STEREOCHEMISTRY OF THE OXIDATIVE LACTONIZATION OF 2- AND 3-METHYLPENTANOIC ACIDS IN THE SODIUM PEROXYDISULFATE–METAL CHLORIDE SYSTEM

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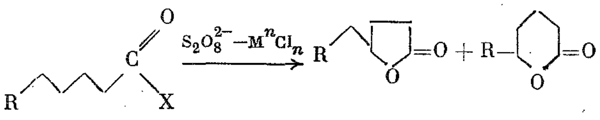
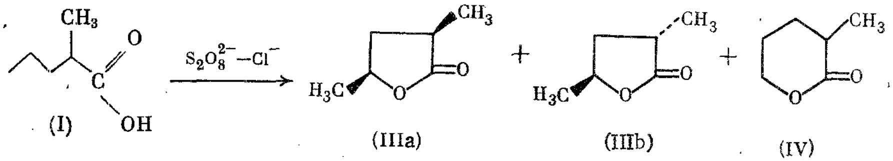
Reactions involving distant functional substitution of carboxylic acids and their derivatives number among the most important transformations of these classes of organic compounds and open up approaches to the synthesis of various polyfunctional compounds. Recently we discovered the direct oxidative lactonization of alkanoic acids by the action of the sodium peroxydisulfate–metal chloride oxidizing systems [1, 2]. This reaction is also typical of the amides of alkanoic acids [2, 3], and alkanehydroxamic acids [4]:



R = H or Alk, X = OH, NH_2, NHOH, $M^nCl_n = CuCl_2$, NaCl.

In a continuation of research into the one-electron oxidation of alkanoic acids in the sodium peroxydisulfate–chloride ion systems we studied the regioselectivity and diastereoselectivity of the oxidative lactonization (OL) of 2-methylpentanoic (I) and 3-methylpentanoic (II) acids in the $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl systems.

During oxidation in aqueous solutions at 85-90°C with equimolar amounts of $Na_2S_2O_8$ and $CuCl_2$ or two molar equivalents of sodium chloride 2-methylpentanoic acid is converted into a mixture of cis- and trans-2,4-dimethyl-4-butanolides (IIIa, b) [with the (2R*, 4S*) and (2S*, 4S*) configurations respectively] and 2-methyl-5-pentanolide (IV) (Table 1). The ratio of the lactones (IIIa, b) and (IV) was determined by PMR spectroscopy (250 MHz) and GLC.



Thus, the acid (I) undergoes OL with high regioselectivity at the γ-carbon atom, and this agrees fully with data on the OL of pentanoic acid [1, 2]. The lactonization of (I) in both oxidizing systems takes place nonstereoselectively and leads to the formation of the lactones (IIIa) and (IIIb) in a ratio of 1:1.

Under analogous conditions 3-methylpentanoic acid (II) gives cis- and trans-3,4-dimethyl-4-butanolides (Va, b) with the (3S*, 4S*) and (3S*, 4R*) configuration respectively, 3-methyl-5-pentanolide (VI), and also 3-chloro-3-methylpentanoic acid (VII) (Table 2).

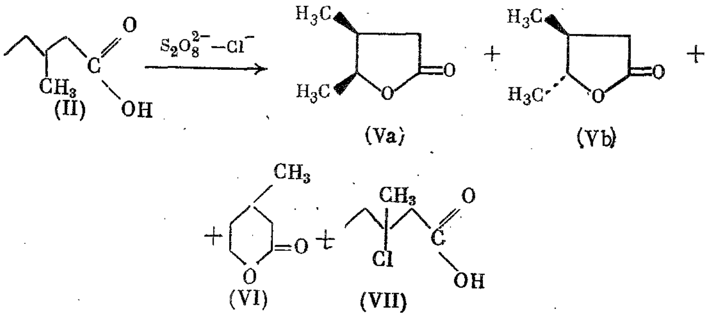


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TABLE 1. Oxidation of 2-Methylpentanoic Acid (I) in the $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl* Systems

Oxidizing system	Conversion of (I), %	Reaction products and yield, % on reacted substrate		
		(IIIa)	(IIIb)	(IV)
$Na_2S_2O_8$ – $CuCl_2$	40	42	42	11
$Na_2S_2O_8$ – NaCl	40	40	40	3

*85-90°C, 6 h, 50 mmole of (I), 50 mmole of $Na_2S_2O_8$, 50 mmole of $CuCl_2 \cdot 2H_2O$ or 100 mmole of NaCl, 100 ml of water.

