(21) In the experiments with trivinylstannylsodium the combined yields of benzene and phenyltrivinylstannane were uniformly greater than 90% when *tert*-butyl alcohol was present in the reaction mixture. However, in the absence of the alcohol only 4% of benzene and 48% of phenyltrivinylstannane were observed, and tetravinylstannane and diphenyldivinylstannane were present in substantial amounts. This observation provides substantiation for the dissociation step (a) of Scheme I, followed by step (b) and steps (c) and (d).
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Three-Electron Oxidations. 13. Intramolecular Cooxidation of 2,7-Dihydroxyheptanoic Acid. Structure of the Transition State in the Chromium(VI) Oxidation of Alcohols[1,2]

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Abstract: The investigation of the chromic acid oxidation of a series of dihydroxy acids $HO(CH_2)_nCHOHCO_2H$ revealed that 2,7-dihydroxyheptanoic acid ($n = 5$) reacts entirely differently than other members of the series. It undergoes a very rapid cooxidation on both functional groups to yield carbon dioxide and the free radical $OCH(CH_2)_4\dot{C}HOH$ as primary products. The radical is subsequently oxidized to the dialdehyde 1,6-hexanedial. The reaction obeys a simple rate law $v = k[HCrO_4^-][C_7 \text{ acid}]$ over a 10^5 range in hydrogen ion concentrations. Depending on the reaction conditions, 6-hydroxyhexanal and 1,6-hexanediol can also be formed. The formation of the free-radical intermediate is interpreted in terms of a three-electron transfer within the chromium(VI)-dihydroxy acid complex. None of the two neighboring homologues, 2,6-dihydroxyhexanoic and 2,8-dihydroxyoctanoic acids, give any evidence of oxidation of the terminal alcoholic group. The requirement that the two reaction centers are separated by a chain of four carbon atoms leads to the following conclusions: (1) the carboxylate group forms a ligand to chromium; (2) in the reaction intermediate chromium(VI) has at least five oxygen ligands; (3) the transfer of hydrogen in the oxidation of the alcoholic function is intramolecular; and (4) in the oxidation step hydrogen cannot be transferred as a proton. The last two points should hold generally for chromium(VI) oxidations of alcohols. A general procedure for the synthesis of the dihydroxy acids (n = 2, 4, 5, 6) is reported.

Several years ago we reported[3] that chromic acid reacts with a mixture of oxalic acid and isopropyl alcohol by several orders of magnitude faster than it does with either of the two substrates. We have shown that this rapid reaction is a cooxidation process in which both substrates are oxidized simultaneously. Later we found additional examples of cooxidation reactions involving oxalic acid[4] and, more recently, α-hydroxy acids.[5] The rate-limiting step in all cooxidation reactions is the oxidative decomposition of a negatively charged termolecular intermediate complex. In this step chromium(VI) is reduced directly to chromium(III) by a synchronous three-electron transfer. While the kinetic data provided sufficient information about the composition and the charge of the activated complex, no definite conclusion could be derived about its detailed structure and geometry, about the coordination number of chromium(VI) in the intermediate, and about the nature of hydrogen transfer process.

We hoped that these questions could be answered if we succeeded in incorporating all functional groups into a single molecule and achieved an "intramolecular cooxidation". The structural requirements for a substrate capable of undergoing such an oxidation should provide considerable insight into the structure and configuration of the transition state. Further, since one component of the cooxidation reaction is the oxidation of an alcoholic hydroxyl group to a carbonyl group, the results and conclusions should be applicable to the important and much investigated chromium(VI) oxidation of alcohols.[6]

With this goal in mind we decided to investigate the chromic acid oxidation of a series of α,ω-dihydroxy acids of the general formula $HO(CH_2)_nCHOHCO_2H$.

Experimental Section

Materials. Glycolic acid (99+%, Gold Seal, Aldrich) and glyceric acid (Aldrich) were used without further purification. Perchloric acid solutions were prepared from 70% perchloric acid (Fisher). Chromium solutions were prepared from sodium dichromate (J. T. Baker, reagent). Lactic acid (Baker analyzed reagent, 0.90 g, 0.01 mol) was dissolved in water (20 mL) and then refluxed for 3 h with calcium carbonate (Fisher reagent, 2.0 g, 0.020 mol). The solution was filtered hot and water removed on a rotary evaporator. The powdered calcium salt (1.6 g) was crystallized from MeOH (25 mL). The dried calcium salt was dissolved in water (20 mL) and passed through a cation-exchange resin column (Dowex 50W-X8, H^+ form, 20–50 mesh, 15 g). The resulting solution was evaporated in vacuo.

Synthesis of α,ω-Dihydroxy Acids. The dihydroxy acids of the general formula $HO(CH_2)_nCHOHCO_2H$ (n = 2, 4, 5, 6) required for the study were prepared by a four-step synthesis summarized in Scheme I (cf. Results). A typical experimental procedure is given for 2,7-dihydroxyheptanoic acid:

$HO(CH_2)_5CN$. 5-Chloro-1-pentanol (Aldrich, 12.25 g 0.10 mol) was added in 10–15 min to a rapidly stirred suspension of powdered potassium cyanide (Fischer, reagent grade, 9.76 g, 9.15 mol) in dimethyl sulfoxide (Fischer, reagent grade, 50 mL) at 110 °C, kept at

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Table I. Yields and Physical Constants of Dihydroxy Acids $HO(CH_2)_nCHOHCO_2H$

n	% yield	Mp (bp (Torr)), °C
2	32	102 (3)[a]
4	54	84–86 dec
5	52	162–164 dec
6	56	162–163

[a] Lit.[11] bp 100–103 °C (3 Torr).

this temperature for 45 min, and then cooled. After dilution with water to 500 mL, the product was extracted with ether (3 × 10 mL) and the extract was washed with 6 N hydrochloric acid (25 mL) and water and dried over $MgSO_4$. Ether was removed and the crude syrupy liquid (10.3 g, 91%) was used as such in the next experiment.

