Stereoselective electrochemical transformation of 4-substituted cyclohexanones into *cis*-5-substituted 2,2-dimethoxycyclohexanols

M. N. Elinson, S. K. Feducovich, D. E. Dmitriev, A. S. Dorofeev, A. N. Vereshchagin, and G. I. Nikishin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: elinson@ioc.ac.ru

Electrolysis of 4-substituted cyclohexanones in methanol in the presence of sodium halides as mediators in an undivided cell results in the stereoselective formation of *cis*-5-substituted 2,2-dimethoxycyclohexanols in 70—80% yields.

Key words: electrolysis, electrochemical oxidation, stereoselectivity, substituted cyclohexanones, mediators, 5-substituted 2,2-dimethoxycyclohexanols.

Reactions of ketone oxidation are well known in the classical organic chemistry and are used for the synthesis of carboxylic acids, α-hydroxy ketones, diketones, and some other bifunctional compounds, which are useful in the organic synthesis.[1] The synthesis of adipic acid by the oxidation of cyclohexanone is a known industrial process. α-Hydroxy ketones are widely used in the synthesis of natural and pharmacologically active compounds.[2—5]

The intense development of works on the electrochemistry of organic compounds in the last three decades made it possible to transfer the organic electrosynthesis from the area of special interest of a narrow range of electrochemists to a group of methods used in the organic synthesis.[6]

The electrochemical synthesis of organic compounds presently gains an increasing significance due to wide, and sometimes unique, possibilities of application of the electric current as a universal oxidant and a reducing agent for various transformations of organic compounds and development of economical and ecologically safe processes.[7]

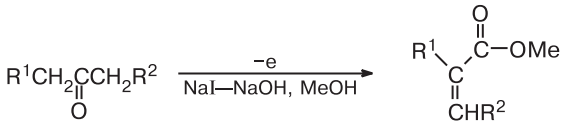
However, only in particular cases, the electrochemical oxidation of ketones was accomplished under conditions providing selectivity, which is necessary for the use in the organic synthesis. Besides, we do not know examples of stereoselective electrochemical oxidation of ketones.

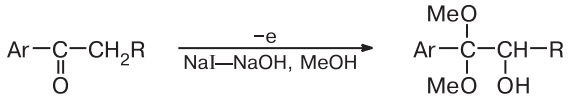
The direct electrochemical oxidation of ketones affords a mixture of carboxylic acids, saturated and unsaturated hydrocarbons, and carbon oxide and dioxide.[8—11] When electrooxidation was carried out in acetonitrile or trifluoroacetic acid, the nonselective remote functionalization of ketones occurred due to the subsequent transformations and decomposition of the primarily formed radical cations $R^1R^2C{=}O^{\bullet+}$.[12,13]

In some oxidative transformations of ketones, such as the haloformic reaction, the preliminary α-halogenation of ketones is a key stage.[14] Therefore, in some cases, the indirect electrochemical oxidation of ketones using halide ions as mediators was realized. For example, the electrocatalytic variant of the haloformic reaction is well known: electrochemical transformation of aryl and alkyl methyl ketones into methyl carboxylates by electrolysis in methanol in the presence of alkaline metal bromides.[15]

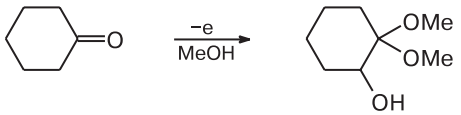
The NaI—NaOH mediator system was used for the indirect electrochemical oxidation of aldehydes and cyclic ketones.[16,17]

We have recently performed the indirect electrochemical oxidation of aliphatic ketones to esters of unsaturated carboxylic acids[18] and of alkyl aryl ketones to α-hydroxy ketals[19] in the presence of the NaI—NaOH system.





The electrochemical oxidation of cyclohexanone to 2,2-dimethoxycyclohexanol in methanol in the presence of the NaI—NaOH system[16] and using NaBr[20] or NaI[17] as mediators is known.



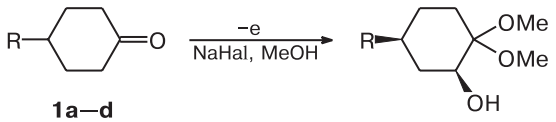
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1365—1368, August, 2002.