TABLE 2. Oxidation of 3-Methylpentanoic Acid (II) in the $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl* Systems

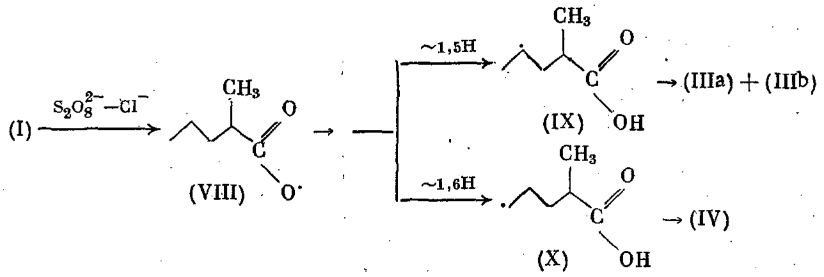
Oxidizing system	Conversion of (II), %	Reaction products and yields, % on reacted substrate			
		(Va)	(Vb)	(VI)	(VII)
$Na_2S_2O_8$ – $CuCl_2$	40	25	40	10	14
$Na_2S_2O_8$ – NaCl	35	33	33	6	14

*85-90°C, 6 h, 50 mmole of (II), 50 mmole of $Na_2S_2O_8$, 50 mmole of $CuCl_2 \cdot 2H_2O$, or 100 mmole of NaCl, 100 ml of water.

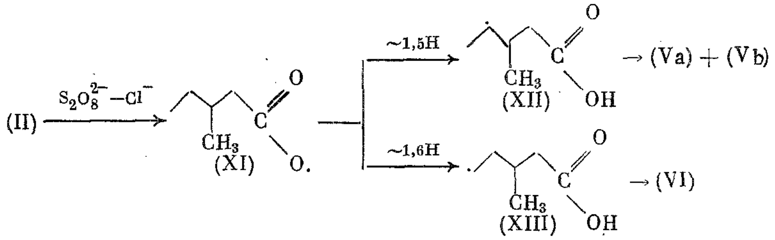
The results show that the acid (II), like 2-methylpentanoic acid (I) and pentanoic acid [1, 2], is converted regioselectively into the γ-lactones (VA) and (Vb). It should be noted particularly that, unlike oxidation in the presence of sodium chloride, during oxidation in the $Na_2S_2O_8$–$CuCl_2$ system the lactonization of (II) is diastereoselective, and the lactones (Va) and (Vb) are formed in a ratio of 1:1.6.

The compositions and ratios of the products from the OL of the acids (I) and (II) do not depend on the reaction time. As shown by a control experiment, the products retain their configurations under the reaction conditions.

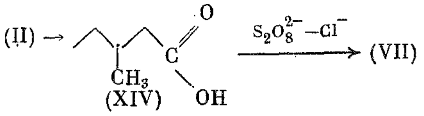
We suppose that the oxidation of substituted pentanoic acids (I) and (II) takes place according to the mechanism previously proposed for the OL of n-alkanoic acids [1, 2]. According to this mechanism, acyloxyl radicals (VIII) are formed during one-electron oxidation of 2-methylpentanoic acid (I) and rearrange as a result of 1,5- and 1,6-migration of a hydrogen atom into 4-carboxypent-2-yl (IX) and 4-carboxypent-1-yl (X) radicals. Oxidative cyclization of the radicals (IX) leads to the γ-lactones (IIIa, b), and the δ-lactone (IV) is formed from the radicals (X). The preference for 1,5-migration of the hydrogen atom over 1,6-migration is a normal rule for radical rearrangements [5].