$HO(CH_2)_4CHO$. 5-Cyano-1-pentanol (11.3 g, 0.10 mol) and semicarbazide hydrochloride (Aldrich, 11.1 g, 0.10 mol) were dissolved in aqueous ethanol (50% v/v, 60 mL) and hydrogenated for 5 h in a Parr hydrogenator at 50 psi over Raney Ni (Alfa Chemicals, 2.5 g). The product was filtered to remove the catalyst and the filtrate stirred with 2 N HCl (30 mL) at 60 °C for 3 h. The solvent was removed in vacuo and the thick gummy liquid (3.4 g, 29%) used as such in the next step.

$HO(CH_2)_5CHOHCN$. To a well-cooled solution of 6-hydroxyhexanal (1.13 g, 0.010 mol) and potassium cyanide (0.65 g, 0.010 mol) in aqueous dioxane (50% v/v, 25 mL), 6 N hydrochloric acid (5 mL) was added dropwise and the mixture was stirred at 0 °C for 30 min. The solvent was removed in vacuo and the residue continuously extracted with ether (total volume 250 mL) overnight. The extract was dried and the ether removed to obtain the desired 6-cyano-1,6-hexanediol as a semisolid product (0.415 g, 49%).

$HO(CH_2)_5CHOHCO_2H$. A solution of the above cyanohydrin (0.72 g, 0.0050 mol) in water (10 mL) and concentrated hydrochloric acid (10 mL) was heated under reflux for 2 h and cooled. The reaction mixture was evaporated to dryness, the residue dissolved in water (15 mL), refluxed with an excess of calcium carbonate (2.0 g) for 4 h, and filtered hot, and the filtrate concentrated in a rotary evaporator until the beginning of the crystallization of the calcium salt was observed. The solution was allowed to cool and the calcium salt collected. The product was dried in vacuo and the resulting dry powder recrystallized from methanol (15 mL). The purified, dried calcium salt was dissolved in water (15 mL) and passed through a cation-exchange resin column (Dowex 50W-X8, H^+ form, 20–50 mesh, 30 g). The resulting solution was evaporated to dryness in vacuo. The yield of the pure product was 0.45 g (52%) based on the crude cyanohydrin.

The yields and melting or boiling points of the final products are given in Table I.

Satisfactory elementary analyses for all acids were obtained. The free acids are unstable and undergo decomposition or lactonization (n = 2); they were therefore kept as calcium salts from which the free acids were obtained by passing a solution of the salt through a cation-exchange column.

1,6-Hexanedial (adipaldehyde) bis(2,4-hydrazone) was prepared by the oxidation of cyclohexene with osmium tetroxide[7] in 43% yield, mp 233–234 °C (lit.[7] 232–234 °C).

Product Analysis. Since the presence of oxygen greatly affects the composition of products, analyses were carried out both in the presence of air and under strictly deoxygenated conditions. A typical example of the latter procedure follows. 2,7-Dihydroxyheptanoic acid (0.405 g, 2.5 mmol) was dissolved in aqueous percholoric acid (1.18 M, 2.5 mL), diluted with water to 25 mL, and placed in a 50-mL flask attached to a vacuum line. Another flask on the vacuum system contained a solution of sodium dichromate (0.625 mL, 0.1 M). The two solutions were frozen in liquid nitrogen and the system was evacuated to ~0.01 mmHg; the solutions were allowed to thaw; and the process of freezing, evacuation, and thawing was repeated six times. After the completion of the cycle, the solutions were brought to room temperature and mixed thoroughly; the reduction of chromium(VI) occurred instantaneously. After 10 min the reacted solution was treated with an excess of a saturated solution of 2,4-dinitrophenylhydrazine in 2 N HCl (25 mL), allowed to react at room temperature for 4 h, and then continuously extracted with ether (total volume 500 mL). The aqueous layer was analyzed by HPLC (Waters Associates, Model 440, RI detector), μ-Bondapak C_{18} 4 mm i.d. × 30 cm reverse phase column, acetic acid–water (6:94 v/v). The chromatogram showed only two peaks, of which one corresponded to the unreacted dihydroxy acid and the other was identified as 1,6-hexanediol by comparison of the retention time with that of an authentic sample; the yield of the diol was determined by using a calibration curve. No diol was present in the ether extract.

The ether extract was dried with $MgSO_4$ and evaporated to dryness. The residue was analyzed by column chromatography on silica gel, using hexane–benzene (50:50 and 25:75 v/v) as eluent, and shown to contain only 1,6-hexanedial bis(2,4-dinitrophenylhydrazone) and 6-hydroxyhexanal 2,4-dinitrophenylhydrazone. The dinitrophenylhydrazones were identified by elemental analysis and by comparison of melting points and IR and NMR spectra with those of authentic samples.[8] The unreacted excess of 2,4-dinitrophenylhydrazine remained on the column and could be eluted with benzene.

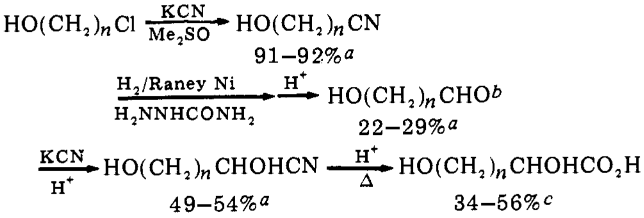
The yield of carbon dioxide was determined manometrically in a Warburg apparatus using fast green FCF dissolved in ethyl lactate as the manometric fluid.[3,9] Reaction solutions were saturated with carbon dioxide at room temperature and then equilibrated for 40–50 min at 25 °C and the solution was mixed with sodium dichromate solution placed in the other arm of the flask. The apparatus was calibrated by carbon dioxide generated from known amounts of sodium dichromate in excess of oxalic acid under the same conditions. No gas evolution was observed when a piece of filter paper moistened with a solution of sodium hydroxide was placed in the "well" of the Warburg flask, eliminating thus the possibility of the formation of carbon monoxide.

