Three-Electron Oxidations. VI. Chromic Acid Cooxidation of Cyclobutanol and Oxalic Acid. The Chromium(V) Oxidation of Cyclobutanol[1,2]

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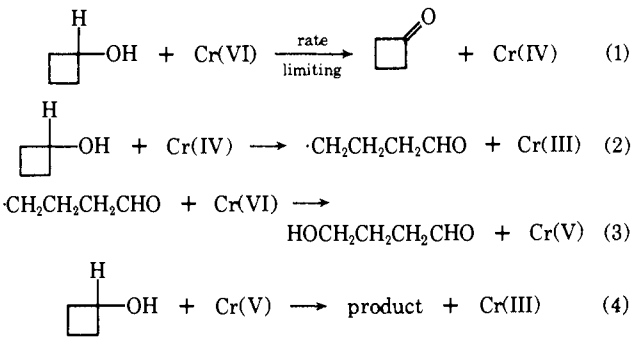
Abstract: The chromic acid cooxidation of cyclobutanol and oxalic acid yields only cyclobutanone and carbon dioxide with the CO_2:cyclobutanone ratio varying from 1:1 to 4:1 depending on the initial ratio of the two substrates. The chromic acid oxidation in the presence of oxalic acid thus provides a quantitative method of converting cyclobutanol to cyclobutanone with complete suppression of ring cleavage side reactions. The chromium(V) oxidation of cyclobutanol yields cyclobutanone. The deuterium isotope effect of the reaction is $k_H/k_D = 4.96$. Cyclobutanol is only 2.3 times more reactive toward chromium(V) than isopropyl alcohol. A mechanism for the chromium(V) oxidation is proposed which is analogous to the mechanism of the chromium(VI) oxidation of alcohols and involves reversible formation of an ester intermediate and carbon–hydrogen bond cleavage in the rate-limiting step. The presence of either acrylonitrile or acrylamide leads to polymer formation during the oxidation; however, with acrylonitrile, a constant 1:1 ratio of cyclobutanone:carbon dioxide is formed, whereas in the presence of acrylamide, the ratio of the two products is a function of the initial concentration of the substrates. The difference between the two monomers is interpreted in terms of different reactivity of the polymer radical toward oxidation. All results obtained in this study are fully consistent with the earlier proposed three-electron mechanism for the cooxidation reaction.

For many years, chromium(V) was held responsible[3,4] for carbon–carbon bond cleavage reactions occasionally observed during chromic acid oxidations of alcohols which are highly branched,[5] contain aryl groups,[6] or are strained.[7,8] However, this assumption has been recently seriously undermined by the demonstration that chromium(IV) oxidations play an important role in the chromic acid oxidation of alcohols,[8,9] and further by the finding that chromium(IV) reacts with carbon–carbon bond cleavage with cyclobutanol,[8] as well as with 1,2-diarylethanols.[10] These results together with the demonstrated similarity between the behavior of chromium(VI)[4] and chromium(V)[11] led to the suggestion that chromium(IV) is the only valence state of chromium responsible for the cleavage process and that chromium(V) reacts with carbon–hydrogen bond cleavage.[8,10]

We have recently shown that cyclobutanol provides a particularly simple and useful example of a compound which reacts with chromic acid to produce a mixture of both the "normal" product, cyclobutanone, and of an "abnormal" cleavage product, γ-hydroxybutyraldehyde.[8,9] The advantage of cyclobutanol is its high water solubility which obviates the necessity of working in a nonaqueous solvent and the fact that the cleavage product is formed in an unusually high yield. Detailed investigation revealed that chromium(VI) oxidizes cyclobutanol to cyclobutanone in a carbon–hydrogen bond cleavage reaction whereas chromium(IV) reacts with carbon–carbon cleavage to give a free-radical intermediate, $\cdot CH_2CH_2CH_2CHO$, which upon further oxidation gives rise to the hydroxyaldehyde. These results led us to propose the reaction mechanism given in Scheme I, which includes a chromium(V) oxidation step. The goal of the present study was to investigate this step of the reaction in the hope of obtaining more definite information about the chromium(V) oxidation of cyclobutanol in particular and about the oxidative properties of chromium(V) in general.

