ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 1, pp. 62–65. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © T.V. Magdesieva, A.V. Dolganov, G.V. Latyshev, A.V. Yakimanskii, M.Ya. Goikhman, I.V. Podeshvo, N.V. Lukashev, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 1, pp. 65–68.

Copper(I) Complexes with Polymeric 2,2′-Biquinoline-Containing Ligands as Electrocatalysts for Selective Oxidation of the Secondary Hydroxy Group in 3,24-Dihydroxy-5β-cholane with Oxygen

T. V. Magdesieva[a], A. V. Dolganov[a], G. V. Latyshev[a], A. V. Yakimanskii[b], M. Ya. Goikhman[b], I. V. Podeshvo[b], and N. V. Lukashev[a]

[a] *Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia*
e-mail: tvm@org.chem.msu.ru

[b] *Institute of High-Molecular Compounds, Russian Academy Sciences, St. Petersburg, Russia*

Received December 17, 2009

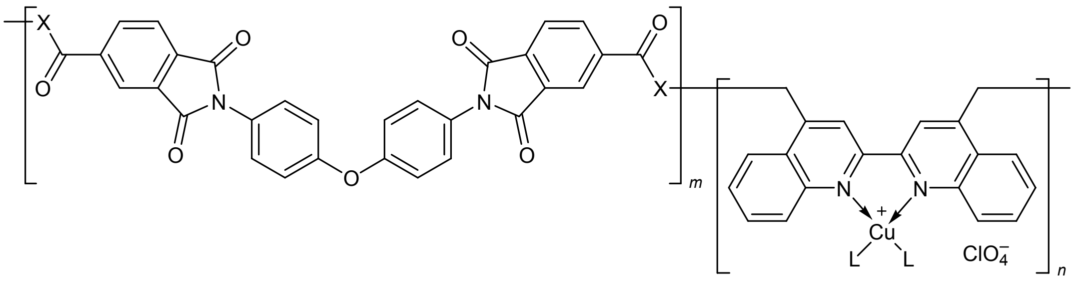
Abstract—Indirect electrocatalytic selective oxidation of the secondary hydroxy group in 3,24-dihydroxy-5β-cholane was performed using atmospheric oxygen in the presence of copper(I) complex with a polymeric 2,2′-biquinoline-containing ligand as catalyst. The reaction was characterized by a high yield (85%), 100% selectivity, and mild conditions, the Cu^{II}/Cu^{I} redox potential being –0.55 V relative to Ag/AgCl/KCl.

DOI: 10.1134/S1070428011010064

The scope of synthetic application of direct electrochemical oxidation of alcohols at a platinum or glassy carbon electrode is strongly limited, for this process occurs at fairly high anode potentials and is generally characterized by low selectivity [1, 2]. In a number of cases, the above problems may be solved by using various mediator or catalytic systems [3–9] (see also references given therein). The selectivity of oxidation is determined by many factors; it is especially important in the synthesis of polyfunctionalized organic compounds, e.g., pharmaceutical agents, organic materials with tunable properties, etc. Up to now, numerous procedures, both electrochemical and purely chemical, for selective oxidation of secondary and primary hydroxy groups have been reported [10], each being characterized by its own advantages and disadvantages. Taking into account continuous extension of the range of problems to be solved by chemists, development of new economic methods for selective catalytic oxidation of hydroxy groups of different origins remains as important as previously.