Table 1. Stereoselective electrooxidation of 4-substituted cyclohexanones **1a—d**

Ketone	R	Mediator	Metal hydroxide	Amount of electricity /F mol^{-1}	Product, yield (%)*
1a	Me	NaBr	—	2.9	**2a**, 73
1a	Me	NaI	—	2.9	**2a**, 79 (68)
1a	Me	NaI	NaOH	2.9	**2a**, 77
1b	Et	NaBr	—	3.0	**2b**, 71
1b	Et	NaI	—	3.0	**2b**, 78 (65)
1b	Et	NaI	NaOH	3.0	**2b**, 74
1c	Bu^t	NaBr		3.1	**2c**, 67
1c	Bu^t	NaI	—	3.1	**2c**, 73 (61)
1c	Bu^t	NaI	NaOH	3.1	**2c**, 69
1d	Ph	NaBr	—	3.3	**2d**, 65
1d	Ph	NaI	—	3.3	**2d**, 69 (58)
1d	Ph	NaI	NaOH	3.3	**2d**, 64

* According to the ^{1}H NMR spectroscopic data, the conversion of compounds **1a—d** is 98—100% (the yield per isolated product is given in parentheses).

In this work we performed the stereoselective indirect electrochemical transformation of 4-substituted cyclohexanones **1a—d** into *cis*-5-substituted 2,2-dimethoxycyclohexanols **2a—d** (Table 1) (for the preliminary report, see Ref. 21).



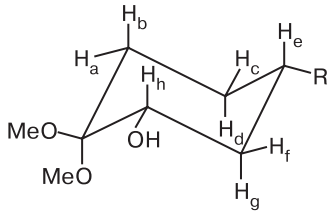
1a—d **2a—d**

As follows from the data in Table 1, NaI turned out to be the optimum mediator for the oxidation of 4-substituted cyclohexanones **1a—d**. The addition of NaOH or an increase in the temperature of electrolysis to 60 °C have no substantial effect on the course of the process. Similar results, but with some decrease in the yield of the final reaction products, were obtained when NaBr was used as the mediator.

The data of ^{1}H and ^{13}C NMR spectroscopy of compounds **2a—d** indicate unambiguously that only one of two possible diastereomers **2a—d** is stereoselectively formed in all experiments. The structure of **2a—d** was established using two-dimensional homonuclear COSY spectra and by the further analysis of the spin system of compounds **2a—d** using the CALM iteration computer program.[22] The spectra of all compounds exhibited two high vicinal spin-spin coupling constants of the H_g proton ($^3J_{e,g}$ and $^3J_{g,h}$), whose values ranged from 11.0 to 12.5 Hz (Table 2).

Table 2. Spin-spin coupling constants of the H_g proton in the spectra of compounds **2a—d**

Constants	**2a**	**2b**	**2c**	**2d**
$^3J_{e,g}$	11.15	11.00	12.00	12.50
$^3J_{g,h}$	11.29	11.20	11.50	11.90



Taking into account the fact that the typical vicinal spin-spin coupling constant for the cyclohexane ring is 10—15 Hz in the case of axial protons and 2—5 Hz in the case of interaction of the axial and equatorial or two equatorial protons[23] and the data in Table 2, we can suggest that the H_h, H_g, and H_e protons occupy the axial position and the OH group and substituent R are in the equatorial position. Thus, compounds **2a—d** are *cis*-substituted 2,2-dimethoxycyclohexanols.

For all compounds, the spin-spin coupling constants obtained using the CALM programs were compared with the values calculated for isomeric **2a—d** with different positions of the R substituent and OH group. The geometry of isomeric compounds **2a—d** was calculated in the MM2 force field.[24,25] The calculated spin-spin coupling constants are closest to the experimental values in the case of the equatorial arrangement of the OH group and R substituent, which additionally confirms that the structures of compounds **2a—d** were correctly determined.

Table 3. Comparison of spin-spin coupling constants (J) determined experimentally and calculated for stereoisomers **2a** and their conformers with different positions of the OH and Me groups

Protons	J/Hz				
	Calculation				Experiment
	ea	*ee*	*ae*	*aa*	
ac	3.08	3.02	3.00	3.20	3.70
ad	3.75	3.63	3.63	3.71	3.42
bc	3.84	3.85	3.87	3.61	3.95
bd	13.66	13.72	13.71	13.71	12.81
ce	1.95	3.61	3.68	1.77	4.00
de	4.97	12.25	12.25	5.26	11.84
ef	1.98	3.57	3.60	1.80	4.56
eg	4.75	12.30	12.26	5.30	11.15
gh	11.44	11.50	2.00	2.40	11.29
fh	3.89	3.85	4.29	4.00	3.76
SSD*	100.29	4.03	90.19	170.29	

* The sum of squared deviations of experimental and calculated spin-spin coupling constants.

