ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 2, pp. 264–268. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © G.V. Gavrilova, A.A. Moiseeva, E.K. Beloglazkina, A.A. Gavrilov, N.V. Zyk, 2009, published in Zhurnal Obshchei Khimii, 2009, Vol. 79, No. 2, pp. 275–279.

Electrochemically Induced Transformation of 4-Halomethyl-4-methylcyclohexa-2,5-dien-1-ones into 3,4-Dimethylphenol

G. V. Gavrilova, A. A. Moiseeva, E. K. Beloglazkina, A. A. Gavrilov, and N. V. Zyk

Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia
e-mail: moiseeva@org.chem.msu.ru; bel@org.chem.msu.ru

Received February 28, 2008

Abstract—Electrochemical behavior of 4-halomethyl-4-methylcyclohexa-2,5-dien-1-ones and 2,6-dibromo-4,4-dimethylcyclohexa-2,5-dien-1-one was studied. Reductive dehalogenation of cyclohexa-2,5-dien-1-ones having a halogen atom at the neopentyl-like carbon atom gives the corresponding carbanion which undergoes anionic cyclopropyl–allyl rearrangement with subsequent addition of proton to form 3,4-dimethylphenol.

DOI: 10.1134/S1070363209020169

Cyclohexadienones and their analogs are polyfunctional organic compounds that are capable of undergoing various chemical transformations. Introduction of halogen atoms into their molecules considerably enhances their synthetic potential, and such derivatives can be modified with the use of not only traditional reagents but also enzymes, as well as by the action of electric current. It is known [1–3] that anions derived from diethyl malonate and diethyl 3-oxopentanedioate are capable of adding at activated unsaturated carbon–carbon bond in dienones according to Michael. The mold fungus *Aspergillus niger* promotes successive reductive dechlorination of the $CHCl_2$ fragment in *trans*-4-dichloromethyl-4-methyl-3-methylidene-3a,7a-dihydro-1-benzofuran-2,7-(3*H*,4*H*)-dione due to the presence of iron-containing enzymes [4]. Analogous process is promoted by *Bacillus mycoides* and *Pseudomonas fluorescens* [5]. 11β,21-Diacetoxy-9α-bromo-17α-hydroxypregna-1,4-diene-3,20-dione undergoes chromium(II) chloride-catalyzed transformation into 11β,21-diacetoxy-17α-hydroxy-5,9-cyclopregn-1-ene-3,20-dione. Heating of the latter in boiling aqueous dioxane in the presence of trace amounts of an acid or alkali leads to opening of the cyclopropane ring with regeneration of the initial dienone [6].

In the present work we found that the above reaction sequence, i.e., reduction of the carbon–halogen bond, intramolecular cyclopropanation, and cyclopropane ring opening, is also typical of electrochemical reduction of 4-halomethyl-4-methylcyclohexa-2,5-dien-1-ones at a glassy carbon electrode in DMF.

We previously examined electrochemical behavior of a number of halogen-substituted cyclohexadienones [7] and found that reductive dehalogenation of 2-bromo-5-dibromomethyl-4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-one involves primarily elimination of the allylic bromine atoms. Next follows elimination of the vinylic bromine in position *2*, and the final step is dehalogenation of the dichloromethyl group. Elimination of the allylic and vinylic bromine atoms occurs in a stepwise mode: in each step one halogen atom is abstracted with simultaneous addition of two electrons and subsequent protonation of intermediate carbanion ($+2e^-$, $+H^+$). Geminal neopentylidene halides undergo two-electron reductive elimination without proton addition; in this case, carbene-like species is formed as intermediate, and its attack on the cyclohexadienone fragment results in ring expansion and formation of tropones [7].

