Chromic Acid Oxidation of Isopropyl Alcohol. The Oxidation Steps[1a]

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Abstract: The oxidation steps in the reaction of chromic acid with its isopropyl alcohol have been found to proceed *via* chromium(V) as an intermediate. This species could be observed by its ultraviolet and esr spectra. The first step, involving chromium(VI), proceed *via* decomposition of the monoester and diester as intermediates, and rate constants for both were determined. The chromium(V) oxidation appeared quite similar to the chromium(VI) oxidation. The details of the oxidation processes are discussed.

In the preceding paper,[2] we have described the very rapid reactions which occur between chromic acid and isopropyl alcohol prior to the oxidation steps. Evidence for no change in the oxidation state of chromium included the absence of a kinetic hydrogen isotope effect and the observation of final absorbancy indices which were characteristic of chromium(VI) esters. We now wish to describe the somewhat slower reactions by which the original alcohol is converted to ketone.

In 97% aqueous acetic acid, ester formation was followed by a decrease in absorbance at 385 mμ with a half-life on the order of 6 sec (Figure 1). Except for the very early points, the data appeared to correspond to a simple first-order decay. However, when the reaction was examined at 510 mμ, a quite different behavior was noted (Figure 2). Here, the absorbance first increased and then decreased to the normal final value. Clearly, the reaction involves the formation of an intermediate which then decays to chromium(III). The net stoichiometry of the set of reactions was determined, and 1.5 equiv of acetone was found for each equivalent of chromium(VI) used. Thus, a quantitative yield of acetone was found based on the expected stoichiometry.

Since an excess of alcohol and of acid was used, the reaction may be described by

$$\mathrm{A} \xrightarrow{k_1} \mathrm{B}$$

$$\mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

The kinetic data were fit to this set of successive first-order reactions by the procedure used previously.[3] The rate constants were calculated for four runs at each concentration and averaged giving the values shown in Tables I and II.

Table I. Effect of Isopropyl Alcohol Concentration on the Rate of Chromic Acid Oxidation[a]

Alcohol	[ROH] × 10^2	k_1, sec^{-1}	k_2, sec^{-1}
H	0.832	0.155	0.0063
H	1.43	0.20	0.013
H	2.72	0.33	0.021
H	5.30	0.44	0.032
H	8.16	0.495	0.035
H	11.6	0.502	0.0395
H	12.8	0.495	0.0375
H	15.6	0.535	0.415
D	1.55	0.0338	0.0019
D	4.61	0.063	0.0028
D	8.81	0.083	0.0039
D	12.9	0.086	0.0049

[a] $T = 15 \pm 0.1°$, $[\mathrm{H^+}] = 0.0125\ M$, $[\mathrm{Cr^{6+}}] = 0.00103\ M$, $\mu = 0.183$ ($NaClO_4$), λ 510 mμ, 97% acetic acid.

Table II. Effect of Acid Concentration on the Rate of Chromic Acid Oxidation[a]

[H$^+$] × 10^1	k_1, sec^{-1}	k_2, sec^{-1}
0.063	0.205	0.0159
0.25	0.471	0.0375
0.375	0.49	0.042
0.469	0.53	0.045

[a] $T = 15 \pm 0.1°$, $[\mathrm{ROH}] = 0.0301\ M$, $[\mathrm{Cr^{6+}}] = 0.00103\ M$, $\mu = 0.183$ ($NaClO_4$), λ 510 mμ, 97% acetic acid.

Before proceeding further, it was necessary to identify the intermediate observed at 510 mμ. Only chromium species could absorb at this wavelength, and so the intermediate could be chromium(IV) or (V). It is known that chromium(V) will give a strong esr signal,[4] and therefore the esr spectrum was examined in reacting solutions as a function of time. A well-defined signal at $g = 1.9805$ was found (Figure 3), and the change in intensity with time is given in Figure 4. The relative concentrations of the intermediate as determined from the spectral data at 510 mμ are also given in Figure 4, and it can be seen that the two curves correspond very well, indicating that the same species is responsible for both phenomena. It is then clear that the intermediate is chromium(V).