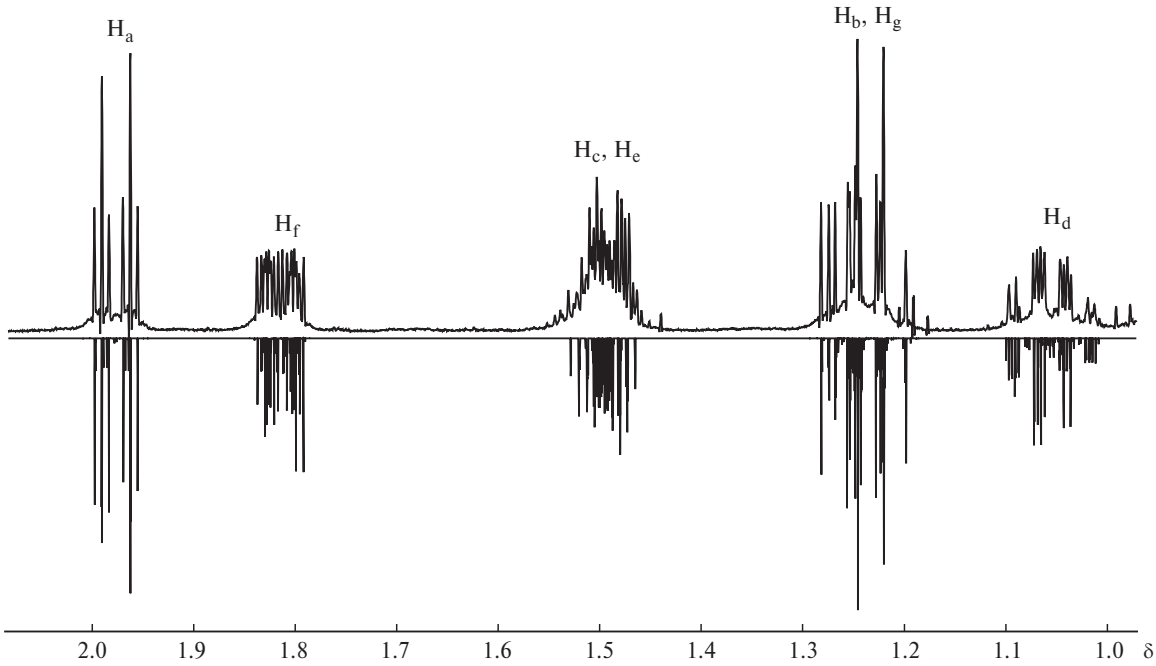


Fig. 1. Comparison of the calculated and experimental ^{1}H NMR spectra of *cis*-2,2-dimethoxy-5-methylcyclohexanol (**2a**).

The calculated and experimental spin-spin coupling constants for compound **2a** are presented in Table 3. The experimental and calculated spectra for compound **2a** are presented in Fig. 1.

Taking into account the results obtained in this work and the data on the mechanisms of electrochemical oxidation of cyclic ketones and alkyl aryl ketones in the presence of mediators (metal halides), we proposed the following mechanism of stereoselective electrochemical transformation of 4-substituted cyclohexanones **1a—d** into 5-substituted *cis*-2,2-dimethoxycyclohexanols **2a—d**.

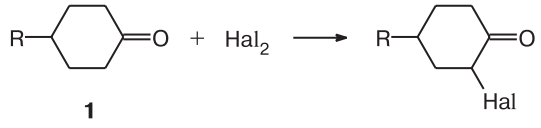
The reactions on electrodes, which occur in the oxidation of ketones **1a—d** in methanol, are standard for the mediator used (metal halide) and involve the formation of halogen on the anode and hydrogen evolution on the cathode accompanied by the generation of the methoxide ions

Anode: $2\,Hal^- - 2\,e \longrightarrow Hal_2$

Cathode: $2\,MeOH + 2\,e \longrightarrow 2\,MeO^- + H_2$

Hal = I, Br

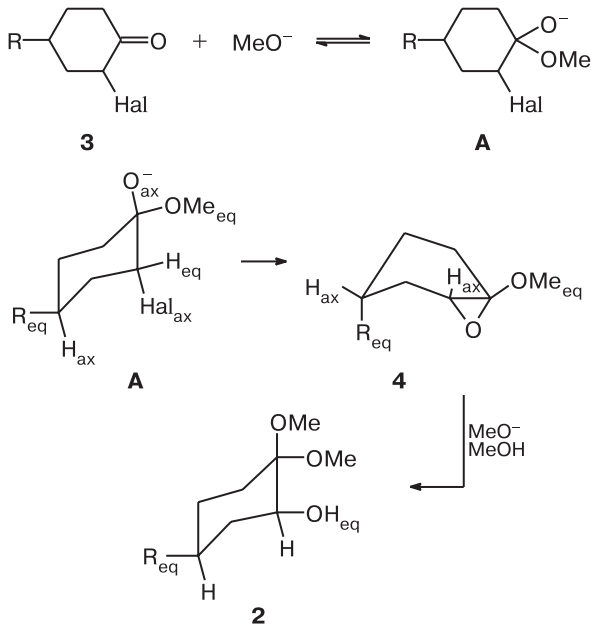
The α-halogenation of the enole form of ketones **1a—d** occurs in a solution, like in the case of the electrochemical oxidation of cyclic[16,17] and aliphatic ketones[18] and alkyl aryl ketones.[19]