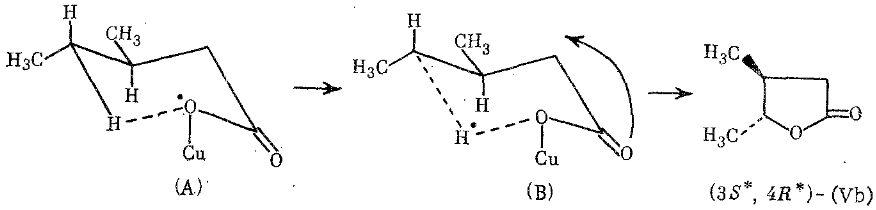
Similarly, the alkoxyl radicals (XI) are formed during the one-electron oxidation of 3-methylpentanoic acid (II). They undergo rearrangement with 1,5- and 1,6-migration of a hydrogen atom into 3-methyl-4-carboxypent-2-yl (XIII) and 3-methyl-4-carboxypent-1-yl (XIII)

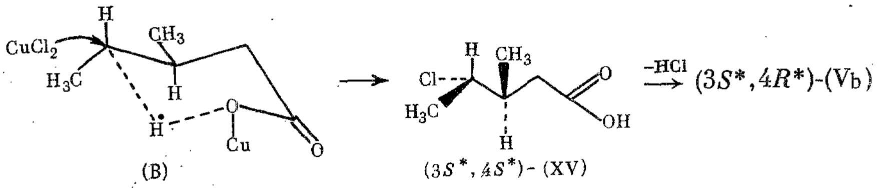


radicals. The oxidative cyclization of the radicals (XII) and (XIII) leads to the γ-lactones (Va, b) and the δ-lactone (VI) respectively. The 1-carboxy-2-methylbut-2-yl radicals (XIV) are generated as a result of abstraction of the mobile methine hydrogen atom from the C^3 atom of the acid (II) by the radicals present in the reaction mixture. The radicals (XIV) are oxidized by a mechanism with ligand transfer into 3-chloro-3-methylpentanoic acid (VII).



The observed diastereoselectivity of the OL of the acid (II) in the $Na_2S_2O_8$—$CuCl_2$ system can be regarded as a further argument in favor of the proposed reaction mechanism. The acyloxyl radicals (XI) generated during one-electron oxidation of the acid (II) are present both in the free state and combined into a complex with the copper ions (Cu^{2+} and/or Cu^{3+}) [6]. The conformational rigidity of the oxygen atom carrying the unshared electron, due to complex formation, secures the stereochemical nonuniformity of the diastereotopic hydrogen atoms at the C^4 atom in the 1,5-migration of the hydrogen atom. The most thermodynamically favorable six-membered transition state of this reaction, characterized by comparatively reduced destabilizing interactions between the substituents, can be represented by formula A. The copper ions which take part in complex formation must here prevent inversion of the indicated "prechair" conformation and promotes the display by the COOH group, after rearrangement, of a "buttressing" effect, similar to that observed during investigation of the stereochemistry of the oxidative chlorination of cyclohexane carboxylic acid in the $Na_2S_2O_8$—$CuCl_2$ system [7]. The simultaneous appearance of complex formation and the buttressing effect of the COOH group makes it possible for oxidative cyclization of the rearranged radical B to occur only "from the rear," i.e., from the side opposite the migrating hydrogen atom (the direction in which the C=O group moves during cyclization is indicated by the arrow) with the formation of (3S*, 4R*)-(Vb). If the stage of cyclization to the lactones is preceded by oxidation of B with ligand transfer, the product from such oxidation (which is also realized from the "rear" for the reasons considered above) is (2S*, 4S*)-4-chloro-3-methylpentanoic acid (XV). Cyclization of the latter by a mechanism of the S_{N2} type with inversion of the configuration at the C^4 atom must also lead to (3S*, 4R*)-(Vb).





The comparatively not very high diastereoselectivity in the OL of the acid (II) in the $Na_2S_2O_8$—$CuCl_2$ system [(Va):(Vb) ratio 1:1.6] is most likely explained by the insufficiently full bonding of the intermediate radicals, including acyloxyl radicals of the (XI) type, into complexes with the copper ions, and this leads to the presence in the reaction mixture of a significant amount of the uncomplexed radicals (XI), the H migration and OL processes of which are practically nonstereoselective. According to the proposed explanation, the OL of the acid (II) in the $Na_2S_2O_8$—NaCl system not containing metal ions capable of complex formation is fully nonstereoselective.

In the absence of any metal salts during the homolytic addition of ethanol to ethyl crotonate, initiated by di(tert-butyl) peroxide, a mixture of lactones (Va) and (Vb) was obtained in a ratio of 1.2:1, i.e., with a preponderance of the cis-lactone (Va) (see the experimental section).

