STEREOCHEMISTRY OF OXIDATIVE CHLORINATION OF CYCLOHEXANECARBOXYLIC ACID AND ITS METHYL ESTER IN THE SODIUM PEROXYDISULFATE–COPPER CHLORIDE SYSTEM

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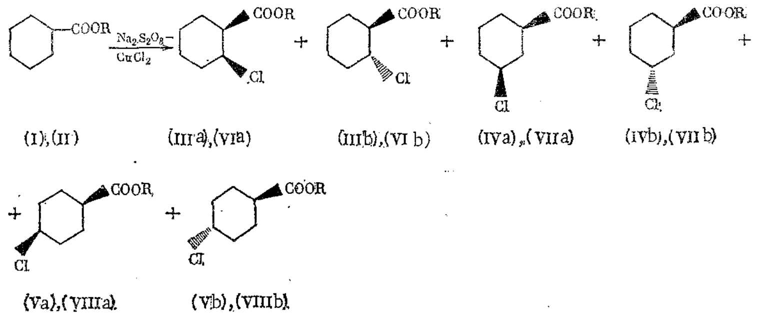
Continuing our investigations of the one-electron oxidation of alkanoic acids and their amides in sodium peroxydisulfate–chloride ion systems [1, 2], we studied the regio- and stereoselectivity of oxidative chlorination of cyclohexanecarboxylic acid (I) and its methyl ester (II) in the $Na_2S_2O_8-CuCl_2$ system.

During one-electron oxidation in aqueous solutions at 85-90°C with the use of equimolar amounts of $Na_2S_2O_8$ and $CuCl_2$, the acid (I) was converted to a mixture of cis and trans isomers of 2-, 3-, and 4-chlorocyclohexanecarboxylic acids (IIIa, b)-(Va, b) (Table 1). The correlation of chloro acids (IIIa, b)-(Va, b) was determined by proton NMR spectroscopy (250 MHz) as the methyl esters (VIa, b)-(VIIIa, b) after methylation with diazomethane.



R = H (I), (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb); R = CH_3 (II), (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb).

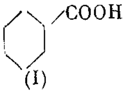
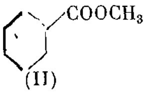
Under analogous conditions in the presence of the $Na_2S_2O_8-CuCl_2$ system, as a result of oxidative chlorination ester (II) was converted into a mixture of esters (VIa, b)-(VIIIa, b), the correlation of which was also determined by proton NMR spectroscopy.

The 2-, 3-, and 4-chlorocyclohexanecarboxylic acids were formed with due regard for the statistical factor 2 for substitution at the C^4 atom in the correlation 0.65:1:1.18. Thus, oxidative chlorination of the acid (I) occurred preferentially at the 3 and 4 positions of the cyclohexane ring. The composition and the correlation of the products of oxidative chlorination of the acid (I) did not depend on time, and, as was shown by a control experiment run, the products retained their configuration under the reaction conditions. On the basis of the correlation of the esters of the 2-, 3-, and 4-chlorocyclohexanecarboxylic acids equal to 0.60:1:1.18 (with due regard for the statistical factor), the regioselectivity of oxidative chlorination of ester (II) practically did not differ from that observed in the case of the acid (I), and, therefore, the nature of the electron-acceptor substituent, namely, carboxyl or methoxycarbonyl group, in the cyclohexane ring did not affect the regioselectivity of oxidative chlorination.

However, the nature of this substituent affected the reaction stereochemistry very significantly: from acid (I), all the chlorocyclohexanecarboxylic acids were formed preferentially as trans isomers, while oxidative chlorination of ester (II) at the 3 and 4 positions occurred nonstereoselectively. Chlorination of acid (I) by molecular chlorine occurred just as nonstereoselectively during irradiation or in the presence of PCl_3 [3].

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 7, pp. 1537-1540, July, 1983. Original article submitted November 1, 1982.