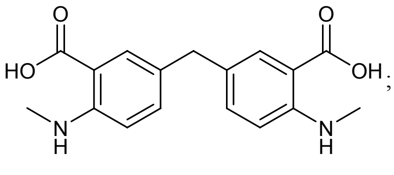
Steroidal alcohol molecules often contain different kinds of hydroxy groups; therefore, they may be convenient models for studying oxidative selectivity of catalytic systems. Interest in such studies originates from their significance from the viewpoints of both fundamental and applied science, in particular taking into account wide application of steroids in pharmaceutical practice. Considerable difference in the reactivity of primary and secondary hydroxy groups was observed in reactions performed in the presence of electrochemically generated nickel hydroxide oxidative systems like $Ni^{III}(O)OH$. For example, 3α- or 3β-hydroxy group can be selectively oxidized in the presence of 17β-hydroxy group [11], but the yield is fairly low (28%). Selective oxidation of cholic acid at the 3α-hydroxy group was reported, the 7α- and 12α-hydroxy groups remaining unchanged [11]. The yield of the oxidation product was relatively low (38%) as a result of side oxidative decomposition at the $C^3–C^4$ bond and subsequent lactonization. Selective electrocatalytic oxidation of the 3β-hydroxy group in the presence of 11β- and 20β-hydroxy groups was reported to provide a yield of 78% [11]. For comparison, it should be noted that the yield in well known Oppenauer oxidation of the 3β-hydroxy group in structurally related steroids generally does not exceed 30% [12].

High selectivity observed in electrochemical process may be rationalized by preferential adsorption of



$[Cu^I(PA)L_2][ClO_4]$

X =



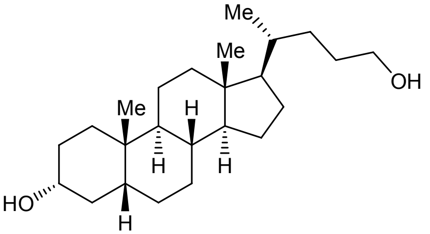
; $m:n = 8:2$; L is solvent.

steroid molecule on the electrode surface at the less sterically hindered α-side. Therefore, in most cases less sterically hindered hydroxy groups are oxidized first. The reactivity of different hydroxy groups over nickel hydroxide electrode decreases in the following series [13]: 3β-OH ≈ 3α-OH > 17β-OH >> 20β-OH > 11β-OH. This experimental reactivity series is determined primarily by spatial accessibility of hydroxy groups, and 11β-, 17β-, and 20β-hydroxy groups appear most sterically shielded.

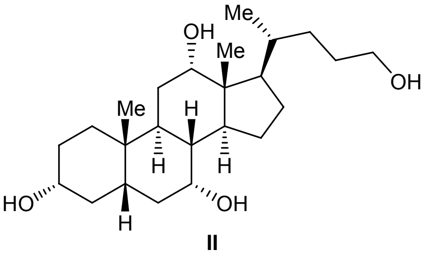
We recently proposed [14, 15] an electrochemical synthetic approach (using soluble anodes) to new redox-active catalytic systems on the basis of poly(amido acids) (PA) containing biquinoline fragments capable of coordinating copper(I) ions. These polymeric ligands are especially interesting due to their ability to stabilize copper(I) complexes which tend to undergo disproportionation in solution to give Cu(0) and Cu(II) species.

The polymeric copper(I) complex whose structure is shown above exhibits a high electrocatalytic activity in aerobic oxidation of aliphatic and aromatic alcohols in the presence of atmospheric oxygen [14]. The voltammetric curves observed for $[Cu(PA)L_2]ClO_4$ in an argon atmosphere containing molecular oxygen, reaction mechanism, and the relative catalytic activities of polymeric copper complexes having different structures were discussed in detail in [14–16]. Electrocatalytic aerobic oxidation of alcohols leads to the formation of the corresponding carbonyl compounds in high yield, while molecular oxygen is reduced to water [14]. No further oxidation of carbonyl compounds (to carboxylic acids) is observed.

Analysis of the current density in the oxidation of simple model primary and secondary alcohols showed that secondary hydroxy groups are oxidized more readily than primary hydroxy groups (see table). These findings prompted us to examine the possibility of using previously proposed [14, 15] catalytic system for selective oxidation of secondary hydroxy group in model steroidal alcohols whose molecules also contain primary hydroxy groups. As models for studying the selectivity of electrocatalytic aerobic oxidation in the presence of polymeric copper(I) complex we selected steroidal alcohols **I** and **II** possessing both primary and secondary hydroxy groups.