Kinetic Measurements. Rates of chromium(VI) oxidation of the dihydroxy acids were determined spectrophotometrically at 350 nm using a Cary 15 spectrophotometer equipped with thermostatic cell holders. Pseudo-first-order rate constants were calculated from slopes of log (absorbance) vs. time plots.

Results and Discussion

Synthesis of α,ω-Dihydroxy Acids. The dihydroxy acids of the general formula $HO(CH_2)_nCHOHCO_2H$ (n = 2, 4, 5, 6) were prepared by the general procedure shown in Scheme I.

Scheme I



$$HO(CH_2)_nCl \xrightarrow[Me_2SO]{KCN} \underset{91\text{–}92\%^a}{HO(CH_2)_nCN} \xrightarrow[H_2NNHCONH_2]{H_2/Raney\ Ni} \xrightarrow{H^+} \underset{22\text{–}29\%^a}{HO(CH_2)_nCHO^b} \xrightarrow[H^+]{KCN} \underset{49\text{–}54\%^a}{HO(CH_2)_nCHOHCN} \xrightarrow[\Delta]{H^+} \underset{34\text{–}56\%^c}{HO(CH_2)_nCHOHCO_2H}$$

[a] Yields of crude products. [b] Not isolated for n = 4; cyanohydrine prepared directly from semicarbazone. [c] Yields of purified product.

The commercially available chlorohydrins $HO(CH_2)_nCl$ were converted to the corresponding cyanohydrins by potassium cyanide in dimethyl sulfoxide using the procedure of Friedman and Shechter;[8] although the original procedure was developed for simple halides, it gave excellent yields when applied to the hydroxy halides. The resulting cyanohydrins were reduced to hydroxy aldehydes by hydrogenation over Raney Ni in the presence of semicarbazide followed by subsequent acid hydrolysis of the resulting semicarbazones; the yields were slightly lower than those reported for unsubstituted nitriles.[10] 3-Hydroxypropionaldehyde (n = 2) was prepared by acid-catalyzed hydration of acrolein[11] (yield 42%). The hydroxy aldehydes were converted to ω-hydroxy-α-cyanohydrins by treatment with potassium cyanide and acid using Gaudry's procedure for glyconitrile;[12] although the yields were lower than for glyconitrile, they were quite satisfactory. The desired dihydroxy acids were obtained by acid hydrolysis of the hydroxy cyanohydrins.[11] The intermediate cyanides and cyanohydrins were identified by IR and TLC and used without purification in subsequent steps. The dihydroxy acids were purified through their calcium salts, from which the free acids were regenerated using a cation-exchange resin in the acid form.

Table II. Chromic Acid Oxidation of Dihydroxy Acids and Related Compounds[a]

Substrate	10^6k_{exptl}, s^{-1}
$HOCH_2CHOHCO_2H$	2.33
$HO(CH_2)_2CHOHCO_2H$	1.48
$HO(CH_2)_4CHOHCO_2H$	1.45
$HO(CH_2)_5CHOHCO_2H$	31 400
$HO(CH_2)_6CHOHCO_2H$	5.04
$HOCH_2CO_2H$	4.10
$CH_3CHOHCO_2H$	2.75
$CH_3CH_2CH_2CH_2OH$	0.14

[a] Substrate 0.0058 M, perchloric acid 0.0118 M, chromium(VI) 5×10^{-4} M; 25 °C.

Table III. Chromic Acid Oxidation of $HO(CH_2)_5CHOHCO_2H$[a]

Substrate, M	10^2k_{exptl}, s^{-1}	k, M^{-1} s^{-1}
0.0029	1.52	5.24
0.0058	3.14	5.41
0.0076	4.10	5.39
0.0058[b]	3.22	5.55
0.0058[c]	3.17	5.47
0.0058[d]	3.19	5.50
0.0058[e]	3.15	5.43

[a] Chromium(VI) 5×10^{-4} M, perchloric acid 0.0118 M; temperature 25 °C. [b] 0.05 M acrylamide. [c] 0.05 M acrylonitrile. [d] 0.05 M $HgCl_2$. [e] Degassed.

Table IV. Acidity Dependence of Chromic Acid Oxidation of $HO(CH_2)_5CHOHCO_2H$[a]

H^+, M	10^2k_{exptl}, s^{-1}
10^{-5} [b]	2.82
10^{-4} [c]	2.85
10^{-3} [d]	2.90
0.003[d]	3.04
0.01[d]	3.17
0.03[d]	3.36
0.1[d]	3.49
0.3[d]	3.59
1.0[d]	3.67

[a] Substrate 0.0058 M, chromium (VI) 5×10^{-4} M; 25 °C. [b] Buffer, pH 5.0 (0.2 M NaOAc, 1.2 M HOAc). [c] Buffer, pH 4.0 (0.85 M NaOAc, 0.47 M HOAc). [d] $HClO_4$.