Scheme I



The approach used in this study was made possible by our recent observation of a rapid cooxidation reaction taking place when chromic acid reacts with a mixture of

(1) (a) Part V: F. Hasan and J. Roček, *J. Org. Chem.*, **38**, 3812 (1973). (b) Presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, Apr 1973.

(2) This investigation was supported by the National Science Foundation.

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(6) (a) W. A. Mosher and H. A. Neidig, *J. Amer. Chem. Soc.*, **72**, 4452 (1950); (b) H. A. Neidig, D. C. Funck, R. Uhrich, R. Baker, and W. Kreiser, *ibid.*, **72**, 4617 (1950); (c) W. A. Mosher, W. H. Clement, and R. L. Hillard, "Selective Oxidation Process," American Chemical Society, Washington, D. C., 1965, p 81.

(7) W. A. Mosher and E. O. Langerak, *J. Amer. Chem. Soc.*, **73**, 1302 (1951).

(8) J. Roček and A. E. Radkowsky, *J. Amer. Chem. Soc.*, **90**, 2986 (1968); **95**, 7123 (1973).

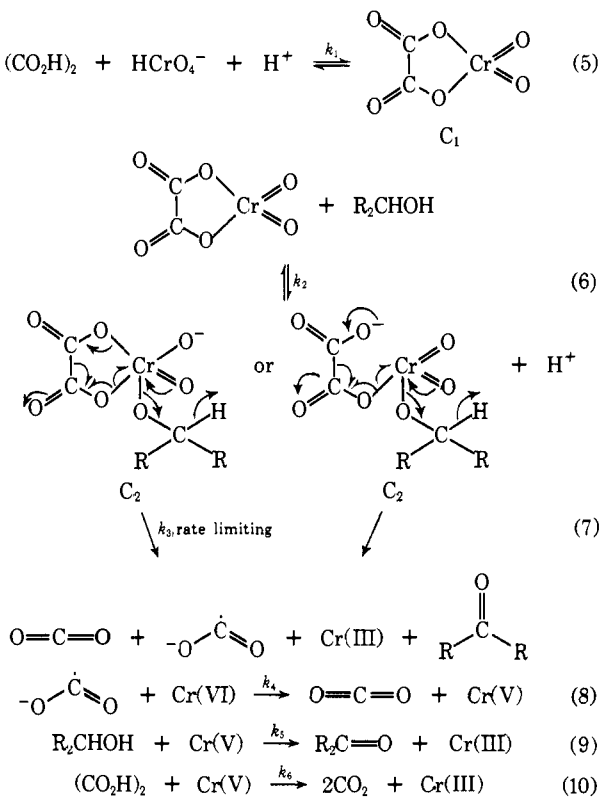
(9) M. Rahman and J. Roček, *J. Amer. Chem. Soc.*, **93**, 5455, 5462 (1971).

(10) P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **92**, 1120 (1970); **93**, 4536 (1971).

(11) K. B. Wiberg and H. Schäfer, *J. Amer. Chem. Soc.*, **89**, 455 (1967); **91**, 927, 933 (1969).

an alcohol and oxalic acid, an α-hydroxy acid, or another related compound.[1a,12] The mechanism proposed for rapid cooxidation reaction is given in Scheme II; the rate-limiting step of the reaction is a one-step

Scheme II



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three-electron oxidative decomposition of a ternary complex formed from chromic acid, oxalic acid, and the alcohol (reaction 6). The most striking difference between Schemes I and II is the absence of the chromium(IV) oxidation of the alcohol in the cooxidation reaction. On the other hand, the chromium(V) oxidation step is present in both schemes.

This difference provides an opportunity to examine the products of the chromium(V) oxidation of cyclobutanol without interference from the chromium(IV) oxidation which is known to yield cleavage products. If chromium(V) reacts with carbon–carbon bond cleavage, then the formation of cleavage products should still be observed. On the other hand, if chromium(V) reacts like chromium(VI) to give the "normal" product with carbon–hydrogen bond cleavage, then the formation of cleavage products should be suppressed by the presence of oxalic acid.