I



II

The reactions were carried under mild conditions at room temperature under an oxygen pressure equal to atmospheric, and the Cu^{II}/Cu^I redox potential was equal to –0.55 V relative to silver chloride electrode (Ag/AgCl/KCl), as was proposed in [14]. The general

Scheme 1.

$$Cu^+ + O_2 + RCH_2OH + e^- + 2H^+ \longrightarrow Cu^{2+} + RCHO + 2H_2O$$

Yields of carbonyl compounds and current densities in electrocatalytic aerobic oxidation of alcohols in the presence of $[Cu(PA)L_2]ClO_4$ (0.03 mol %) immobilized on the surface of a graphite electrode, CH_2Cl_2, –0.55 V (relative to Ag/AgCl/KCl), 20°C

Initial alcohol	Current density, mA/cm^2	Oxidation product	Yield, %
$PhCH_2OH$	1.00	PhCHO	94
BuOH	1.10	BuCHO	93
PhCH(OH)Me	1.25	PhCOMe	94
cyclo-$C_6H_{11}OH$	1.25	Cyclohexanone	91
I	1.27	**III**	85

reaction scheme is illustrated by Scheme 1. The catalyst was polymeric complex $[Cu(PA)L_2]^+\ ClO_4^-$ (its preparation was described in [14]) which was immobilized on a graphite electrode. For this purpose, a conductive graphite fabric with a high specific surface area (12 m^2/g) was impregnated with a dilute solution of the polymer in *N*-methylpyrrolidin-2-one, and polymeric copper(I) complex was obtained using a soluble copper anode as source of Cu(I) ions. The graphite fabric treated in such a way was used as working electrode in the electrocatalytic process which was performed in the potentiostatic mode at a potential of –0.55 V. The catalytic surface was examined by cryogenic transmission electron microscopy (Cryo-TEM) to estimate the width of the polymer layer. A section of the fabric looked like dark graphite fibers with cavities between them.* The polymer was distributed fairly uniformly over the fiber surface, and the average width of the polymer layer was ~10 nm. The catalytic surface was fairly stable. No appreciable change in the catalytic activity was observed after 20-h electrolysis or 10^4–10^5 catalytic cycles. The immobilized catalyst exhibited high activity even at a fairly low concentration of copper, 0.03 mol % with respect to the substrate.

The reaction can be carried out in both acetonitrile and methylene chloride, and the yields of the corresponding carbonyl compounds were fairly high (see table). Methylene chloride turned out to be the optimal solvent for the oxidation of steroid **I**. Unfortunately, steroid **II** was poorly soluble in methylene chloride, as well as in other solvents suitable for electrolysis (acetonitrile, DMF, DMSO), so that we failed to perform electrochemical reaction and identify products.

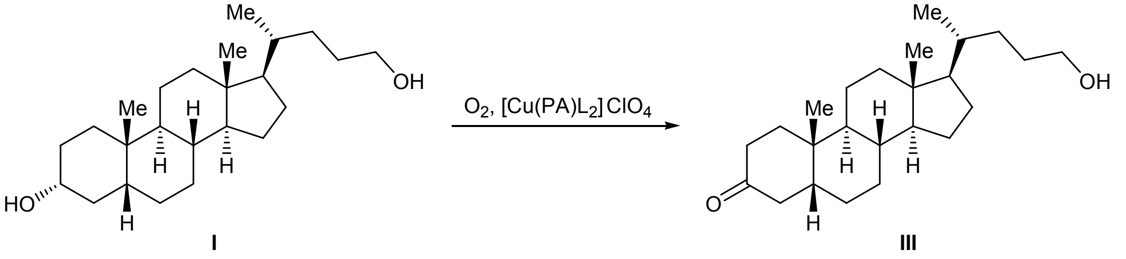
Catalytic oxidation of compound **I** under the above conditions (the amount of electricity passed through the solution was 2 F/mol), gave 24-hydroxy-5β-cholan-3-one in 85% yield and 100% selectivity (Scheme 2). Even traces of oxidation products of both hydroxy groups or oxidative decomposition products were not detected in the reaction mixture.