Rate Studies. Table II gives the experimental rate constants for the series of dihydroxy acids $HO(CH_2)_nCHOHCO_2H$ for $n = 1, 2, 4, 5$, and 6. Also included in the table are two monohydroxy acids, glycolic acid and lactic acid, and 1-butanol. With the exception of the C_7 acid ($n = 5$), all dihydroxy and monohydroxy acids show comparable oxidation rates. Since the rates are by more than an order of magnitude higher than for 1-butanol, this finding suggests that all dihydroxy acids undergo oxidation on the α-hydroxycarboxyl end of the molecule. 2,7-Dihydroxyheptanoic acid (the C_7 acid, $n = 5$) exhibits a strikingly different behavior. It reacts 2×10^4 times faster than its nearest lower homologue, 6×10^3 faster than the higher homologue, and more than 2×10^5 times faster than 1-butanol. This unusually high reactivity is strongly indicative of a participation of all three functional groups in the rate-limiting step of the oxidation process. The oxidation of this substrate was therefore investigated in detail.

The reaction is first-order in chromium(VI) as demonstrated by excellent pseudo-first-order plots obtained in all kinetic measurements. As the results in Table III show, the oxidation of the C_7 acid is also first order in the substrate and the oxidation rate is not significantly influenced by the presence of acrylonitrile, acrylamide, mercuric chloride, or by deoxygenation. Table IV shows that the oxidation rate is independent of the acidity of the solution in a very wide range from pH 5 up to a 1.0 M solution of perchloric acid. This acidity independence is rather unusual and stands in sharp contrast to the first-order dependence of the oxidation of glycolic acid[13] and to the first- and second-order acidity dependence of alcohols.[14,15]

Reaction Products. The results of the product studies are summarized in Table V. In the absence of air, 2,7-dihydroxyheptanoic acid yields three products: 1,6-hexanedial, 6-hydroxyhexanal, and 1,6-hexanediol. The yields refer to available oxygen (1.5 per chromium(VI)) (one oxygen atom is required per molecule of hydroxyaldehyde, two per dialdehyde, none per diol). The last two columns give the total yield of products in millimoles and in percent of available oxygen. When the reaction is carried out in the absence of air but in the presence of mercuric chloride, only the dialdehyde is formed. The reaction is accompanied by the precipitation of 0.5 mol of mercurous chloride, Hg_2Cl_2, per 1 mol of chromium(VI). When the reaction was carried out in the presence of either acrylonitrile or acrylamide, extensive polymer formation oc-

Table V. Products of Chromic Acid Oxidation of $HO(CH_2)_nCHOHCOOH$[a]

		$OHC(CH_2)_{n-1}CHO$		$HO(CH_2)_nCHO$		$HO(CH_2)_{n+1}OH$	Total yield	
n	Conditions	mmol	%	mmol	%	mmol	mmol	%
5	Degassed	2.98	79.5	1.01	13.5	0.81	4.80	93
5	Degassed	3.13	83.5	0.95	12.7	0.79	4.82	96
5	Degassed	3.09	82.4	1.06	14.1	0.79	4.84	97
5	In air	4.56	122	None		None	4.56	122
5	In air	4.26	114	None		None	4.26	114
5	In air	4.48	120	None		None	4.48	120
5	In 0.2 M acrylamide[b]	None		None		None		
5	In 0.2 M acrylonitrile[b]	None		None		None		
5	In 0.2 M $HgCl_2$	4.80	96	None		None	4.80	96[c]
5	In 0.2 M $HgCl_2$	4.65	93				4.65	93[d]
4	Degassed	None		7.62	101	2.44	9.06	101
4	Degassed	None		6.94	88	3.30	10.24	88
4	In air	None		7.30	97	2.52	9.82	97
4	In 0.2 M acrylamide[b]	None		None			None	
6	Degassed	None		7.10	94.6	2.00	9.10	94.6
6	In air	None		7.30	97.3	2.16	9.46	97.3
6	In air	None		7.42	98.9	2.19	9.61	98.9
6	In 0.2 M acrylamide[b]	None		None		None	None	

[a] Substrate 0.1 M, perchloric acid 0.118 M, chromium(VI) 5.0 mmol. [b] Only polymeric material was obtained. [c] 0.1142 g (2.42 mmol) of Hg_2Cl_2 precipitate formed. [d] 0.1038 g (2.20 mmol) of Hg_2Cl_2 precipitate formed.

Table VI. Yields of Carbon Dioxide in the Chromic Acid Oxidation of $HO(CH_2)_nCHOHCO_2H$[a]

n	Condition	CO_2, mmol	CO_2/Cr(VI)
5		3.50	1.11
		3.22	1.02
5	Degassed	3.44	1.09
5	0.2 M acrylamide	3.34	1.06
5	0.2 M acrylonitrile	3.54	1.12
5	0.2 M $HgCl_2$	3.42	1.08
4		6.35	2.01
		6.48	2.05
4	Degassed	6.38	2.02
4	0.2 M acrylamide	6.29	1.99
6		6.13	1.94
		6.38	2.02
6	Degassed	6.38	2.02
6	0.2 M acrylamide	6.35	2.01

[a] Substrate 0.0058 M, perchloric acid 0.0118 M, chromium(VI) 3.16 mmol; 25 °C.

curred but none of the normally observed products could be isolated. In the presence of air, only the dialdehyde was formed, and its yield was actually higher (almost 1 mol of dialdehyde/mol of chromium(VI)) than could be accounted for by the available amount of chromium(VI), indicating that oxygen dissolved in the solution participated in the oxidation process.

2,5-Dihydroxyhexanoic ($n = 4$) and 2,7-dihydroxyoctanoic ($n = 6$) acids show very different behavior. In both cases the hydroxy aldehydes constitute the main product together with a sizable amount of the diol. In neither case could we detect the formation of any dialdehyde. The presence of oxygen does not appear to have any effect on the composition of the reaction products.

Table VI shows the yields of carbon dioxide obtained in the oxidation of the C_7, C_6, and C_8 acids. In contrast to its next lower and higher homologues, the C_7 acid gives on oxidation only 1 mol of carbon dioxide/mol of chromium(VI). The formation of carbon dioxide is unaffected by the presence of acrylamide, suggesting that carbon dioxide is formed directly and not through a free-radical intermediate. The yield of carbon dioxide is also unaffected by degassing the sample.