It has been shown earlier that the composition of the oxidation products obtained in the cooxidation reaction varies with the initial concentrations of the alcohol and oxalic acid.[13] As these variations are due to the competition between the two chromium(V) oxidation steps (reactions 9 and 10), the relative rate data for chromium(V) oxidations can be obtained from a systematic study of the composition of the oxidation products. The study of the cooxidation of cyclobutanol and oxalic acid thus should permit the determination of the relative reactivity of cyclobutanol toward chromium(V). As cyclobutanol oxidations involving a cleavage of the cyclobutanol ring proceed usually much faster[8] than similar oxidations of strain free alcohols yielding "normal" products, the determination of the chromium(V) oxidation rate would provide additional information concerning the mechanism of the reaction.

Experimental Section

Materials. Cyclobutanol was prepared from cyclopropylcarbinol[14] and purified by preparative glpc on a Carbowax column. 1-Deuteriocyclobutanol was prepared by lithium aluminum deuteride reduction of cyclobutanone.[8]

Oxalic acid (Mallinckrodt AR), sodium dichromate (J. T. Baker, Reagent), and acrylamide (Eastman Kodak) were used without further purification. Perchloric acid solutions were prepared from 60% perchloric acid (B & A Reagent).

Acrylonitrile (Practical Grade) was freshly distilled and the 78–79° fraction used.

Kinetic Measurements. Rates of chromium(VI) oxidations were determined spectroscopically;[12] rates of chromium(V) oxidations were determined by earlier described competitive methods.[13] All rate measurements were carried out at 25 ± 0.05°.

Product Analysis. Cyclobutanone. In a typical experiment cyclobutanol (6.0 ml, 0.131 *M*), oxalic acid (0.2 ml, 0.781 *M*), perchloric acid (0.2 ml, 6.28 *M*), and distilled water (3.5 ml) were mixed in a 50-ml erlenmeyer flask and a solution of sodium dichromate (0.1 ml, 0.157 *M*) was added. After completion of the reaction (about 10 min) a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid was added. The reaction mixture was kept in the refrigerator for 12 hr, the precipitate was filtered and dried, and the product was dissolved in methylene chloride and passed through a silica gel (0.05–0.2 mm, E. Merck) column using methylene chloride as eluent.[15] Only one visible band was observed and identified as cyclobutanone 2,4-dinitrophenylhydrazone by comparison with an authentic sample (mp and mmp 143–145°). After the visible band was eluted, the column was washed with methylene chloride in order to remove even traces of other products and particularly of γ-hydroxybutyraldehyde 2,4-dinitrophenylhydrazone. The eluate was analyzed spectrophotometrically at 360 nm where the 2,4-dinitrophenylhydrazone of the hydroxyaldehyde absorbs strongly (ϵ 2.23 × 10^4); the absence of any noticeable absorption indicated that no hydroxyaldehyde was formed in the oxidation.

Since the precipitation of 2,4-dinitrophenylhydrazone of cyclobutanone is not complete in the presence of acrylamide or acrylonitrile, the yields of cyclobutanone in these cases were determined by glpc on a Hewlett-Packard Model 5750 Research Chromatograph with a 10-ft 10% Carbowax 20M 80–100 WAW 5754A column; acetone was used as internal standard.

Carbon Dioxide. The yield of carbon dioxide was determined manometrically in a Warburg apparatus following the procedure described earlier.[12]

Test for Free-Radical Formation. When acrylonitrile (0.0230 *M*) or acrylamide (0.138 *M*) was present in the cooxidation of cyclobutanol (0.0278 *M*) and oxalic acid (0.011 *M*) by sodium dichromate (0.0025 *M*), the formation of polymers could be observed after diluting the reaction mixture with an equal volume of methanol.

Results and Discussion

Chromic Acid Cooxidation of Cyclobutanol and Oxalic Acid. In a recent study of the effect of oxalic acid on the chromic acid oxidation[16] of hydrogen iodide, it was found that oxalic acid can act as a highly effective catalyst in chromic acid oxidation without itself being oxidized. According to this observation, the cooxidation reaction could also be explained by the alternative mechanism (Scheme III), in which the chromium(IV) intermediate produced (reaction 11) reacted only with oxalic acid (reaction 12). This would assume that chromium(IV) is sufficiently more reactive toward oxalic acid than toward alcohol to make the chro-

(12) (a) F. Hasan and J. Roček, *J. Amer. Chem. Soc.*, **94**, 3181 (1972); (b) *ibid.*, **95**, 5421 (1973).