Recently a significant effect from complex-forming metal salts on the electrophilicity and associated chemical characteristics was discovered [8] in alkoxyl radicals, which can be regarded as sufficiently close analogs of the acyloxyl radicals.

As shown by examination of molecular models, the methyl group at the C^2 atom in the alcyloxyl radicals (VIII), combined into a complex with copper ions, interacts with the C=O group but does not interact sterically with the CH_3 at the C^4 atom. The interaction of two CH_3 groups is observed in the complexes of the acyloxyl radicals (IX) with copper ions with the absence of interaction between the CH_3 at the C^3 atom and the C=O group, and this is consistent with the stereodifferentiation in the OL of the radicals (XI).

The assignment of the signals in the PMR spectra of the mixtures of diastereoisomeric lactones (Va, b) was made by the double resonance and INDOR techniques. Irradiation of the quintet at 4.05 ppm leads to the coalescence of the doublet at 1.33 ppm into a singlet. Irradiation of the quintet at 4.60 ppm leads to the coalescence of the doublet at 1.20 ppm into a singlet. During irradiation of the multiplets at 2.15 and 2.60 ppm the splitting of the quintet at 4.05 ppm disappears, and the quintet at 4.60 ppm coalesces into a quartet. The interrelationship between the signals at 1.33 and 4.05 ppm and also between the signals at 0.95 and 2.60 ppm was confirmed by the INDOR technique. From the obtained results with due regard to published data on the PMR spectra of the PMR spectra of the stereoisomeric butanolides [9, 10] it follows unambiguously that the signals at 1.07, 1.33, 2.15, and 4.05 ppm, correspond to the lactone (Va), and the signals at 0.95, 1.20, 2.60, and 4.60 ppm correspond to the lactones (Vb), i.e., the signals of the CH_3 groups in the cis isomer appear in the downfield region, while the signal of the methine proton of the CHO group appears in the upfield region from the trans isomer.

EXPERIMENTAL

The GLC analysis was performed on a LKhM-8MD chromatograph with a flame-ionization detector in a stream of nitrogen (stainless steel column, 3000 × 3 mm, 5% PEGS on Chromosorb P, 120-140 mesh, treated with dimethyldichlorosilane). The PMR spectra of solutions in deuterochloroform were measured on Bruker WM-250 (250 MHz) and Tesla BS-497 (60 MHz) spectrometers from TMS. The IR spectra were obtained in thin layers and in carbon tetrachloride solutions on a UR-20 instrument. The $Na_2S_2O_8$ of analytical grade, $CuCl_2 \cdot 2H_2O$ of pure grade, and sodium chloride of analytical grade were used without further purification. The 3-methylpentanoic acid (II) was purified by vacuum distillation; bp 101°C (14 mm Hg) (cf. [11]). The PMR spectrum of the acid (II) is given in Table 3.

2-Methylpentanoic Acid (I). Propylmalonic ester was synthesized with a yield of 75% by alkylation of malonic ester with 1-bromopropane according to [12]; bp 107-108°C (13 mm Hg) (cf. [12]). By alkylation of the last compound with methyl iodide [12] we obtained methylpropylmalonic ester with a yield of 70%; bp 120-122°C (13 mm Hg) (cf. [13]), which we saponified with the formation of methylpropylmalonic ester; yield 70%, mp 105°C (cf. [13]). By decarboxylation of the latter according to [12] we obtained compounds (I) with a yield of 75%; bp 100°C (14 mm Hg), n_D 1.4125 (cf. [14]). The spectral characteristics of the acid (I) are given in Table 3.

Oxidation of 2- and 3-Methylpentanoic Acids (I, II) in the $Na_2S_2O_8$—$CuCl_2$ and $Na_2S_2O_8$—NaCl Systems. To a mixture of 50 mmole of the acid (I) or (II) and 50 mmole of $CuCl_2 \cdot 2H_2O$ or 100 mmole of sodium chloride in 50 ml of water at 85-90°C we added dropwise over 1 h with effective stirring a solution of 50 mmole of NaS_2O_8 in 50 ml of water. The mixture was stirred for a further 5 h at 85-90°C, cooled, and extracted with 3 × 100 ml of ether. The extract was dried with magnesium sulfate and evaporated. The residue was analyzed by PMR spectroscopy and quantitative GLC. To isolate the products we treated the evaporated residue with a saturated solution of sodium bicarbonate (50 ml) and concentrated ammonia (20 ml) and extracted it with 3 × 50 ml of ether. The extract was dried with magnesium sulfate, evaporated, and distilled, giving the lactones (IIIa, b, IV) [bp 110-115°C (13 mm Hg)] from the oxidation of (I) and the lactones (Va, b, VI) [bp 111-117°C (13 mm Hg)] from the oxidation of (II). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with 3 × 50 ml of ether. The extract was dried with magnesium sulfate and evaporated,