TABLE 1. Oxidation of Cyclohexanecarboxylic Acid (I) and Its Methyl Ester (II) in the $Na_2S_2O_8-CuCl_2$*

Substrate	Conversion, %	Reaction products and yields, % † based on the converted substrate	Overall yield, %
 (I)	55	(IIIa), 7, (IIIb), 19, (IVa), 15, (IVb), 26, (Va), 10, (Vb), 14	91
	70 ‡	(IIIa), 8, (IIIb), 17, (IVa), 15 (IVb), 30, (Va), 9, (Vb), 15	94
 (II)	50	(VIa), 9, (VIb), 16, (VIIa), 20, (VIIb), 22, (VIIIa), 13, (VIIIb), 11	91

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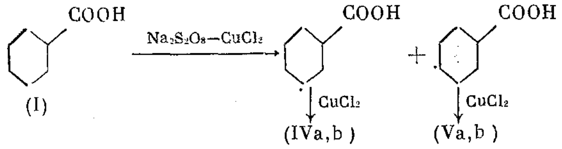
* 85-90°C, 6 h, 100 mmoles of (I) or (II), 100 mmoles of $Na_2S_2O_8$, 100 mmoles of $CuCl_2 \cdot 2H_2O$, and 100 ml of water.

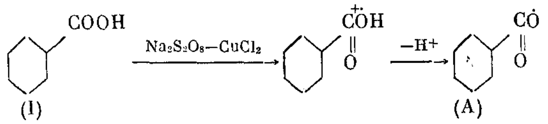
† The oxidation products of acid (I) were analyzed as their methyl esters after methylation with CH_2N_2.

‡ The reaction time was 12 h.

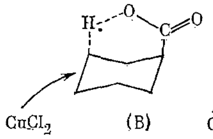
We feel that, unlike in the case of substitution at C^2, the trans stereoselectivity of chlorination of acid (I) at the C^3 and C^4-atoms in the $Na_2S_2O_8-CuCl_2$ system was due to the occurrence of the reaction according to two mechanisms simultaneously. As a result of substitution of the hydrogen at the C^3 and C^4 atoms by chlorine via intermediate "classical" 3- and 4-carboxycyclohexyl radicals with flattening at the radical center, (IVa) and (IVb) and also (Va) and (Vb) were formed nonstereoselectively:



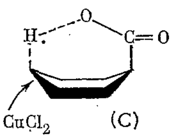
Concurrently, during one-electron oxidation of (I) at the COOH group, cyclohexylcarbonyloxy radicals (A) were generated:



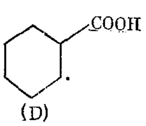
which, with 1,5 and 1,6 migration of the H atom [4] via transition states (B) and (C) were rearranged into 3- and 4-carboxycyclohexyl radicals, the configuration of which was apparently fixed because of the "buttressing" effect of the carboxyl group. One-electron oxidation of these radicals with transfer of a Cl atom occurred preferentially "from the rear," something that determined the predominance of the trans isomers of the resulting 3- and 4-chlorocyclohexanecarboxylic acids.



(B)



(C)



(D)

The six-membered transition state (B) was more favorable energetically than the seven-membered transition state (C), something that determined the greater stereoselectivity of oxidative chlorination at the C^3 atom than at C^4 (the ratios (IVb)/(IVa) and (Vb)/(Va) were equal to 1.7 and 1.4, respectively). In our opinion, the combination of these two mechanisms was responsible for the stereoselectivity of the oxidative chlorination of acid (I) at the C^3 and C^4 atoms.

The 2-carboxycyclohexyl radicals (D) were formed from (I) only as a result of intermolecular abstraction of an H atom, without participation of the reaction with rearrangement. The predominant formation of trans-2-chlorocyclohexanecarboxylic acid (IIIb) from (C), just as of its ester (VIb) from 2-(methoxycarbonyl)cyclohexyl radicals, was probably due to polar shielding of cis transfer of the chlorine atom by a COOR group (R = H or CH_3).

