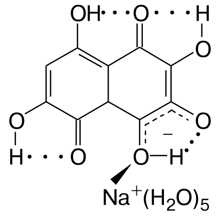


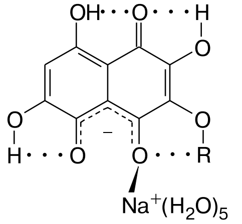
Fig. 4. Clusters of spinochrome D monosodium salt (**7**) in three different projections.

Table 1. Torsion angles (θ) and bond angles (φ) in molecules **7a**,**b**, **8a**, and **9a**,**b**

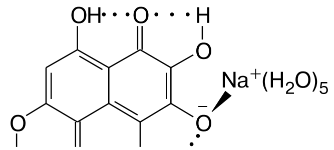
Compound	Torsion angle	θ /deg	Bond angle	φ /deg
7a	Na—O—C(4)—C(4a)	~85	Na—O—C(4)	~100
7b	Na—O—C(4)—C(4a)	~55	Na—O—C(4)	~160
8a	Na—O—C(4)—C(4a)	~89	Na—O—C(4)	~154
9a	Na—O—C(3)—C(4)	~98	Na—O—C(2)	~113
9b	Na—O—C(2)—C(1)	~65	Na—O—C(2)	~132



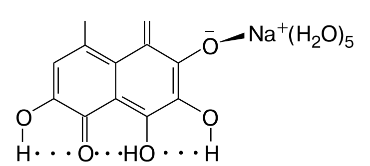
7a



7b, 8a



9a



9b

R = OH (**7b**), O$^•$ (**8a**)

diameter estimated as the distance between oxygen atoms of the water molecules located on different sides of the Na$^+$ cation is about 5.0 Å. At the same time, the distance between the oxygen atoms, *e.g.*, O(1) and O(3), O(2) and O(4), O(3) and O(5), is nearly 4.7 Å. This allows the water molecules constituting the solvation shell to form not only coordination bonds with the Na$^+$ cation, but also hydrogen bonds with one another and with oxygen atoms of spinochrome D (see Fig. 4, *c*).

Such an interaction may simultaneously involve up to three oxygen atoms of spinochrome D (as in, *e.g.*, the structures **7a**, **9a**, and **9b**). As a consequence, an important factor determining the conformational mobility of the cluster of spinochrome D monosodium salt (and, as can be expected, echinochrome A) is the structural flexibility of the solvation shell. Our simulation showed that rearrangement of the solvation shell can lead to switching of the hydrogen bonds mentioned above and to the appearance of additional channels of migration of the heavy cation along the outer framework of the molecule.

As a result, transfer of the sodium cation from α- to β-position (steps I—III for the gas phase, see Fig. 1) may proceed *via* various stable intermediates, *e.g.*, structure **7b**. The height of the potential barrier to reaction **7** → **7b** is about 10 kcal mol^{-1} and the corresponding Gibbs free energy is nearly 3.5 kcal mol^{-1}.

Nevertheless, branching of the reaction channels of the cationotropic rearrangement under study does not affect an important feature of this gas-phase migration, *viz.*, transfer of the sodium cation from α- to β-position creates prerequisites for transfer, in some step, of the H$^+$(15) proton to the O(4) atom to which the sodium cation is bound. Unlike the gas-phase conditions, structures **7a** and **9a** correspond to the minima on the PES of the cluster, whose energies are about 19 and 12 kcal mol^{-1} higher than the energy of the main isomer **7**, respectively. "Displacement" of a water molecule from the first to the second solvation shell and binding of this molecule to the O(3) atom promote this reaction step.

Solvation considerably reduces the energy expenditures for the cationotropic rearrangement. In particular, the height of the potential barrier to transformation **7** → **7a** is nearly 22 kcal mol^{-1}; this is approximately half the height of the barrier to the gas-phase reaction.

The enthalpies of reactions (ΔH_r) of isomers of the clusters of spinochrome D monosodium salts with the hydroperoxyl radical were estimated as the differences between the total enthalpies of products and reactants:

$$\mathbf{7} + {}^{\cdot}\mathrm{OOH} \longrightarrow \mathbf{8} + \mathrm{HOOH}, \qquad (1)$$

$$\mathbf{9b} + {}^{\cdot}\mathrm{OOH} \longrightarrow \mathbf{10} + \mathrm{HOOH}. \qquad (2)$$