TABLE 3. Spectral Characteristics of 2- and 3-Methylpentanoic Acids (I, II), 4-Butanolides (IIIa, b, Va, b), 5-Pentanolides (IV, VI), and 3-Chloro-3-methylpentanoic Acid (VII)

Compound	IR spectrum ν, cm^{-1}	PMR spectrum, δ, ppm
(I)	1710, 3100–3200	0,85 t (3H, CH_3CH_2), 1,10 d (3H, CH_3CH), 1,20–1,70 m (4H, CH_2CH_2), 2,35 m (1H, CHCO), 12,0 bs (1H, OH)
(II)	1710, 3100–3200	0,85 t (3H, CH_3CH_2), 0,95 d (3H, CH_3CH), 1,10–1,70 m (3H, CH_3CH_2CH), 2,15 m (2H, CH_2CO), 10,5 bs (1H, OH)
(IIIa)	1780	1,23 d (3H, $CH_3CHC{=}O$), 1,35 d (3H, CH_3CHO), 2,30–2,50 m (3H, $CH_2CHC{=}O$), 4,43 m (1H, CHO)
(IIIb)	1780	1,17 d (3H, $CH_3CHC{=}O$), 1,31 d (3H, CH_3CHO), 2,55–2,65 m (3H, $CH_2CHC{=}O$), 4,63 m (1H, CHO)
(IV)	1730	1,15 d (3H, $CH_3CHC{=}O$), 1,40–1,60 m (4H, CH_2CH_2CH), 2,65 m (1H, CH_3CH), 4,05 m (2H, CH_2O)
(Va)	1780	1,07 d (3H, CH_3CHCH_2), 1,33 d (3H, CH_3CHO), 2,15 m (3H, $CHCH_2C{=}O$), 4,05 m (1H, CHO)
(Vb)	1780	0,95 d (3H, CH_3CHCH_2), 1,20 d (3H, CH_3CHO), 2,60 m (3H, $CHCH_2C{=}O$), 4,60 m (1H, CHO)
(VI)	1730	0,93 d (3H, CH_3CHCH_2), 1,50 m (2H, CH_2CH_2O), 2,05 m (1H, CH_3CHCH_2), 2,35 m (2H, $CH_2C{=}O$), 4,30 m (2H, CH_2O)
(VII)	800, 1710, 3100–3200	0,82 t (3H, CH_3CH_2), 1,50 s (3H, CH_3CCl), 1,64 m (2H, CH_3CH_2CCl), 2,70 m (2H, $CH_2C{=}O$)

giving, either the acid (I) or a mixture of the acids (II) and (VII). The spectral characteristics of the lactones (III-VI) and the chloro acid (VII) are given in Table 3.

Configurational Stability of the Lactones (IIIa, b, Va, b). To 20 mmole of the mixture of lactones (IIIa, b) or (Va, b) in a ratio of 1:1, containing <5% of the lactone (IV) or (VI) as impurity, and 20 mmole of $CuCl_2 \cdot 2H_2O$ or 40 mmole of sodium chloride in 30 ml of water at 85-90°C we added a solution of 20 mmole of $Na_2S_2O_8$ in 20 ml of water. The mixture was heated at 85-90°C for 2 h and was then treated according to the general method of analysis. We obtained 19 mmole of a mixture of the lactones (IIIa, b) or (Va, b) in a ratio of 1:1.

Homolytic Addition of Ethanol to Ethyl Crotonate [15]. A mixture of 50 mmole of ethyl crotonate, 10 mmole of di(tert-butyl) peroxide, and 500 mmole of absolute ethanol was heated at 170°C for 8 h in a sealed tube. The mixture was cooled, the alcohol was distilled, and the residue was poured into 200 ml of iced water and extracted with 4 × 50 ml of ether. The extract was washed with saturated sodium bicarbonate solution, dried with magnesium sulfate, and evaporated. By fractional distillation we isolated 15 mmole (yield 30%) of a mixture of lactones (Va) and (Vb) in a ratio of 1.2:1; bp 111-113°C (13 mm Hg).