In the present work we examined electrochemical reduction of 4-chloromethyl-4-methylcyclohexa-2,5-dien-1-one (**I**), 4-bromomethyl-4-methylcyclohexa-2,5-dien-1-one (**II**), and 2,6-dibromo-4,4-dimethylcyclohexa-2,5-dien-1-one (**III**) in DMF in the presence of Bu_4NClO_4 using cyclic voltammetry (CV) at a glassy carbon electrode and rotating disk electrode (RDE) technique. The results are collected in table, and cyclic voltammetry curves are shown in Figs. 1

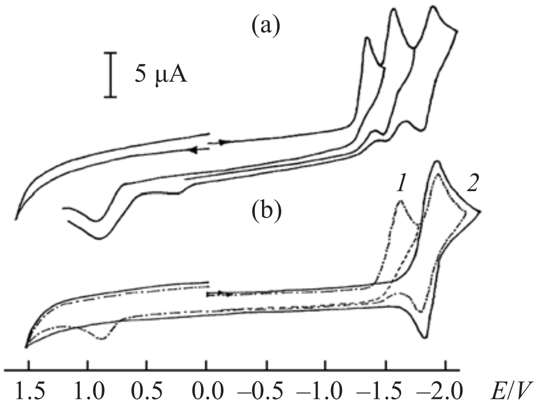


Fig. 1. Cyclic voltammograms of (a) 2,6-dibromo-4,4-dimethylcyclohexa-2,5-dien-1-one (**III**) and (b) (*1*) 2-bromo-4,4-dimethylcyclohexa-2,5-dien-1-one (**V**) and (*2*) 4,4-dimethylcyclohexa-2,5-dien-1-one (**VI**); concentration 10^{-3} M, glassy carbon electrode, DMF, 0.1 M Bu_4NClO_4.

and 2. None of the examined compounds (**I–III**) was oxidized at a glassy electrode under the given conditions, so that we were able to follow the formation of halide ions by their reoxidation peaks upon reversal of the potential after the corresponding cathodic peaks. Compounds **I–III** displayed only two-electron reduction steps corresponding to elimination of halogen atoms.

Cyclic voltammetry of solutions of dibromo derivative **III** showed two peaks on the cathodic branch, resulting from stepwise elimination of two halogen atoms, and the reversible peak corresponding to the reduction of 4,4-dimethylcyclohexa-2,5-dien-1-one (**VI**) to stable radical anion **VII** (Scheme 1, Fig. 1). Obviously, as we showed previously for analogous monobromo derivative [7], electrochemical reduction of compounds containing two halogen atoms) gives rise to reversible peak corresponding to the formation of radical anion **VII** provided that **VI** is formed as intermediate (Fig. 1).

The CV curves obtained for solutions of cyclohexadienones **I** and **II** having one halomethyl groups revealed only one reduction peak due to elimination of halide ion: upon reversal of the potential reoxidation peak of chloride (E_{ap} = 1.18 V) or bromide ion (E_{ap} = 0.83 V), respectively, was observed in the anodic region after the reduction peak (Fig. 2). Obviously, carbanion **A** generated by reductive dehalogenation is not converted into cyclohexadienone **VI** (product of two-step reduction of dibromoketone **III** through intermediate monobromo derivative **V**; see Scheme 1) since no peak corresponding to reduction of dienone **VI** is observed on the CV curve. In the course of reverse potential scans, compounds **I** and **II** showed reoxidation peak on the cathodic branch, which completely coincided with the oxidation peak of 3,4-dimethylphenol (**IV**). We found that the latter is not reduced under the given conditions. Figure 2 shows that the CV curves for cyclohexadienones **I** and **II**, excluding the peaks corresponding to reductive elimination of halide ion, almost completely coincide with the curves obtained for 3,4-dimethylphenol (**IV**).