Reaction (1) is endothermic, *viz.*, $\Delta H_r = 0.2$ kcal mol^{-1}. Reaction (2) is exothermic, namely, $\Delta H_r = -7.0$ kcal mol^{-1}. Similar gas-phase reactions are exothermic: $\Delta H_r = -1.0$ and -11.3 kcal mol^{-1}, respectively.[2] Thus, solvation reduces the ability of each isomeric form of spinochrome D monosodium salt to reduce the hydroperoxyl radical to hydrogen peroxide. At the same time, now these reactions may occur using a much larger number of stable isomeric forms, *e.g.*, **7b**:

$$\mathbf{7b} + {}^{\cdot}\mathrm{OOH} \longrightarrow \mathbf{8a} + \mathrm{HOOH}. \qquad (3)$$

For this reaction, one has $\Delta H_r = -8.6$ kcal mol^{-1}. Structure **7b** is only about 3.5 kcal mol^{-1} less stable than the isomeric forms **7** and **9b**.

Thus, we studied a new mechanism of intramolecular metallotropic rearrangement along the outer molecular framework formed by the chain of the chelate rings acting as cation acceptors. In this case, the role of the "driving force" is played by the ability of the heavy cations (Na^+ and K^+) to form extended multicenter bonds including bonds with the carbon atoms of these chelate rings. As a consequence, passage of heavy cations in the region of the binding sites occupied by hydrogen atoms occurs almost without changing the energy of the electronic subsystem of the molecule.

An unusual structure corresponds to the transition of the Na^+ or K^+ cation from the six-membered chelate ring to the adjacent five-membered ring. Large deviation of the cation from the molecular plane (the corresponding dihedral angle is nearly 90.0°) and its simultaneous motion toward the five-membered ring induce such a strong redistribution of the electron density that the shape of the potential of the hydrogen bond for this ring changes. As a result, tautomeric proton transfer occurs, which creates prerequisites for further barrierless transfer of the heavy cation across the molecular plane over a distance of about 2.5 Å ("jump-over step") and its subsequent bonding to oxygen atoms of the adjacent five-membered chelate ring.

This mechanism of asynchronous migration of protons and heavy cations within the echinochrome A molecule is due to the fact that some binding sites in this molecule and in echinochrome A sodium salts (and moreover in their radicals and anions) are vacant. To fill an unoccupied site, migration occurs in a "jumpwise" manner, namely, a "jump" of the heavy cation is followed by that of the proton. The corresponding potential barriers are much lower than the homolytic and heterolytic O—H bond dissociation energies (*cf.* 55—70 and 308—325 kcal mol^{-1}, respectively) or the heterolytic Na—O bond dissociation energy (nearly 120—130 kcal mol^{-1}).

According to calculations of the cluster of spinochrome D monosodium salt (analog of echinochrome A), rearrangement in the solvation shell plays an important role in establishment of the detailed mechanism of intramolecular migration of the proton and sodium cation. Displacement of water molecules from the first to the second solvation shell can play the role of a switch of different channels of cationotropic isomerism. Solvation not only facilitates intramolecular migration of the heavy cations, but also creates prerequisites for more efficient antioxidant action of spinochrome D and echinochrome A because clusters can exist in a much larger number of stable isomeric forms compared to the gas phase.

To gain a deeper insight into these action mechanisms, it seems important to simulate the reactions considered taking into account the effects of several solvation shells as well as using more extended basis sets. Nevertheless, the results obtained in the present study suggest that solvation influences the antioxidant properties of spinochrome D and, therefore, echinochrome A.

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References

1. V. P. Glazunov, D. V. Berdyshev, V. L. Novikov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2010, 2131 [*Russ. Chem. Bull.*, *Int. Ed.*, 2010, **59**, 2185].
2. D. V. Berdyshev, V. P. Glazunov, V. L. Novikov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 400 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 413].
3. V. P. Glazunov, D. V. Berdyshev, V. L. Novikov, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 44 [*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 43].
4. G. N. Patwari, J. M. Lisy, *J. Chem. Phys.*, 2003, **118**, 8555.
5. A. V. Vorontsov, Yu. V. Novakovskaya, *Zh. Fiz. Khim.*, 2007, 877 [*Russ. J. Phys. Chem.* (*Engl. Transl.*), 2007, **81**, 759].
6. A. A. Granovsky, *Firefly version* 7.1.*G*, http://classic.chem.msu.su/gran/firefly/index.html.
7. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347.
8. P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623.
9. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, *Revision D.01*, Gaussian, Inc., Wallingford CT, 2004.
10. M. Llano-Restrepo, W. G. Chapman, *J. Chem. Phys.*, 1994, **100**, 8321.
11. M. Carillo-Tripp, H. Saint-Martin, I. Ortega-Blake, *J. Chem. Phys.*, 2003, **118**, 7062.

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