1 **3**

In the presence of methoxide ions, two possible isomers of α-halogen ketone **3** with the axial and equatorial arrangement of the halogen atom are at equilibrium in a solution.

α-Halogen ketone **3** is reversibly attacked by the methoxide ion at the carbonyl group to produce anion **A**. The subsequent intramolecular nucleophilic substitution of halogen affords epoxide **4**.[17,20,26]



In all possible isomers of anion **A**, the R substituent is predominantly located in the equatorial position. It is

known that the isomer containing the axial halogen atom and oxide anion much more rapidly undergo cyclization to the corresponding *cis*-epoxide **4**.[27,28] *cis*-Epoxide **4** has a conformation of a strongly distorted chair with one axial and one equatorial C—O bonds.[29,30] Since the R substituent and MeO group in the formed *cis*-epoxide **4** are equatorial, the $O—C_{(OMe)}$ bond is axial and the $O—C_{(H)}$ bond is equatorial.[29,31]

The subsequent attack of *cis*-epoxide **4** by the second equivalent of the methoxide ion results in the formation of ketal **2** with equatorial both R substituent and OH group.[31,32] It is important that in the stereoselective electrochemical transformation of **1a—d** into **2a—d** found in this work the kinetic and thermodynamic factors control the process similarly and result in the same type of compounds, *viz.*, *cis*-hydroxy ketals **2a—d**.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer with working frequencies of 500.13 and 125.4 MHz, respectively, in a solution of $CDCl_3$. Chemical shifts in NMR spectra are presented in the δ scale relatively to Me_4Si.

Mass spectra (EI, 70 eV) were obtained on a Hewlett-Packard 5988A spectrometer.

The conversion of the initial ketones was monitored by GLC on an LKhM-80 chromatograph with a flame-ionization detector using nitrogen as the carrier gas, a flow rate of 30 mL min^{-1}, and a glass column (2500×3 mm) packed with 5% SE-Superphase on Inerton Super (0.16—0.20 mm).

The initial ketones were commercial reagents (Aldrich).

Electrolysis (general procedure). Ketone **1a—d** (20 mmol) and a mediator (10 mmol) (in some cases, with an addition of NaOH (1 mmol)) in MeOH (20 mL) were placed in an undivided cell with external cooling equipped with a Fe cathode, a C anode (the distance between the electrodes was ~5 mm), a magnetic stirrer, a thermometer, and a reflux condenser. Electrolysis was carried out at 30 °C in the dc mode (the current density was 100 mA cm^{-2}), passing the amount of electricity indicated in Table 1 through the solution. The reaction mixture was concentrated, and the products were extracted with $CHCl_3$ (30 mL). The extract was concentrated by evaporation, and ethers **2a—d** were isolated by distillation *in vacuo*.

2,2-Dimethoxy-5-methylcyclohexanol (2a), b.p. 67—69 °C (0.5 Torr). ^1H NMR, δ: 0.94 (d, 3 H, CH_3, J = 6.4 Hz); 1.07 (m, 1 H, H_d); 1.25 (m, 2 H, H_b, H_g); 1.50 (m, 2 H, H_c, H_e); 1.82 (m, 1 H, H_f); 1.98 (dt, 1 H, H_a, J_1 = 14.0 Hz, J_2 = 3.4 Hz); 2.25 (s, 1 H, OH); 3.34 (s, 3 H, OCH_3); 3.39 (s, 3 H, OCH_3); 3.68 (m, 1 H, H_h). ^{13}C NMR, δ: 21.52 (CH_3); 30.50 (CH); 30.51 (CH_2); 30.67 (CH_2); 40.53 (CH_2); 48.70 (OCH_3); 50.37 (OCH_3); 74.80 (OCH); 99.36 (O—C—O). MS, m/z (I_{rel} (%)): 174 $[M]^+$ (10), 143 (18), 142 (5), 102 (9), 101 (100), 88 (21), 57 (9). Found (%): C, 61.87; H, 10.47. $C_9H_{18}O_3$. Calculated (%): C, 62.04; H, 10.41.