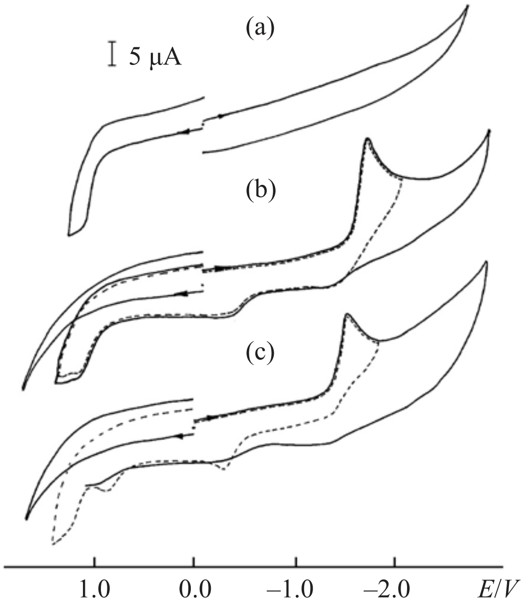
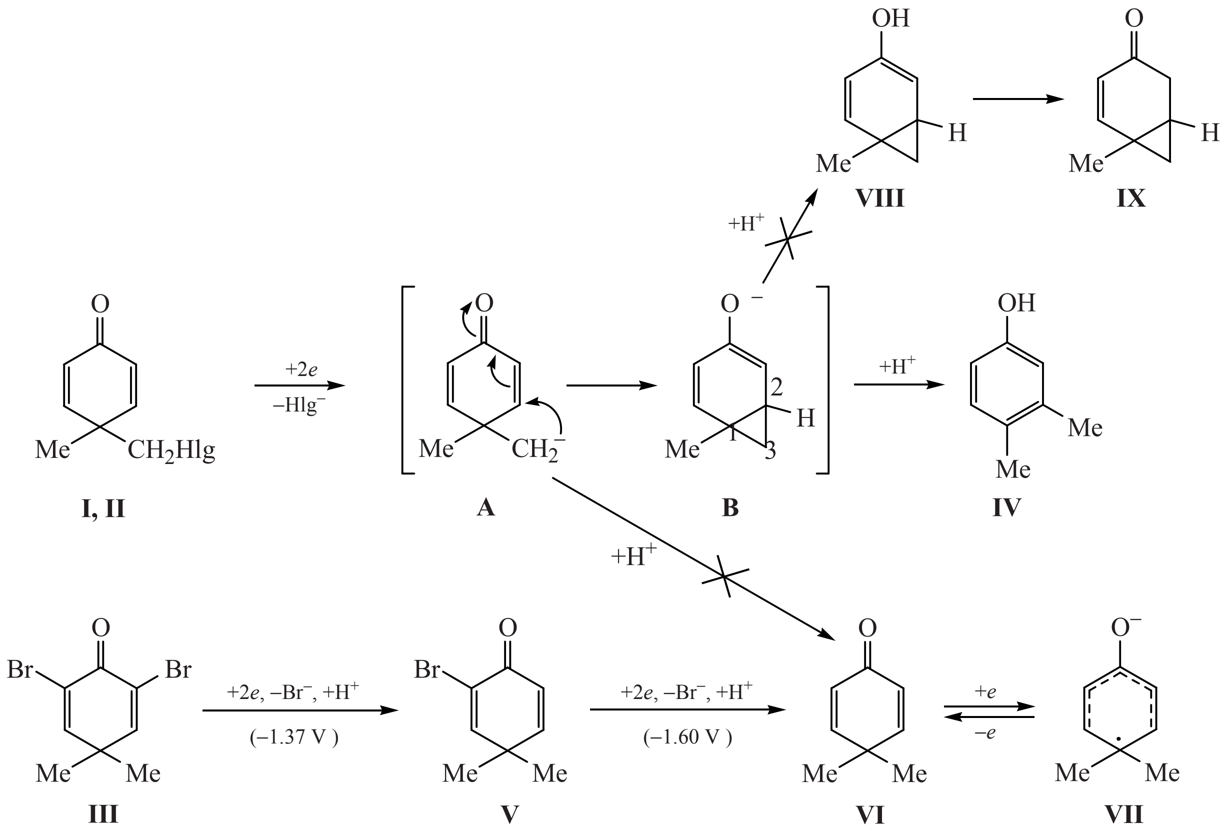


Fig. 2. Cyclic voltammograms of (a) 3,4-dimethylphenol (**IV**), (b) 4-chloromethyl-4-methylcyclohexa-2,5-dien-1-one (**I**), and (c) 4-bromomethyl-4-methylcyclohexa-2,5-dien-1-one (**II**); concentration 10^{-3} M, glassy carbon electrode, DMF, 0.1 M Bu_4NClO_4.