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(14) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960).

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(16) G. F. Vandegrift and J. Roček, to be submitted for publication.

Table I. Effect of Cyclobutanol Concentration on the Ratio of the Products in 0.126 *M* Perchloric Acid[a]

[Cyclobutanol], *M*	[Cyclobutanol]/[oxalic acid]	Cyclobutanone yield— Mmol	%	Carbon dioxide yield— Mmol	%	Carbon dioxide/cyclobutanone
0.133	24.25[b]	0.0312	66	0.0314	33	1.01
0.132	12.00	0.0314	67	0.0304	32	0.97
0.124	11.27	0.0308	65	0.0317	34	1.03
0.117	10.63	0.0295	63	0.0348	37	1.17
0.105	9.55	0.0294	63	0.0358	38	1.21
0.079	7.18	0.0290	62	0.0377	40	1.30
0.052	4.73	0.0265	56	0.0400	42	1.51
0.026	2.36	0.0230	49	0.0469	50	2.04
0.013	1.18	0.0204	43	0.0528	56	2.59
0.0065	0.59	0.0189	40	0.0565	60	2.99
0.0022	0.20	0.0162	34	0.0611	65	3.82
0.0011	0.10	0.0154	33	0.0619	66	4.02

[a] Oxalic acid = 0.011 *M*, chromium(VI) = 0.0314 *M*. [b] Oxalic acid = 0.0055 *M*.

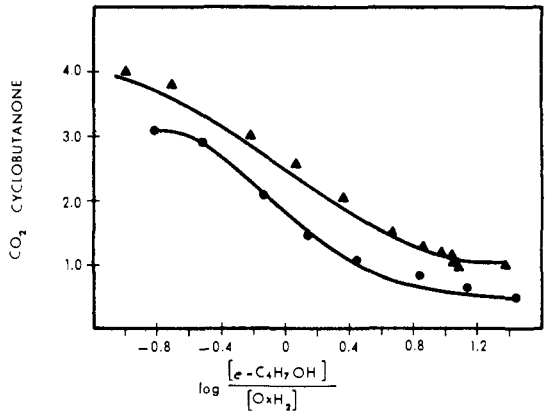


Figure 1. The dependence of the ratio of oxidation products on the substrate ratio in the chromic acid cooxidation of cyclobutanol and oxalic acid. The solid lines are calculated using the values of the relative rate: (▲) acrylamide = 0, (●) acrylamide = 0.189 *M*.

Scheme III

$$(CO_2H)_2 + HCrO_4^- + H^+ \rightleftharpoons C_1 \quad (5)$$

$$C_1 + R_2CHOH \rightleftharpoons C_2 \quad (6)$$

$$C_2 \xrightarrow{\text{rate limiting}} Cr(IV) + R_2CO + (CO_2H)_2 \quad (11)$$

$$Cr(IV) + (CO_2H)_2 \longrightarrow Cr(III) + CO_2 + \cdot CO_2H \quad (12)$$

$$Cr(IV) + R_2CHOH \longrightarrow Cr(III) + R_2COH \quad (13)$$

mium(IV) oxidation of an alcohol (reaction 13) in the presence of oxalic acid unimportant. Chromium(IV) indeed reacts with oxalic acid 44 times faster than with isopropyl alcohol[17] and it is therefore difficult to make an unambiguous distinction between mechanisms II and III based on studies with isopropyl alcohol alone. On the other hand, it can be shown from previously obtained data[9,17] that oxalic acid is only 2.1 times more reactive toward chromium(IV) than cyclobutanol. Consequently, Schemes II and III lead to very different predictions: in the presence of a large excess of cyclobutanol only an oxalic acid catalyzed oxidation of cyclobutanol, rather than a cooxidation of both substrates, should be observed if mechanism III were operative. The study of the cooxidation of cyclobutanol and oxalic acid therefore should permit making a clear distinction between mechanisms II and III.