The data in Table I include rate constants for the reaction of isopropyl-α-*d* alcohol. An average isotope effect $k_\mathrm{H}/k_\mathrm{D} = 6.2 \pm 0.5$ was found for the first step in which chromium(VI) is reduced, and $k_\mathrm{H}/k_\mathrm{D} = 9.1 \pm 0.8$ was found for the second step in which chromium(V) is reduced.

In the study of the preoxidation equilibria, we found that both the monoester and diester were formed. Presumably, both will react to give acetone.

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(1) (a) This investigation was supported by the National Science Foundation. (b) Organic Chemistry Institute, University of Göttingen.

(2) K. B. Wiberg and H. Schäfer, *J. Am. Chem. Soc.*, **91**, 927 (1969).

(3) K. B. Wiberg and A. Lepse, *ibid.*, **86**, 2612 (1964).

(4) A. Carrington, D. J. E. Ingram, H. Schonland, and M. C. R. Symons, *J. Chem. Soc.*, 4710 (1956); H. Kon, *J. Inorg. Nucl. Chem.*, **25**, 933 (1963).

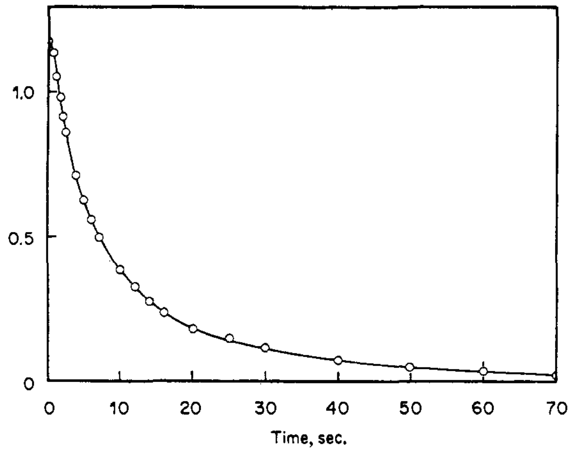


Figure 1. Change in absorbance with time at 385 mμ for the chromic acid oxidation of isopropyl alcohol ([H^+] = 0.0125 *M*, [ROH] = 0.082 *M*, [Cr^{6+}] = 0.00103 *M*, 15°).

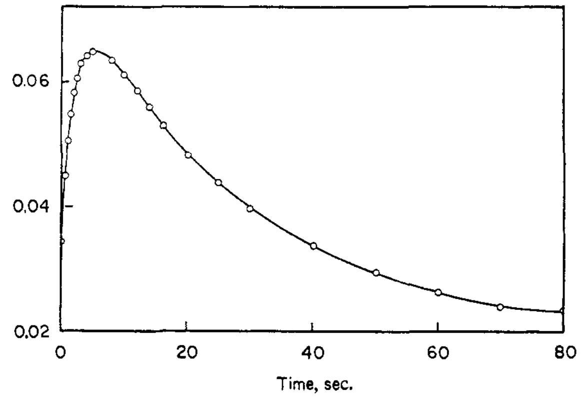


Figure 2. Change in absorbance with time at 510 mμ for the chromic acid oxidation of isopropyl alcohol ([H^+] = 0.0125 *M*, [ROH] = 0.125 *M*, [Cr^{6+}] = 0.00103 *M*, 15°).

$$ROCrO_2OH \xrightarrow{k_M} \text{acetone} + Cr^{4+}$$

$$ROCrO_2OR \xrightarrow{k_D} \text{acetone} + Cr^{4+}$$

$$Cr^{4+} + Cr^{6+} \longrightarrow 2Cr^{5+}$$

The experimental rate constant for the first step will be given by

$$-\frac{d[Cr^{6+}]}{dt} = (f_M k_M + f_D k_D)[Cr^{6+}]$$

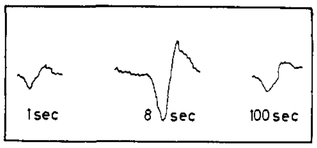


Figure 3. Esr signal observed during the chromic acid oxidation of isopropyl alcohol.