Reduction potentials of compounds **I–III** according to the cyclic voltammetry data; Ag/AgCl/KCl (sat.), glassy carbon electrode, DMF, 0.05 M Bu_4NClO_4 as supporting electrolyte[a]

Comp. no.	E_{cp}, V	$E_{1/2}$, V
I	–1.66/1.18[b]; 1.24[c]	–1.65 (2)
II	–1.56/0.83[d]; 1.24[c]	–1.55 (2)
III	–1.37/0.84[d]; –1.60/0.84[d]; –1.92/–1.82	–1.36 (2); –1.65 (2)

[a] E_{cp} is the cathodic peak potential (200 mV s^{-1})/reverse peak potential; $E_{1/2}$ is the half-wave potential measured at a rotating disk electrode (2800 rpm); the number of electrons determined by comparing with the one-electron oxidation wave of ferrocene is given in parentheses. [b] Reoxidation of chloride ion. [c] Reoxidation of newly formed 3,4-dimethylphenol (**IV**) (irreversible oxidation potential E_{ap} = 1.22 V). [d] Reoxidation of bromide ion.



Hlg = Cl (**I**), Br (**II**).

Thus the results of our electrochemical study on 4-methyl-4-halomethylcyclohexa-2,5-dien-1-ones **I** and **II** showed that their electrochemical reduction in DMF at a glassy electrode leads to the formation of 3,4-dimethylphenol (**IV**). This was also confirmed by studying the behavior of compounds **I** and **II** in the presence of phenol **IV**. Neither "doubling" nor change of the reoxidation peak shape (as compared to electrochemical reduction of individual compounds **I** and **II**) was observed on the CV curves upon reversal of the potential in the cathodic region. These findings suggest that the system contains no oxidizable compounds other than phenol **IV**.

Presumably, initial two-electron reduction with elimination of halide ion from compound **I** or **II** gives carbanion **A** which undergoes intramolecular Michael addition at the β-carbon atom in the dienone system. Protonation of bicyclo[4.2.0]heptadienone anion **B** thus formed yields phenol **IV**. The possibility for formation of intermediate **B** follows from the results of semiempirical quantum-chemical calculations, according to which the optimized geometry of the anion [**I** – Cl]$^-$ corresponds to just bicyclo[4.2.0]heptadienone structure (Fig. 3) where the C^1–C^2, C^1–C^3, and C^2–C^3 distances are 1.525, 1.511, and 1.515 Å, respectively. It is interesting that the rate of the transformation **A** → **B** is higher than the rate of possible protonation of intermediate **A**, which could give rise to dienone **VI** (cf. the data for other halogen-substituted cyclohexadienones [7]).

Examples of anionic cyclopropylcarbinyl–homoallyl rearrangement have been reported [6, 8]. In our case, the isomerization process is favored by the presence of conjugated carbonyl group in the substrate molecule [9], as well as by the formation of energetically favorable aromatic structure **IV**. According to the calculations, the heat of formation of phenoxide ion [**IV** – H]$^-$ is lower by 43.4 kcal mol^{-1} than that found for anion **B** (–62.14 and –19.54 kcal mol^{-1}, respectively). Alternative pathway involving protonation of anion **B** with conservation of the bicyclo[4.2.0]-heptadienone structure should be ruled out, for dienol **VIII** isomeric to **IV** should undergo tautomerization into enone **IX**, while the latter cannot be electrochemically inert. In addition, electrochemical oxidation of enone **IX** should occur at a potential value of higher than 1.5 V rather than at E_{ra} = 1.24 V typical of phenol [10].

Thus we have shown that the behavior of halogen-containing cyclohexadienones under electrochemical reduction conditions is determined by the position of halogen atom in the substrate molecule. If vinyl- or allyl-type halogen atom (or atoms) is present, the process occurs as successive reductive dehalogenation with conservation of the cyclohexadienone fragment [7]. If the substrate molecule contains a halo- or dihalomethyl group attached to tertiary ring carbon atom, the reduction process is also accompanied by dehalogenation, but the cyclohexadiene fragment is transformed into cycloheptatrienone (dihalo derivatives) [7] or phenol (one halogen atom).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were measured at 25°C from solutions in $CDCl_3$ on a Varian VXR-400 spectrometer using tetramethylsilane as internal reference. The IR spectra were recorded on a UR-20 instrument from samples dispersed in mineral oil. The UV spectra were obtained on a Specord M-40 spectro-photometer from solutions in ethanol.