Thus the results of our experimental study indicated that the catalytic system proposed by us previously [14] on the basis of copper(I) complex with polymeric 2,2′-biquinoline-containing ligand is effective for selective oxidation of secondary hydroxy groups in the presence of primary ones. An important advantage of the proposed approach is electrocatalytic character of the process. Chemical oxidants inevitably give rise to by-products resulting from reduction of the oxidant, whereas in our case electric current acts as additional reagent.

EXPERIMENTAL

Acetonitrile of pure grade was stirred for 12 h over calcium hydride, distilled, heated for 2 h under reflux over phosphoric anhydride, and distilled again; a fraction with bp 81–82°C was collected. *N*-Methylpyrrolidin-2-one (from Aldrich) was dehydrated over calcium hydride and distilled under reduced pressure; a fraction with bp 35°C (5 mm) was collected. Methylene chloride of pure grade was distilled over calcium

Scheme 2.



---

* The corresponding image is available from the authors by e-mail.

hydride, and a fraction with bp 41°C was collected. The PA polymer was synthesized according to the procedure reported in [17]. Steroids **I** and **II** were synthesized by standard methods [18, 19]; the other examined alcohols were commercially available products (from Aldrich).

Mass-spectrometric analysis of reaction mixtures was performed on a GC–MS system including a Hewlett–Packard 5973 mass selective detector (HP-5MS column; detector and injector temperature 280°C; oven temperature programming from 70 to 320°C at a rate of 15 deg/min). The NMR spectra were measured on a Bruker Avance 400 spectrometer. Electrochemical oxidation was performed in a 100-ml diaphragmless cell using a P-5827 M potentiostat. Graphite fabric with a specific surface area of 12 m^2/g, 5×25 mm, containing preliminarily immobilized $[Cu^I(PA)L_2]\cdot ClO_4$ complex [14] was used as working electrode, and a platinum electrode was used as auxiliary one. In all cases, a saturated silver chloride electrode was used as reference (redox potential –0.43 V in acetonitrile relative to Fc/Fc^+).

Electrocatalytic oxidation of alcohols with atmospheric oxygen in the presence of $[Cu^I(PA)L_2]\cdot ClO_4$ immobilized on the surface of a graphite electrode. Alcohol **I**, 0.125 mmol, was dissolved in 50 ml of acetonitrile containing 0.05 mol/l of Bu_4NBF_4 or in methylene chloride containing 0.15 mol/l of $LiClO_4$, and preparative electrolysis was performed in the potentiostatic mode at a working electrode potential of –0.55 V relative to Ag/AgCl/KCl. During the electrolysis process, a 1 : 1 mixture of argon with air was passed through the solution at a flow rate of 24 ml/min. The reaction was terminated when 2 F/mol of electricity (calculated on the initial alcohol) was passed. The reaction mixture was analyzed by GC–MS in the presence of mesitylene as standard, as well as by ^1H and ^{13}C NMR spectroscopy.

24-Hydroxy-5β-cholan-3-one [20]. ^1H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm (*J*, Hz): 3.59 m (2H), 2.68 t (1H, *J* = 14.1), 2.32 t.d (1H, *J* = 14.5, 5.3), 2.14 m (1H), 2.02 m (3H), 1.82 m (3H), 1.65–1.04 m (20H), 1.00 s (3H), 0.92 d (3H, *J* = 6.44), 0.67 s (3H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz), δ_C, ppm: 213.5, 63.5, 56.3, 56.1, 44.3, 42.7, 42.3, 40.7, 40.0, 37.2, 37.0, 35.5 (2C), 34.8, 31.8, 29.3, 28.2, 26.6, 25.7, 24.1, 22.6, 21.1, 18.6, 12.0. The product structure was confirmed by independent synthesis from 24-(triphenylmethyloxy)-5β-cholan-3-ol.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 08-03-00142, 07-03-00619, 07-03-90824).