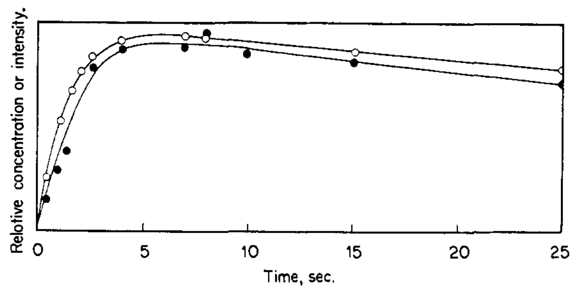


Figure 4. Change in the chromium(V) concentration with time as determined from the kinetic analysis (○) and the change in the intensity of the esr signal (●) for the chromic acid oxidation of isopropyl alcohol. The two curves are displaced from each other so that they may more easily be compared.

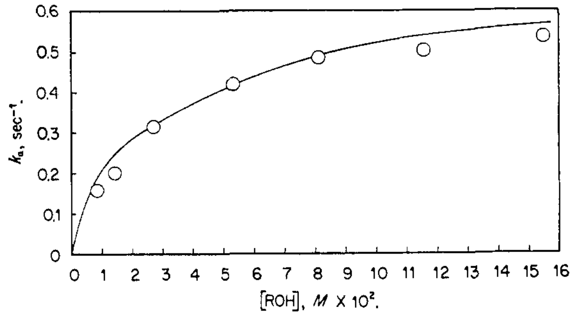


Figure 5. Effect of isopropyl alcohol concentration on the rate of the oxidation of isopropyl alchol by chromium(VI). The line represents the calculated rate constants; [Cr^{6+}] = 1.03 × 10^{-3} *M*, [H^+] = 0.0125 *M*, *T* = 15.0°.

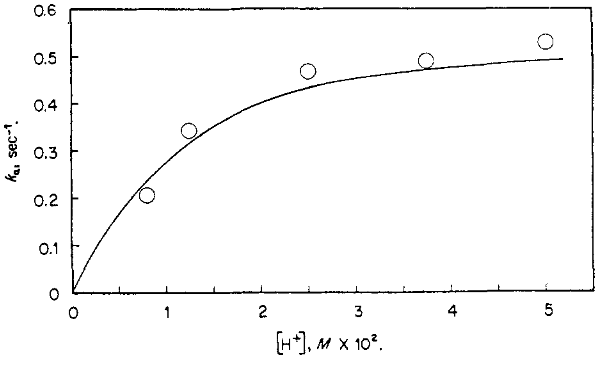


Figure 6. Effect of acid concentration on the rate of the oxidation of isopropyl alcohol by chromium(VI). The line represents the calculated rate constants; [Cr^{6+}] = 1.03 × 10^{-3} *M*, [ROH] = 0.0301 *M*, *T* = 15.0°.

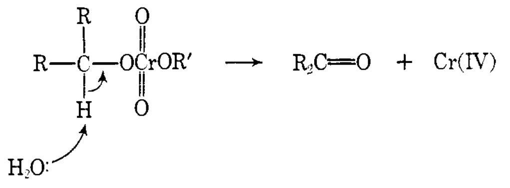
where f_M is the fraction of chromium(VI) in the monoester form, and f_D is the fraction in the diester form. The concentrations of mono- and diesters could be calculated from the equilibrium constants obtained previously,[2] and the experimental data were fit to the above expression using k_M and k_D as the variables. The best values of k_M and k_D were 0.559 and 0.911 sec^{-1}, respectively, and the fit to the experimental data is indicated in Figures 5 and 6. It will be seen that a satisfactory fit is obtained for the rate constant both as a function of isopropyl alcohol concentration and acid concentration. Because of the high formation constant for the monoester, the change in rate constant with changing acid concentration is then largely due to the conversion of the monoester anion to the monoester. The ratio of k_M to k_D is about 1:2, and on statistical grounds the diester would be expected to be twice as reactive as the monoester.