Electrochemical studies were performed using a PI-50-1.1 potentiostat coupled with a PR-8 prog-rammer. A glassy carbon electrode (d = 2 mm) was used as working electrode, supporting electrolyte was a 0.1 M solution of Bu_4NClO_4 in DMF, reference electrode was a silver chloride electrode [Ag/AgCl/KCl (sat.)], and a platinum plate served as auxiliary electrode. The substrate concentration was 10^{-3} M. In cyclic voltammetry experiments, the potential scan rate was 200 mV s^{-1}, and in RDE experiments, 20 mV s^{-1}. The potentials are given with account taken of *iR* compensation. The number of electrons transferred in redox processes was determined by comparing the wave limiting current in RDE experiments with the one-electron oxidation current of ferrocene taken at the same concentration.

All measurements were performed under dry argon; samples were dissolved in preliminarily degassed solvent. Dimethylformamide of pure grade was stirred over freshly calcined potassium car-bonate over 4 days and distilled under reduced pres-sure first over P_2O_5 and then over anhydrous $CuSO_4$.

Quantum-chemical calculations were performed using semiempirical SCF PM3 approximation [11] extended via inclusion of parameters of all first-row transition metals and some second- and third-row metals. The geometric parameters were optimized with a convergence gradient of no larger than 10 cal Å^{-1} mol^{-1}.

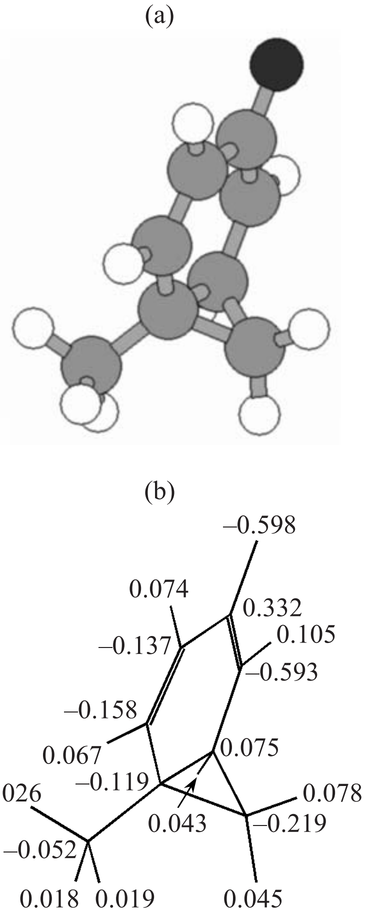


Fig. 3. (a) Optimized structure of anion [**I** – Cl]$^-$ and (b) distribution of charge density therein.

2-Bromo-4,4-dimethylcyclohexadien-1-one [12] and 4,4-dimethylcyclohexa-2,5-dien-1-one [13] were synthesized according to known procedures.

4-Chloromethyl-4-methylcyclohexa-2,5-dien-1-one (I) was synthesized according to the procedure described in [14]. UV spectrum: λ_{max} 233 nm (logε 3.84). IR spectrum, ν, cm^{-1}: 1630, 1660. ^{1}H NMR spectrum, δ, ppm: 1.35 s (3H, 4-Me), 3.54 s (2H, 4-CH_2), 6.34 d (2H, 2-H, 6-H, ^3J = 9.8 Hz), 6.83 d (2H, 3-H, 5-H, ^3J = 9.8 Hz). ^{13}C–{^{1}H} NMR spectrum, δ_C, ppm: 23.09 (4-Me), 42.42 (C^4), 63.91 (4-CH_2Cl), 104.21 (C^2, C^6), 129.87 (C^3, C^5), 152.05 (C=O). Found, %: C 61.59; H 5.55. C_8H_9ClO. Calculated, %: C 61.73; H 5.75.