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CONCLUSIONS

1. The oxidative lactonization of 2- and 3-methylpentanoic acids in the sodium peroxydisulfate—copper chloride or sodium chloride systems takes place regioselectively at the C^4 atom with the formation of 2,4- and 3,4-dimethyl-4-butanolides.

2. The oxidative lactonization of 3-methylpentanoic acid in the $Na_2S_2O_8$—$CuCl_2$ system takes place diastereoselectively and leads to trans- and cis-3,4-dimethyl-4-butanolides in a ratio of 1.6:1. The diastereoselectivity of the reaction is explained by complex formation between the intermediate acyloxyl radicals and the copper ions.

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TELOMERIZATION OF 1,3-BUTADIENE BY CARBON TETRABROMIDE AND DIBROMODICHLOROMETHANE

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The telomerization of 1,3-butadiene with polybromo- and polybromochloromethanes with isolation of the individual telomers has not been achieved. The polymerization of butadiene in the presence of CBr_4, giving a mixture of oligomers $CBr_3(CH_2CH{=}CHCH_2)_nBr$ has been described [1] where n = 4-10. Attempts to telomerize butadiene by CBr_4 and $CHBr_3$ under the action of Cu ions [2] or $Ru(Ph_3P)_3Cl_2$ [3] did not lead to telomers.

We have achieved telomerization of butadiene with CBr_4 as well as with CBr_2Cl_2 with the isolation of the first two members of the series of telomer homologs. In the presence of azobis-isobutyronitrile (AIBN) at 80° the reaction proceeds according to the usual scheme

$$\begin{gathered}
\mathrm{CBr_2X_2} \rightarrow \mathrm{\dot{C}BrX_2}\\
\mathrm{\dot{C}BrX_2} + \mathrm{CH_2{=}CHCH{=}CH_2} \rightarrow \mathrm{CBrX_2CH_2CH{=}CH\dot{C}H_2}\\
\mathrm{A} + \mathrm{CBr_2X_2} \rightarrow \underset{(\mathrm{Ia,\ b})}{\mathrm{CBrX_2CH_2CH{=}CHCH_2Br}} + \mathrm{\dot{C}BrX_2}
\end{gathered} \qquad (\mathrm{A})$$

$$\begin{gathered}
\mathrm{A} + \mathrm{CH_2{=}CHCH{=}CH_2} \longrightarrow \left[\begin{array}{l}\rightarrow \mathrm{CBrX_2CH_2CH{=}CHCH_2CH_2CH{=}CH\dot{C}H_2} \rightarrow\\ \rightarrow \mathrm{CBrX_2CH_2CH{=}CHCH_2CH_2\dot{C}HCH{=}CH_2} \xrightarrow{+\mathrm{CBr_2X_2}}\end{array}\right.\\
\rightarrow \mathrm{CBrX_2CH_2CH{=}CHCH_2CH_2CH{=}CHCH_2Br} \quad (\mathrm{IIa,\ b})\\
\rightarrow \mathrm{CBrX_2CH_2CH{=}CHCH_2CH_2CHBrCH{=}CH_2} \quad (\mathrm{IIIa,\ b})\\
\mathrm{X} = \mathrm{Br}\ (\mathrm{a});\ \mathrm{Cl}\ (\mathrm{b})
\end{gathered}$$

It must be pointed out that only 1,4-addition is achieved in both cases in the first stage; on the other hand, the growing radical attaches itself to the second butadiene molecule less selectively in the 1,4 position (IIa, b) as well as in the 1,2-position (IIIa, b). In the case of CBr_4 the ratio of the isomers is (IIa):(IIIa) ∿ 80:20, while in the case of CBr_2Cl_2 the ratio is (IIb):(IIIb) ∿ 50:50. Telomers (Ia, b) with one monomer unit in the molecule have been isolated individually, while the telomers with two monomer units in the molecule have been obtained as a mixture of isomeric products of the 1,4- and 1,2-addition ((IIa) + (IIIa) and (IIb) + (IIIb) respectively).

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