With respect to the stereoselectivity of oxidative chlorination of acid (I) in the $Na_2S_2O_8-CuCl_2$ system, the obtained results are in good agreement with the general scheme of one-electron oxidation of alkanoic acids in this system to alkylcarbonyloxy radicals, which were further rearranged into 3- and 4-carboxyalkyl radicals [1]. In our opinion, in contrast to the principles observed in the aliphatic series, the preferred formation of products of the reaction of 4-carboxycyclohexyl radicals in comparison with 3-carboxycyclohexyl radicals was due to the polar effect of the COOH group on intermolecular abstraction of the *H* atom. Because of conformational convergence, this group in the cyclohexane system deactivated hydrogen abstraction from the C^3 atom to a greater degree than from the C^4 atom, favoring the generation of 4-carboxycyclohexyl radicals.

It should be noted that rearrangement of radicals (A) with migration of hydrogen into 3- and 4-carboxycyclohexyl radicals should contribute to an increase of the regioselectivity of oxidative chlorination of (I) at C^3 and C^4 atoms in comparison with oxidative chlorination of ester (II). However, this was not observed, probably because of the great steric demands of the $COOCH_3$ group in comparison with the COOH group during oxidative chlorination of (II) at the C^2 atom, leading to an increase of the amount of oxidative chlorination of (II) at the C^3 and C^4 atoms.

EXPERIMENTAL

The GLC analysis was carried out on an LKhM-8MD chromatograph with a flame-ionization detector in a stream of N_2, and the columns (stainless steel) were 3000 × 3 mm with 10% Carbowax 20M treated with H_3PO_4 [5] on Celite 545 (52-60 mesh) and 1700 × 3 mm with 3% PEGS on Chromosorb G (120-140 mesh) treated with dimethyldichlorosilane. The proton NMR spectra of solutions in $CDCl_3$ were measured on Brucker WM-250 (250 MHz) and Tesla BS-497 (100 MHz) spectrometers from HMDS. The IR spectra were obtained on a Perkin–Elmer instrument in a thin layer in a solution in CCl_4. The oxidizing agent was analytically pure $Na_2S_2O_8$, the $CuCl_2$ was a pure-grade reagent, and acid (I) was a Merck reagent, mp 29-30°C (cf. [6]); they were used without additional purification. Ester (II) was purified by distillation in vacuo, bp 71-73°C (15 mm).

Oxidation of Cyclohexanecarboxylic Acid (I) and Its Methyl Ester (II) in the $Na_2S_2O_8-CuCl_2$ System. This reaction was carried out in accordance with the general procedure for oxidation of alkanoic acids [1]. The residue after evaporation of the ether extract of the products of oxidation of (I) were methylated with excess CH_2N_2 [7]. After separation of (II) by fractionation in vacuo, the obtained mixture of methyl esters (VIa, b)-(VIIIa, b), just as the mixture of products of the oxidation of ester (II), was analyzed quantitatively by proton NMR spectroscopy (250 MHz) according to the correlation of the integrated intensities of the signals of CH_3O groups in the region of 3.62-3.70 ppm and of CHCl groups in the region of 3.98-4.52 ppm. The chemical shifts, the nature of the signals, and the values of the spin–spin coupling constants were identical to the data of [8] for individual (VIa, b)-(VIIIa, b). The correlations of esters (VIa, b)-(VIIIa, b) were determined from the results of four independent experiment runs.

Configurational Stability of Acids (IIIa, b)-(Va, b). To 30 mmoles of a mixture of chloro acids (IIIa, b)-(Va, b), during methylation of which with diazomethane (VIa, b)-(VIIIa, b) were formed in a correlation of 7:19:15:26:10:14 and 30 mmoles of $CuCl_2 \cdot 2H_2O$ in 40 ml of water, a solution of 30 mmoles of $Na_2S_2O_8$ in 25 ml of water was added at 85-90°C, the whole was heated for 2 h at 85-90°C and extracted with ether (3 × 50 ml), and the extract was dried with $MgSO_4$ and evaporated. We obtained 25 mmoles of a mixture of chloro esters (VIa, b)-(VIIIa, b) in a correlation of 8:18:14:25:10:15.