Mechanisms. The oxidation of the 2,7-dihydroxyheptanoic acid is first order in monochromate ion and in the substrate; the activated complex of the reaction thus is composed of one molecule of the acid, contains one chromium atom, and carries one negative charge.

$$\frac{-d[Cr^{VI}]}{dt} = k[C_7\ \text{acid}][HCrO_4^-] \tag{1}$$

Both the very high reactivity of the 2,7-dihydroxyheptanoic acid and the composition of the reaction products indicate that we have succeeded in our search for a substrate which would undergo a cooxidation reaction on two separated sites within the same molecule.

It is significant that the reaction has such a simple rate law and that no evidence for the existence of another kinetic term has been found in spite of the fact that the acidity of the reaction medium was varied by five orders of magnitude. This is quite exceptional: most chromic acid oxidations have rate laws with at least two, but very frequently with many more terms resulting from the fact that there are several transition states, differing in composition but similar in energy, through which the reduction of chromium(VI) can proceed. The existence of only a single term for the oxidation of the C_7 acid provides evidence that one particular transition state (and mechanism) offers unique advantages which are absent in all other potential reaction routes.

Since the change in reaction conditions affects the reaction products but not the oxidation rate, the rate-limiting step must be the same and must consist of the oxidative decomposition of the negatively charged complex of chromium(VI) with the C_7 acid. The most likely mechanism consists of the reversible formation of the complex and of its decomposition to oxidation products in the rate-limiting step:

$$HO(CH_2)_5CHOHCO_2H + HCrO_4^- \rightleftharpoons HO(CH_2)_5CHOHCO_2H \cdot HCrO_4^- \tag{2}$$

$$HO(CH_2)_5CHOHCO_2H \cdot HCrO_4^- \xrightarrow[\text{limiting}]{\text{rate}} OCH(CH_2)_4\dot{C}HOH + CO_2 + Cr^{III} \tag{3}$$

Reaction 3 is consistent with the observation that the presence of free-radical scavengers like acrylonitrile or acrylamide in the oxidation of the C_7 acid does not affect the yield of carbon dioxide but completely suppresses the formation of the dialdehyde. The oxidation step in reaction 3 is shown as a three-electron cooxidation process in which the terminal hydroxy group undergoes a two-electron oxidation to an aldehydic function while at the same time a one-electron oxidation takes place on the other end of the molecule. The oxidation of the terminal alcoholic function involves the breaking of a carbon-hydrogen bond, while the oxidation of the α-hydroxy acid group results in carbon-carbon bond cleavage. This interpretation is consistent with the most generally accepted conclusion that the chromium(VI) oxidation of alcohols to aldehydes or ketones is a two-electron oxidation process,[6] with the known higher reactivity of α-hydroxy acids toward one-electron oxidants,[17] and with the results obtained in our earlier study of the cooxidation of isopropyl alcohol and glycolic acid in which we demonstrated that the acid, but not the alcohol, is oxidized to a free-radical intermediate.[5]

The very high reaction rate and the uniqueness of the products formed in the oxidation of the C_7 acid provides very strong support for the above interpretation. The direct reduction of chromium(VI) to chromium(III) in a single step avoiding thus the formation of a very unstable and therefore high energy intermediate chromium(IV) species makes this interpretation particularly attractive and provides an excellent rationalization for the unique reactivity of this particular substrate.

It must, however, be admitted that at this time we cannot completely rule out an alternative mechanism in which the terminal hydroxyl group would be oxidized first, followed by a rapid decomposition of the resulting chromium(IV) complex with the carboxyl and α-hydroxyl groups.

$$HO(CH_2)_5CHOHCO_2H \cdot HCrO_4 \xrightarrow[\text{limiting}]{\text{rate}} OCH(CH_2)_4CHOHCO_2H \cdot Cr^{IV} \tag{4}$$

$$OCH(CH_2)_4CHOHCO_2H \cdot Cr^{IV} \rightarrow OCH(CH_2)_4CHOH + CO_2 + Cr^{III} \tag{5}$$

This alternative has to be considered since we have shown that oxalic acid[18,19] and hydroxy acids,[20] which can participate in rapid cooxidation reaction with some substrates, notably alcohols, can also act as effective catalysts in the oxidations of other substrates, e.g., iodide[18] or tris(1,10-phenanthroline)-iron(II).[19] However, the decomposition of the chromium(IV) complex (reaction 5) would have to be extremely fast, since we never obtained any evidence that it could oxidize any other molecule than the one with which it is already complexed.[4]

The subsequent reaction of the free radical found in reaction 3 depends on the reaction conditions. The simplest and most revealing result was obtained in the oxidation of the substrate in the presence of mercuric chloride. Mercuric chloride is known to react with free radicals with the formation of the insoluble mercurous chloride.

$$\mathrm{R\cdot + HgCl_2 \rightarrow RCl + \tfrac{1}{2}Hg_2Cl_2} \quad (6)$$

In the presence of mercuric chloride the oxidation of the C_7 acid ($n = 5$) yields 1 mol of the dialdehyde, 1 mol of carbon dioxide, and 0.5 mol of mercurous chloride for every mole of chromium(VI) reduced.

$$\mathrm{HO(CH_2)_5CHOHCO_2H + Cr^{VI} + HgCl_2 \rightarrow OCH(CH_2)_4CHO + CO_2 + \tfrac{1}{2}Hg_2Cl_2 + Cr^{III}} \quad (7)$$

This result is consistent with the reaction sequence shown in Scheme II, where reaction 8 is the sum of reactions 2 and 3.