Other models also were tried. It can be shown that the data are incompatible with a mechanism involving the direct reaction of acetochromic acid with the alcohol. The only model which gave a satisfactory fit was the one described above in which both the mono- and diesters are reactive intermediates. Thus, we believe we have been able to establish that the oxidation reaction proceeds *via* the esters.[5]

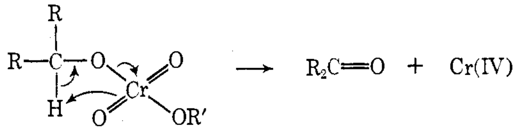
The oxidation *via* chromium(V) may now be considered. The rate constants show the same type of behavior as those for the chromium(VI) oxidation. In fact, there is approximately a constant ratio between k_1 and k_2. This strongly suggests that chromium(VI) and chromium(V) are quite similar in behavior, and that chromium(V) forms both monoesters and diesters. The similarity in rate between chromium(V) and chromium(VI) stands in marked contrast to the results of Roček and Riehl[6] who suggested that chromium(V) is 15,000 times more reactive toward adipic acid than chromium(VI). The data for isopropyl alcohol and the similar observations in the oxidation of benzaldehyde[3,7] suggest that some species other than chromium(V) must be responsible for the oxidation of adipic acid.

It seems appropriate to summarize what is now known about chromic acid oxidation of alcohols. The chromium(VI) mono- and diesters have been shown to be involved in the oxidative processes. The ester may decompose in any one of three ways.

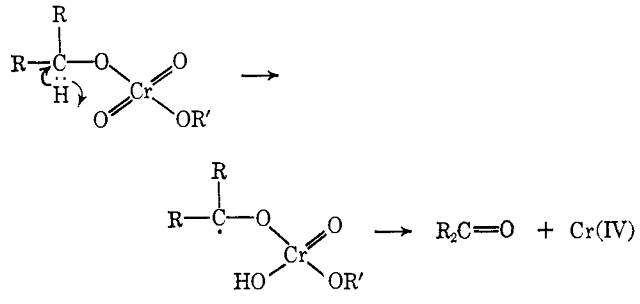
Mechanism A



Mechanism B



Mechanism C



Mechanism B appears to be favored at the present time,[8] although mechanism A involving an internal base has not definitely been ruled out. Mechanism C, which involves two successive one-electron transfers, cannot easily be distinguished from A and B since the transfer of the second electron presumably would occur rapidly.

The next steps of the reaction may be either

Mechanism D

$$R_2CHOH + Cr^{4+} \longrightarrow R_2\underset{\cdot}{C}OH + Cr^{3+}$$
$$R_2\underset{\cdot}{C}OH + Cr^{6+} \longrightarrow R_2C{=}O + Cr^{5+}$$
$$R_2CHOH + Cr^{5+} \longrightarrow R_2C{=}O + Cr^{3+}$$

Mechanism E

$$Cr^{4+} + Cr^{6+} \longrightarrow 2Cr^{5+}$$
$$2(R_2CHOH + Cr^{5+} \longrightarrow R_2C{=}O + Cr^{3+})$$

Sequence D has been favored by Roček[9] whereas sequence E is that suggested by Watanabe and Westheimer.[10] Either of these sets of reactions are compatible with the present data. However, the possibility of observing chromium(V) permits an experimental differentiation between the two sets of reactions. In D, the steps which lead to chromium(V) produce 2 equiv of acetone for each equivalent of chromium(V) whereas in E, 1 equiv of acetone is formed for 2 equiv of chromium(V). Thus, by quenching the solution at the time when the chromium(V) reaches its maximum concentration, and analyzing the solution for the amount of acetone formed, it should be possible to determine the stoichiometry of the steps leading to chromium(V) and to differentiate between D and E. Such experiments are now in progress.