4-Bromomethyl-4-methylcyclohexa-2,5-dien-1-one (II). The UV, IR, and mass spectra of **II** were consistent with those reported in [14]. ^{1}H NMR spectrum, δ, ppm: 1.36 s (3H, 4-Me), 3.41 s (2H, 4-CH_2Br), 6.32 d (2H, 2-H, 6-H, ^3J = 9.7 Hz), 6.81 d (2H, 3-H, 5-H, ^3J = 9.7 Hz). ^{13}C–{^{1}H} NMR spectrum, δ_C, ppm: 24.26 (4-Me), 41.55 (C^4), 63.89 (4-CH_2Br), 104.23 (C^2, C^6), 129.77 (C^3, C^5), 152.18 (C=O).

2,6-Dibromo-4,4-dimethylcyclohexa-2,5-dien-1-one (III). The UV, IR, and mass spectra of **III** were consistent with those reported in [15]. ^{1}H NMR spectrum, δ, ppm: 1.32 s (6H, 4-Me), 7.28 s (2H, 3-H, 5-H). ^{13}C–{^{1}H} NMR spectrum, δ_C, ppm: 26.10 (4-Me), 44.06 (C^4), 120.48 (C^2, C^6), 156.64 (C^3, C^5), 172.42 (C=O).

REFERENCES

1. Stetter, H. and Mayer, J., *Chem. Ber.*, 1959, vol. 92, no. 10, p. 2664.
2. Wenkert, E., Haviv, F., and Zeitlin, A., *J. Am. Chem. Soc.*, 1969, vol. 91, no. 9, p. 2299.
3. Stefanovic, M., Jeremic, D., Solujic, S., and Sukodlak, S., *J. Serb. Chem. Soc.*, 1986, vol. 51, nos. 9–10, p. 429.
4. Schlegel, H.J., *Allgemeine Mikrobiologie*, Stuttgart: Georg Thieme, 1985. Translated under the title *Obshchaya mikrobiologiya*, Moscow: Mir, 1987, p. 234.
5. Sukodlak, S., Solujic-Sukdolak, S., and Krstic, Lj., *J. Serb. Chem. Soc.*, 2000, vol. 65, no. 2, p. 103.
6. Rakhit, S. and Gut, M., *J. Am. Chem. Soc.*, 1964, vol. 86, no. 7, p. 1432.
7. Gavrilova, G.V., Moiseeva, A.A., Beloglazkina, E.K., Gavrilov, A.A., and Butin, K.P., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2006, no. 9, p.1558; *Russ. Chem. Bull.*, 2006, vol. 55, no. 9, p. 1617.
8. Stork, G. and Tsuji, J., *J. Am. Chem. Soc.*, 1961, vol. 83, no. 12, p. 2783.
9. Reutov, O.A., Kurts, A.L., and Butin, K.P., *Organicheskaya khimiya* (Organic Chemistry), Moscow: Binom, 2004, vol. 4, p. 273.
10. *Organic Electrochemistry: An Introduction and a Guide*, Baizer, M.M., Ed., New York: Marcel Dekker, 1973.
11. Gavrilova, G.V., Gavrilov, A.A., Krut'ko, D.P., and Butin, K.P., *Russ. J. Org. Chem.*, 2003, vol. 39, no. 3, p. 361.
12. Zimmerman, H.E., Hackett, P., Juers, D.F., McCall, J.M., and Shroder, B., *J. Am. Chem. Soc.*, 1971, vol. 93, no. 15, p. 3653.
13. Stewart, J.P., *J. Comput. Chem.*, 1989, vol. 10, no. 2, p. 209.
14. Gavrilova, G.V., Nikanorov, V.A., Yur'ev, A.V., Rozenberg, V.I., and Reutov, O.A., *Metalloorg. Khim.*, 1990, vol. 3, no. 2, p. 333.
15. Bordwell, F.G. and Wellman, K.M., *J. Org. Chem.*, 1963, vol. 28, no. 10, p. 2544.