Scheme II

$$\mathrm{HO(CH_2)_5CHOHCO_2H + Cr^{VI} \rightarrow OCH(CH_2)_4\dot{C}HOH + CO_2 + Cr^{III}} \quad (8)$$

$$\mathrm{OCH(CH_2)_4\dot{C}HOH + HgCl_2 \rightarrow OCH(CH_2)_4CClHOH + \tfrac{1}{2}Hg_2Cl_2} \quad (9)$$

$$\mathrm{OCH(CH_2)_4CClHOH \rightarrow OCH(CH_2)_4CHO + HCl} \quad (10)$$

The free radical formed in the rate-limiting step 8 reacts with mercuric chloride to produce mercurous chloride and an α-chlorohydrin which by loss of hydrogen chloride gives the dialdehyde.

If the oxidation of the C_7 acid is carried out in the presence of air (without degassing), only the dialdehyde could be isolated; its yield was substantially higher than the theoretical yield based on chromium(VI); it is therefore obvious that oxygen participates in the oxidation. A possible reaction scheme is given in Scheme III. This sequence would lead to approximately the right amount of dialdehyde. However, it suggests the formation of hydrogen peroxide which we were unable to detect.

Scheme III

$$\mathrm{HO(CH_2)_5CHOHCO_2H + Cr^{VI} \rightarrow OCH(CH_2)_4\dot{C}HOH + CO_2 + Cr^{III}} \quad (8)$$

$$\mathrm{OCH(CH_2)_4\dot{C}HOH + O_2 \rightarrow OCH(CH_2)_4CHO + \cdot OOH} \quad (11)$$

$$\mathrm{OCH(CH_2)_4\dot{C}HOH + \cdot OOH \rightarrow OHC(CH_2)_4CHO + H_2O_2} \quad (12)$$

If the reaction is carried out in the absence of air, the formation of two additional products, 6-hydroxyhexanol and 1,6-hexanediol, is observed. In a formal sense the diol is not an oxidation product but would result from the decarboxylation of the dihydroxy acid. We have checked for the possibility of a decarboxylation reaction taking place under the reaction conditions but failed to find any evidence for it. We therefore conclude that the diol is formed in the course of the oxidation reaction, most likely by disproportionation of the free radical $\mathrm{HO(CH_2)_5\dot{C}HOH}$.

$$\mathrm{2HO(CH_2)_5\dot{C}HOH \rightarrow HO(CH_2)_5CHO + HO(CH_2)_5CH_2OH} \quad (13)$$

The radical could be formed from the dihydroxy acid by one-electron oxidation

$$\mathrm{HO(CH_2)_5CHOHCO_2H \xrightarrow{-H\cdot} HO(CH_2)_5\dot{C}HOH + CO_2} \quad (14)$$

where the oxidant could either be a radical formed in reaction 8 or chromium(IV). The latter interpretation is more probable since the former would predict much higher yields of 6-hydroxyhexanal than are actually formed. The overall reaction sequence could then be summarized as shown in Scheme IV, of which the first two reactions would have to occur four times and reaction 16 and 17 twice for each reaction 18.

Scheme IV

$$\mathrm{HO(CH_2)_5CHOHCO_2H + Cr^{VI} \rightarrow OCH(CH_2)_4\dot{C}HOH + CO_2 + Cr^{III}} \quad (8)$$

$$\mathrm{OCH(CH_2)_4\dot{C}HOH + Cr^{VI} \rightarrow OCH(CH_2)_4CHO + Cr^{V}} \quad (15)$$

$$\mathrm{2Cr^{V} \rightarrow Cr^{VI} + Cr^{IV}} \quad (16)$$

$$\mathrm{HO(CH_2)_5CHOHCO_2H + Cr^{IV} \rightarrow HO(CH_2)_5\dot{C}HOH + CO_2 + Cr^{III}} \quad (17)$$

$$\mathrm{2HO(CH_2)_5\dot{C}HOH \rightarrow HO(CH_2)_5CHO + HO(CH_2)_5CH_2OH} \quad (18)$$

The overall stoichiometry would then be

$$\mathrm{6HO(CH_2)_5CHOHCO_2H + 6Cr^{VI} \rightarrow 4OCH(CH_2)_4CHO + HO(CH_2)_5CHO + HO(CH_2)_5CH_2OH + 6CO_2 + 4Cr^{III}} \quad (19)$$

which is in approximate agreement with the observed result. However, we do not find this mechanism completely satisfactory. First, if this mechanism were correct, then the trapping of the free radical formed in reaction, e.g., with mercuric chloride, should lead to a 33% reduction in the observed rate of disappearance of chromium(VI); however, no reduction in the rate was observed. Second, it is probably unrealistic to propose that one type of radicals would react with chromium(VI) while the other would undergo bimolecular disproportionation, although one could possibly make a case for a considerably different reactivity of the two radicals of which the first might exist predominantly as a cyclic hemiacetal. We would therefore prefer considering reactions 15 to 18 only as examples of the types of processes likely to take place after the rate-limiting step rather than to propose Scheme IV as an exact reaction mechanism.

The mechanism for the oxidation for the lower and higher homologues, the C_6 and C_8 acids, is quite different as is obvious not only from the rates but also from the doubling of the yield of carbon dioxide and particularly from the complete absence of a dialdehydic product. Thus, no oxidation on the terminal hydroxyl group takes place. The only products formed are the corresponding hydroxy aldehydes and diols. The reactions could be interpreted by the sequence shown in Scheme V, in which the hydroxy acids undergo only one-electron oxidations. This assumption is made to explain the observation that in the presence of acrylamide or acrylonitrile we were unable to recover any monomeric aldehyde and obtained only polymeric products and carbon dioxide.