Finally, the reaction of isopropyl alcohol with chromium(V) appears to involve an ester intermediate. The larger isotope effect for the chromium(V) reaction (9.1) as compared to that for chromium(VI) (6.5) is interesting in that a smaller isotope effect was found for chromium(V) in aqueous solution *via* a competitive technique,[11] and here the isotope effect was found to be markedly acid dependent. One might conclude that whereas the chromium(VI) reaction has similar characteristics in water and in aqueous acetic acid, the reaction of chromium(V) may change significantly with solvent. It does appear that the reaction of chromium(V) responds differently to changes in solvent composition than does chromium(VI) because there is a significant difference in the relative reactivity of the two species with a change in the water content of the solvent.

One factor may be important in this regard. Most of the chromium(VI) is in the form of the mono- or diesters at the alcohol concentrations used. Thus, most of the chromium(V) will be formed as its isopropyl ester. This is not the case in aqueous solution where most of the chromium(VI) is in the form of the acid chromate ion. It clearly will be necessary to investigate the effect of a variation in reaction conditions on the rate of oxidation by chromium(V). It also will be

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(5) It has been shown in the case of a hindered alcohol that the ester is an intermediate (J. Roček, F. H. Westheimer, A. Eschenmoser, L. Moldovânyi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962)). However, it has not previously been possible to demonstrate that it is an intermediate with simple alcohols.

(6) J. Roček and A. Riehl, *Tetrahedron Letters*, 1437 (1966).

(7) K. B. Wiberg and G. Szeimies, unpublished results.

(8) The evidence is reviewed by K. B. Wiberg, in "Oxidation in Organic Chemistry," Academic Press, New York, N. Y., 1965.

(9) J. Roček and A. E. Radkowsky, *J. Am. Chem. Soc.*, **90**, 2986 (1968).

(10) W. Watanabe and F. H. Westheimer, *J. Chem. Phys.*, **17**, 61 (1949).

(11) L. Kaplan, *J. Am. Chem. Soc.*, 77, 5469 (1955).

necessary to examine the effect of reaction medium on cleavage reactions, such as that of phenyl-*t*-butylcarbinol, which are believed to involve chromium(V).[12] Such studies are planned.

Experimental Section

Stoichiometry. To a solution of chromium trioxide (1.425 mmol) in 100 ml of 97% acetic acid which was 0.09 M in perchloric acid was added 1.0 g of isopropyl alcohol. After 1 hr, the solution was diluted with 700 ml of water containing 20 g of sodium acetate, and 40 ml of a 2,4-dinitrophenylhydrazine solution was added. After cooling in a refrigerator for 20 hr, the yellow precipitate was filtered, washed with distilled water, and dried in a vacuum oven at 80°. There was obtained 0.508 mg of acetone 2,4-dinitrophenylhydrazone, mp 124–124.5°, corresponding to 2.14 mmol of acetone. The ratio of acetone to chromium(VI) is 1.502, corresponding to a quantitative yield of acetone.

Kinetics. The kinetic measurements were made using a stopped-flow reactor as described in the previous paper.[2] The rate constants for the two steps in the reaction which could be observed at 510 $m\mu$ were calculated as described previously.[3]

Esr Measurements. A Varian E3 esr spectrometer was adjusted for maximum sensitivity. A flow cell in the spectrometer was connected to two 500-ml reservoirs having stopcocks for flow regulation and fitted with a connection for nitrogen pressure. Each reservoir was connected to the cell *via* a calibrated flowmeter. One reservoir contained 2.06×10^{-3} M chromium(VI) and 0.250 M perchloric acid in 97% acetic acid and the other contained 0.058 M isopropyl alcohol in the solvent. Equal flow rates were established for the two solutions, and the intensity of the esr signal was determined as a function of flow rate. Knowing the geometry of the mixer and flow cell, the flow rates could be converted to reaction times. The experiments were carried out at 25°.