REFERENCES

1. *Organic Electrochemistry*, Baizer, M.M. and Lund, H., Eds., New York: Marcel Dekker, 1983, chap. 16.2.
2. *Technique of Electroorganic Synthesis*, Weinberg, N.L., Ed., New York: Wiley, 1974, vol. 1, p. 435.
3. Rethinam, A.J. and Kennedy, C.J., *J. Appl. Electrochem.*, 2004, vol. 34, p. 371.
4. Tsuboi, T., Ishii, N., Sakai, T., Tari, I., and Utaka, M., *Bull. Chem. Soc. Jpn.*, 1990, vol. 63, p. 1888.
5. Cosnier, S., Deronizier, A., and Roland, J.-F., *J. Mol. Catal.*, 1992, vol. 71, p. 303.
6. De Giovani, W.F. and Deronizier, A., *J. Electroanal. Chem.*, 1992, vol. 337, p. 285.
7. Geneste, F. and Moinet, C., *J. Electroanal. Chem.*, 2006, vol. 594, p. 105.
8. Ruholl, H. and Schaefer, H.-J., *Synthesis*, 1987, p. 408.
9. Schaefer, H.-J., Feldhues, U., Kaulen, H., and Ruholl, H., *Recent Advances in Electroorganic Synthesis, Proc. 1st Int. Symp. on Electroorganic Synthesis, Kurashiki, Japan, Oct 31–Nov 3, 1986*; Torii, S., Ed., Tokyo: Kodansha, 1987, p. 161.
10. Stevens, R., Chapman, K., Stubbs, C., Tam, W., and Albizati, K., *Tetrahedron Lett.*, 1982, vol. 23, p. 4647.
11. Kaulen, J. and Schaefer, H.J., *Tetrahedron*, 1982, vol. 38, p. 3299.
12. Rasmusson, G.H. and Arth, G.E., *Organic Reactions in Steroid Chemistry*, Fried, J. and Edwards, J.A., Eds., New York, Van Nostrand Reinhold, 1972, vol. 1, p. 222.
13. Schaefer, H.-J., *Top. Curr. Chem.*, 1987, vol. 42, p. 101.
14. Magdesieva, T., Dolganov, A., Yakimansky, A., Goikhman, M., Podeshvo, I., and Kudryavtsev, V., *Electrochim. Acta*, 2008, vol. 53, p. 3960.
15. Magdesieva, T.V., Dolganov, A.V., Yakimanskii, A.V., Goikhman, M.Ya., Podeshvo, I.V., and Kudryavtsev, V.V., *Elektrokhimiya*, 2007, vol. 43, p. 1194.
16. Magdesieva, T., Dolganov, A., Yakimansky, A., Goikhman, M., Podeshvo, I., and Kudryavtsev, V., *Electrochim. Acta*, 2009, vol. 54, p. 1444.
17. Polotskaya, G., Goikhman, M., Podeshvo, I., Kudryavtsev, V., Pientka, Z., Brozova, L., and Bleha, M., *Polymer*, 2005, vol. 46, p. 3730.
18. Valkonen, A., Sievänen, E., Ikonen, S., Lukashev, N.V., Donez, P.A., Averin, A.D., Lahtinen, M., and Kolehmainen, E., *J. Mol. Struct.*, 2007, vol. 846, p. 65.
19. Li, H. and Wang, L.-X., *Org. Biomol. Chem.*, 2003, vol. 1, p. 3507.
20. Paglialunga, M. and Zeccini, G.P., *Tetrahedron*, 1981, vol. 37, p. 971.