Scheme V

$$\mathrm{HO(CH_2)_{\mathit{n}}CHOHCO_2H + Cr^{IV} \rightarrow HO(CH_2)_{\mathit{n}}\dot{C}HOH + CO_2 + Cr^{V}} \quad (20)$$

$$\mathrm{HO(CH_2)_4\dot{C}HOH + Cr^{VI} \rightarrow HO(CH_2)_{\mathit{n}}CHO + Cr^{V}} \quad (21)$$

$$\mathrm{2Cr^{V} \rightarrow Cr^{V} + Cr^{IV}} \quad (16)$$

$$\mathrm{HO(CH_2)_{\mathit{n}}CHOHCO_2H + Cr^{IV} \rightarrow HO(CH_2)_{\mathit{n}}\dot{C}HOH + CO_2 + Cr^{III}} \quad (22)$$

$$\mathrm{2HO(CH_2)_{\mathit{n}}\dot{C}HOH \rightarrow HO(CH_2)_{\mathit{n}}CHO + HO(CH_2)_{\mathit{n}+1}OH} \quad (23)$$

$$n = 4, 6$$

It is interesting to note that the dihydroxy acids examined in this study react differently than glycolic acid investigated in an earlier study.[13] While glycolic acid was oxidized predominantly on the hydroxyl group to glyoxalic acid, we found no evidence for the formation of keto acids in the oxidation of dyhydroxy acids.

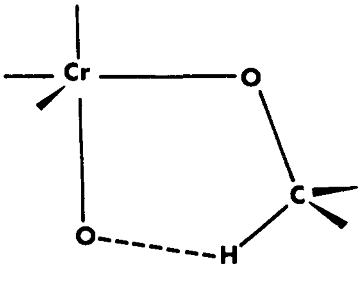
Structure of the Reactive Intermediate and of the Transition State. The kinetic results obtained in this study, in the cooxidation of an alcohol with glycolic acid,[5b] and in the related cooxidation of alcohols and oxalic acid[3,4] show that the rate-limiting step of the cooxidation reaction is the oxidative decomposition of a negatively charged complex formed from chromic acid, the alcohol, and the organic acid. Until now there was, however, insufficient information to allow drawing more definite conclusions concerning the actual structure of the termolecular complex and about the geometry of the transition state.

It is well established that the oxidation of monohydric alcohols by chromium(VI) proceeds via a chromate ester intermediate[14,21] and there is considerable evidence to suggest that α-glycols react preferably by way of a cyclic ester.[22] It is therefore reasonable to assume that a cooxidation reaction in which two hydroxyl groups are oxidized should also proceed through a chromate ester intermediate in which both reacting alcoholic functions have formed C-O-Cr ester bonds. This should be true regardless of whether the two hydroxyl groups are parts of two different molecules (e.g., isopropyl alcohol and glycolic acid) or of a single molecule (the C_7 dihydroxy acid).

What is much less clear is the role of the carboxyl group and its position in the molecule relative to the chromium atom. Since the reactive complex is negatively charged, the carboxyl group could be present as the carboxylate anion. The high reactivity of the complex could be due in part to the negative charge carried by this group and by its facile oxidation to carbon dioxide or to a $\cdot CO_2^-$ radical. If this were the case the complex could maintain the tetrahedral arrangement normally assumed for chromium(VI) compounds. On the other hand, the carboxylate group could be directly bound to the central chromium atom. This would correspond to the formation of a mixed anhydride of a carboxylic acid and chromic acid and would require the expansion of the coordination number of chromium to 5. Both alternatives were considered in previous papers, but no firm conclusions could be drawn.[3,5b]

Another uncertainty concerns the α-hydrogen atom removed from the alcoholic function during the oxidation. It could be transferred either intermolecularly, e.g., as a proton to a solvent molecule, or intramolecularly to one of the oxygens ligands of chromium. Both intra- and intermolecular transfer have been proposed and widely discussed for the closely related chromic acid oxidation of alcohols.[6]

Intramolecular hydrogen transfer must take place through a five-membered cyclic transition state and will be most efficient if the participating atoms can assume a planar configuration (**1**). Assuming a 90° O-Cr-O bond angle, the distance between hydrogen and oxygen would be ~1.6 Å, which is considerably less than the sum of the van der Waals radii (2.6 Å) and not much more than one would expect it to be in the transition state. A 109.5° and 120° O-Cr-O angle would result in a hydrogen-oxygen distance of ~2.2 and 2.5 Å, respectively.



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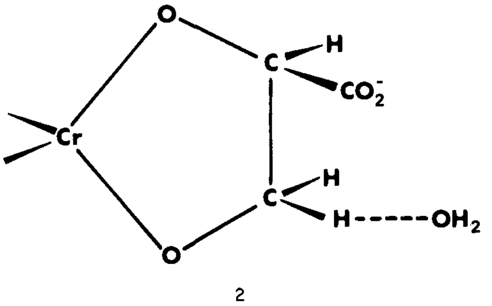
Combining these possibilities leads to four different situations which have distinctly different consequences for the required or preferred distance between the two reaction centers.

The simplest case is a mechanism in which the activated complex contains a free carboxylate group and where the hydrogen atom is transferred to the solvent. In this case the transition state would be monocyclic (**2**) and one can therefore safely assume that the highest reactivity should be observed for glyceric acid (n = 1).