The above reaction solutions also were studied spectrometrically at 510 $m\mu$ and 25°. The rate constants were caculated as before, and from this the concentration of chromium(V) could be calculated as a function of time.

Acknowledgment. We wish to thank Professor J. Sturtevant for making his stopped-flow apparatus available for this study and Professor J. Wang for making his esr spectrometer available.

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[12] J. Hampton, A. Leo, and F. H. Westheimer, *J. Am. Chem. Soc.*, 78, 306 (1956); J. J. Cawley and F. H. Westheimer, *ibid.*, **85**, 1771 (1963).

Polynucleotides. I. Use of Sephadex in the Preparation of Thymidine Homodeoxyribopolynucleotides Bearing a 5′-Phosphomonoester End Group

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Abstract: Thymidine tetracosadeoxyribonucleotide has been synthesized from the trinucleotide by the progression: trinucleotide → hexanucleotide → dodecanucleotide → tetracosanucleotide. At each step a cyanoethyl 5′-phosphate fragment bearing a free 3′-hydroxyl group was condensed in the presence of mesitylenesulfonyl chloride with a 3′-acetyl fragment having a free 5′-phosphate group. The desired products were isolated by column chromatography on Sephadex gels of the appropriate grade size and were characterized by paper chromatography with and without the 5′-phosphomonoester end group. The intermediate compounds were further characterized by degradation with snake venom phosphodiesterase treatment after the enzymic removal of the phosphomonoester group.

In recent years two major approaches have been developed for the chemical synthesis of short-chain deoxyribopolynucleotides, (1) stepwise condensation[2] and (2) polymerization.[3] In each case, the product obtained after each condensation was separated by time-consuming procedures involving mainly ion-exchange DEAE-cellulose chromatography. In order to overcome this difficulty, a polymer support for the speedy synthesis of polynucleotides has been investigated in different laboratories.[4] This method has so far shown limited success up to the hexanucleotide.[5]

In this paper we wish to introduce the use of Sephadex (superfine grade) gel filtration technique for the preparation of deoxyribopolynucleotides. The basic concept developed in the present study is that the chain length should be approximately doubled at each condensation step and the reactants for the condensation should be suitably protected oligonucleotides with 5′-phosphomonoester end groups. Thus, products and reactants differ substantially in molecular weight and

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[1] National Research Council of Canada Postdoctorate Fellow, 1967–1968.

[2] (a) T. M. Jacob and H. G. Khorana, *J. Am. Chem. Soc.*, **87**, 2971 (1965); (b) S. A. Narang and H. G. Khorana, *ibid.*, **87**, 2981 (1965); (c) S. A. Narang, T. M. Jacob, and H. G. Khorana, *ibid.*, **87**, 2988 (1965); (d) H. Kössel, H. Büchi, and H. G. Khorana, *ibid.*, **89**, 2185 (1967); (e) E. Ohtsuka and H. G. Khorana, *ibid.*, **89**, 2195 (1967).

[3] (a) E. Ohtsuka, M. W. Moon, and H. G. Khorana, *ibid.*, **87**, 2956 (1965); (b) S. A. Narang, T. M. Jacob, and H. G. Khorana, *ibid.*, **89**, 2167 (1967); (c) T. M. Jacob, S. A. Narang, and H. G. Khorana, *ibid.*, **89**, 2177 (1967).

[4] (a) R. L. Letsinger and U. Mahadevan, *ibid.*, **87**, 3526 (1965); (b) F. Cramer, R. Helbig, H. Hettler, K. H. Scheit, and H. Seliger, *Angew. Chem.*, 78, 640 (1966); (c) L. R. Melby and D. R. Strobach, *J. Am. Chem. Soc.*, **89**, 450 (1967); (d) H. Hayastu and H. G. Khorana, *ibid.*, **89**, 3880 (1967); (e) G. M. Blackburn, M. J. Brown, and M. R. Harris, *J. Chem. Soc., C*, 2438 (1967).

[5] F. Cramer and H. Köster, *Angew. Chem. Intern. Engl.*, **7**, 473 (1968).