Configurational Stability of Esters (VIa, b)-(VIIIa, b). To 30 mmoles of chloro esters (VIa, b)-(VIIIa, b) in a correlation of 7:19:15:26:10:14 and 30 mmoles of $CuCl_2 \cdot 2H_2O$ in 40 ml of water, a solution of 30 mmoles of $Na_2S_2O_8$ in 25 ml of water was added at 85-90°C, the whole was heated for 2 h at 85-90°C and extracted with ether (3 × 50 ml), and the extract was dried with $MgSO_4$ and evaporated. We obtained 25 mmoles of a mixture of chloro esters (VIa, b)-(VIIIa, b) in a correlation of 7:16:15:28:10:15.

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CONCLUSIONS

1. Oxidative chlorination of cyclohexanecarboxylic acid and its methyl ester in the peroxydisulfate–copper chloride system occurs preferentially at C^3 and C^4 atoms.

2. Oxidative chlorination of cyclohexanecarboxylic acid is a stereoselective reaction, and trans-3- and trans-4-chlorocyclohexanecarboxylic acids are predominantly formed.

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OXIDATIVE CLEAVAGE OF TERTIARY CYCLOALKANOLS BY THE LEAD TETRAACETATE – METAL HALIDE SYSTEM*

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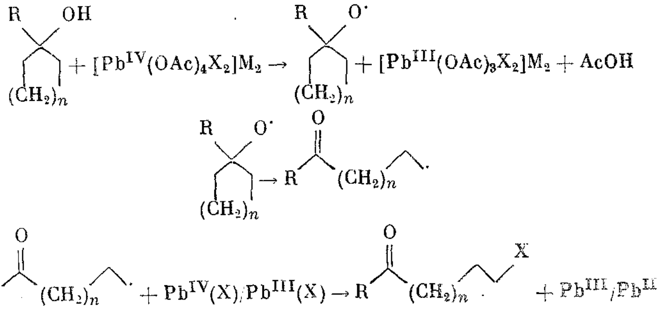
Reaction of tertiary cyclic alcohols with lead tetraacetate (LTA) affords oxoalkyl radicals $RCO(CH_2)_{n+1}\dot{C}H_2$ (n = 1 – 4) [2-4]. These radicals are oxidized by the LTA–$Cu(OAc)_2$ system to ω-unsaturated ketones [2], by the LTA–KSCN system to ω-oxoalkyl thiocyanates [3], and on treatment with the LTA–AgOAc system these radicals recombine to give diketones [4].

We here examine the oxidation of tertiary cyclic alcohols with the LTA–group I metal halide (MX, where M = Li, Na, or K, and X = Cl or Br) system. The reaction is carried out in benzene with the addition of pyridine, which accelerates the oxidative reaction. In the first step, a complex of LTA with MX is probably formed, and this then reacts with the alcohol. Similar complexes $[K_2[Pb(OAc)_6]$ and $K_2[Pb(OAc)_4Cl_2]]$ have been prepared [5, 6].

The mechanism of the oxidative cleavage may be represented as follows

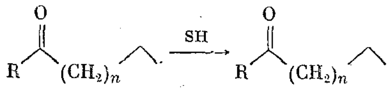
$$Pb^{IV}(OAc)_4 + 2MX \rightleftarrows [Pb^{IV}(OAc)_4X_2]M_2$$



$$[Pb^{III}(OAc)_3X_2]M_2 \rightarrow Pb^{II}(OAc)_2 + AcOM + MX + X^{\ominus}$$

$n = 2$–4; $R = CH_3,\ C_2H_5,\ C_7H_{15},\ C_9H_{19}$; $M = Li,\ Na,\ K$; $X = Cl,\ Br$

Initially, oxidation of the alcohol with the lead complex salt gives cyclic alkoxyl radicals. Reduction of Pb^{IV} to Pb^{III} may occur according to the equation shown in the Scheme, and also probably, to $[Pb^{III}(OAc)_4X]M_2$. The alkoxyl radicals then isomerize to oxoalkyl radicals. The latter are, for the most part, oxidized by Pb^{IV} or Pb^{III} to 1-haloalkanones, and to a very small extent they mediate removal of hydrogen from the H-donor (~ 1-2%)



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* For the previous communication, see [1].

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