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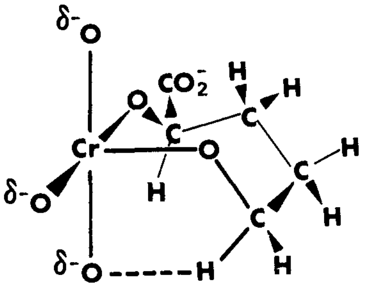
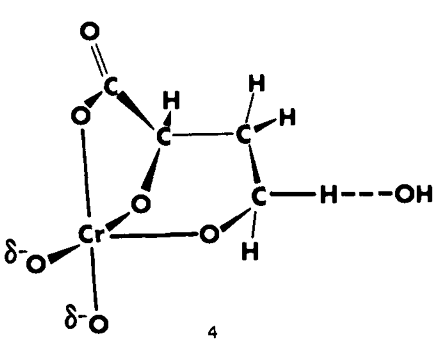
A mechanism with a free carboxylate group but an intramolecular hydrogen transfer requires a bicyclic transition state (**3**) and could be accommodated without excessive strain if the two hydroxyl groups were separated by two or three methylene groups (n = 2 or 3).



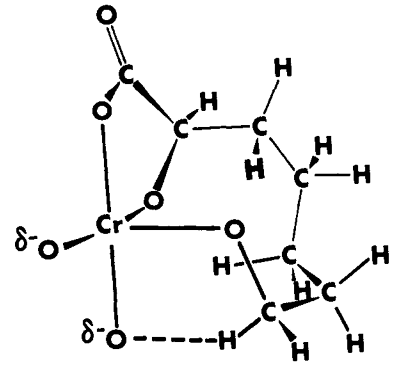
3

A transition state with a carboxylate oxygen-chromium bond and intermolecular hydrogen transfer would also be bicyclic (**4**). This transition state could be easily attained by $HO(CH_2)_2CHOHCO_2H$ provided that the chromium atom is either square pyramidal, octahedral, or trigonal-bipyramidal with two ligands in the basal position.[23]



4

Only a mechanism with a tricyclic transition state which requires both the formation of three Cr-O-C bonds *and* an intramolecular hydrogen transfer requires the large separation of the two functional groups found in this study. Structure **5** shows a square pyramidal chromium atom; octohedral chromium would have the same geometry. A shorter carbon chain makes it impossible to form a planar transition state required



5

for intramolecular hydrogen transfer without introducing severe distortions of bond angles.

Inspection of Dreiding models shows that the tricyclic transition state could be equally well reached with a trigonal-bipyramidal structure with the carboxyl group in the apical and two hydroxyl oxygens in basal positions. The actual geometry could obviously be in between that of a square pyramid and a trigonal bipyramid; such an intermediate geometry is present in the chromium(V) complex with 2-hydroxy-2-methylbutyric acid.[24] On the other hand, a recent study of picolinic acid catalysis of chromium(VI) oxidations[25] led us to conclude that the strong steric hindrance to catalytic activity resulting from the presence of substituents in the 6 positions can be understood only if geometry of the transition state is square pyramidal or octahedral, but not if it were trigonal-bipyramidal. It is in the light of latter result that we prefer the square pyramidal representation for the transition state (**5**).

Since our finding that only the C_7 dihydroxy acid is capable of undergoing intramolecular cooxidation is consistent with only the last of the four hypothetical structures of the transition state, the results demonstrate the following.

1. The Carboxylate Group forms a CO–O–Cr Bond to Chromium. This conclusion applies not only to the tricyclic transition state but also to its precursor, the bicyclic chromium(VI)-substrate complex. It is likely that this holds not only for the reactive intermediate of this reaction but is generally valid for chromium(VI) oxidations of α-hydroxy acids.

2. Chromium(VI) Can Easily Coordinate with More Than Four Oxygen Ligands. This conclusion will force a revision of the widely held assumption that chromium(VI) and chromium(V) in aqueous solutions form preferentially tetracoordinated compounds, unlike chromium(IV) and chromium(III) which normally are surrounded by six ligands. This assumption was used to explain the slow rate of exchange between the two higher and two lower valance states of chromium.[26]

3. Hydrogen is Transferred Intramolecularly from the C–H Bond of the Hydroxyl Carbon to an Oxygen Ligand of Chromium. The results of the present study provide the most convincing evidence of the intramolecular nature of the hydrogen transfer available thus far. As the required configuration for intramolecular transfer in this case is much harder to attain than in the oxidation of a simple alcohol, one can safely conclude that intramolecular hydrogen transfer is required in the chromium(VI) oxidation of alcohols in general.

4. Hydrogen is Transferred as an Atom or Hydride Anion but Not as a Proton. It makes generally little sense to argue the direction of the flow of electrons in a cyclic mechanism. However, in this case we are in an exceptionally favorable position to do so. The fact that the reaction can take place only by a cyclic intramolecular mechanism is fully consistent with either hydride ion or hydrogen atom transfer, but not with a proton-transfer mechanism.

To reconcile proton transfer with the high preference (at least 10^6-fold, based on rate differences and on the absence of detectable cooxidation products in the C_6-acid oxidation) one would have to assume that the Cr–O oxygen is a better proton acceptor than the solvent (water) by some 6 to 12 orders of magnitude (for a Brønsted β between 1.0 and 0.5). While the basicity of $RCO_2Cr(OR)_2O_2^-$ is not known, it is reasonable to assume that it will be within an order of magnitude of $HCrO_4^-$. Comparison of acid dissociation constants[27] of H_2CrO_4, 1.50, and H_3O^+, 55, suggests that the Cr–O oxygen can be no more than 10^2 times more basic than H_2O. The inability of lower dihydroxy acid to react through transition state **4** must therefore mean that water cannot serve as acceptor for the hydrogen atom and hence that the hydrogen cannot be transferred as a proton.

The conclusion that, in a chromic acid oxidation of an alcoholic function, the transfer of the hydrogen occurs either by an hydride ion or hydrogen chain, but not by a proton transfer mechanism, must hold for chromium(VI) oxidations of alcohols generally.

Finally, the fact that intramolecular cooxidation of two separated functional groups does take place at all and, moreover, with such extraordinary ease, provides further support for the three-electron oxidation mechanism on the basis of which this result was predicted and the experimental test designed.

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