5-Ethyl-2,2-dimethoxycyclohexanol (2b), b.p. 77—79 °C (0.5 Torr). ^1H NMR, δ: 0.84 (t, 3 H, CH_3, J = 7.4 Hz); 0.97 (m, 1 H, H_d); 1.13—1.27 (m, 5 H, H_b, H_g, H_e, CH_2); 1.52 (m, 1 H, H_c); 1.85 (m, 1 H, H_f); 1.97 (dt, 1 H, H_a, J_1 = 14.0 Hz, J_2 = 3.6 Hz); 2.47 (s, 1 H, OH); 3.27 (s, 3 H, OCH_3); 3.35 (s, 3 H, OCH_3); 3.62 (m, 1 H, H_h). ^{13}C NMR, δ: 11.59 (CH_3); 28.04 (CH_2); 28.77 (CH_2); 30.49 (CH_2); 37.37 (CH); 38.13 (CH_2); 48.66 (OCH_3); 50.29 (OCH_3); 74.94 (OCH); 99.54 (O—C—O). MS, m/z (I_{rel} (%)): 188 $[M]^+$ (6), 157 (9), 129 (3), 101 (100), 88 (25), 57 (22), 55 (17). Found (%): C, 63.59; H, 10.85. $C_{10}H_{20}O_3$. Calculated (%): C, 63.80; H, 10.71.

5-*tert*-Butyl-2,2-dimethoxycyclohexanol (2c), b.p. 89—91 °C (0.2 Torr). ^1H NMR, δ: 0.74 (s, 9 H, Bu^t); 1.06—1.15 (m, 2 H, H_d, H_e); 1.19 (m, 1 H, H_b); 1.25 (m, 1 H, H_g); 1.57 (m, 1 H, H_c); 1.90 (m, 1 H, H_f); 2.06 (dt, 1 H, H_a, J_1 = 13.1 Hz, J_2 = 3.4 Hz); 2.25 (s, 1 H, OH); 3.32 (s, 3 H, OCH_3); 3.40 (s, 3 H, OCH_3); 3.63 (m, 1 H, H_h). ^{13}C NMR, δ: 23.05 (CH_2); 27.52 (CH_3); 31.16 (CH_2); 32.09 (C); 33.74 (CH_2); 46.18 (CH); 48.73 (OCH_3); 50.55 (OCH_3); 75.93 (O—CH); 99.21 (O—C—O). MS, m/z (I_{rel} (%)): 216 $[M]^+$ (1), 185 (3), 159 (2), 129 (20), 101 (100), 88 (27), 69 (31), 67 (36), 57 (78), 55 (64). Found (%): C, 66.45; H, 11.23. $C_{12}H_{24}O_3$. Calculated (%): C, 66.63; H, 11.18.

2,2-Dimethoxy-5-phenylcyclohexanol (2d), b.p. 101—103 °C (0.05 Torr). ^1H NMR, δ: 1.35 (m, 1 H, H_b); 1.52 (m, 1 H, H_d); 1.67 (m, 1 H, H_c); 1.74 (ddd, 1 H, H_g, J_1 = 11.9 Hz, J_2 = 12.3 Hz, J_3 = 12.5 Hz); 1.99 (m, 1 H, H_f); 2.07 (dt, 1 H, H_a, J_1 = 14.4 Hz, J_2 = 3.3 Hz); 2.57 (m, 1 H, H_e); 2.75 (s, 1 H, OH); 3.32 (s, 3 H, —OCH_3); 3.38 (s, 3 H, —OCH_3); 3.76 (m, 1 H, H_h); 7.10—7.30 (m, 5 H, Ar). ^{13}C NMR, δ: 29.90 (CH_2); 31.26 (CH); 39.62 (CH_2); 42.12 (CH_2); 48.87 (OCH_3); 50.64 (q); 75.37 (O—CH); 99.01 (O-C—O); 126.19, 126.72, 128.35, 145.28 (Ph). MS, m/z (I_{rel} (%)): 236 $[M]^+$ (1), 205 (2), 187 (3), 159 (2), 145 (7), 129 (10), 101 (100), 91 (46), 77 (24), 88 (68). Found (%): C, 70.93; H, 8.47. $C_{14}H_{20}O_3$. Calculated (%): 71.16; H, 8.53.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 00-03-32913a) and the Foundation of Leading Scientific Schools (Project No. 00-15-97328).

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Received October 30, 2001;
in revised form March 13, 2002