The oxidation products obtained in a reaction of chromic acid with different mixtures of cyclobutanol and oxalic acid are given in Table I. No evidence for the formation of a ring-cleavage product was obtained although even traces of hydroxybutyraldehyde would have been safely detected. The two oxidation products account in all cases for the total amount of chromic acid used in the oxidation.

Changing the ratio of cyclobutanol to oxalic acid over a 240-fold range leads to a change in the yields of cyclobutanone from about 67 to 33%, and a change in the yield of carbon dioxide from 33 to 67% (Figure 1). No increase of cyclobutanone beyond the 67% yield can be observed even at the highest cyclobutanol–oxalic acid ratios used. This result combined with the finding[9,17] that oxalic acid reacts with chromium(IV) only 2.1 times faster than cyclobutanol and is clearly incompatible with the alternative mechanism (Scheme III).

It should be noted that the chromic acid oxidation of cyclobutanol in the presence of oxalic acid leads to a quantitative conversion of cyclobutanol to cyclobutanone with carbon dioxide being the only by-product. It is reasonable to expect that the suppression of the side reaction in chromic acid oxidation of alcohols prone to cleavage should hold generally. The chromic acid cooxidation in the presence of oxalic acid thus has the potential for providing an excellent synthetic method for the preparation of ketones from strained and other cleavage prone alcohols.

The chromic acid oxidation of a mixture of cyclobutanol and oxalic acid shows the same type of rate acceleration and a similar rate law (eq 14) as the isopropyl alcohol and oxalic acid system.[12] The third-order term for the cooxidation of cyclobutanol is 1.83 times higher than for isopropyl alcohol.[12] This value is somewhat lower than the relative oxidation rate (3.5) for these two alcohols for normal chromium(VI) oxidation.[8]

$$\text{rate} = 3.40 \times 10^{-2}[HCrO_4^-][H^+]^2[c\text{-}C_4H_7OH] + 16.1[HCrO_4^-][(COOH)_2][c\text{-}C_4H_7OH] + 2.42 \times 10^{-1}[HCrO_4^-][(COOH)_2]^2 \quad (14)$$

Chromium(V) Oxidation of Cyclobutanol. In the presence of a large excess of cyclobutanol, when a 1:1 ratio of cyclobutanone to carbon dioxide is reached, 50% of cyclobutanone is formed in reaction 7 by chro-

(17) F. Hasan and J. Roček, *Tetrahedron*, in press.

mium(VI) oxidation and 50% in reaction 9 by chromium(V) oxidation. As cyclobutanone is the only product formed, it must clearly be the product of both reactions. *Chromium(V) thus oxidizes cyclobutanol to cyclobutanone and is thus not responsible for the cleavage reaction leading to γ-hydroxybutyraldehyde in the chromic acid oxidation of cyclobutanol. It seems safe to generalize that chromium(V) is also not responsible for other cleavage reactions frequently observed during chromic acid oxidations.*[3-7]

Using the approach outlined earlier[13] one can use data given in Table I to obtain rates of chromium(V) oxidation for cyclobutanol relative to isopropyl alcohol. Figure 2 gives the plot[13] according to eq 15

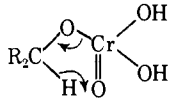
$$\frac{4 - x}{2(x - 1)} = \frac{k_5}{k_6}\frac{[\mathrm{ROH}]}{[(CO_2H)_2]} \qquad (15)$$

which gives the relationship between the product composition (x = CO_2:ketone) and the substrate ratios. From the plot, the chromium(V) reactivity to cyclobutanol relative to oxalic acid (k_5/k_6) was found to be 0.63. The analogous relative reactivity for isopropyl alcohol is[13] 0.27. Cyclobutanol is thus only about 2.3 times more reactive toward chromium(V) than isopropyl alcohol; the corresponding value for chromium(VI) oxidation is 3.1.[8] As it is generally observed that oxidations of cyclobutanol involving ring cleavage proceed considerably faster than oxidations of strain-free alcohols, the above results suggest that the chromium(V) oxidation of cyclobutanol proceeds by carbon–hydrogen rather than by carbon–carbon bond cleavage. This conclusion is further supported by the magnitude of the deuterium isotope effect: using the approach outlined above, we determined the reactivity of chromium(V) relative to oxalic acid for 1-deuteriocyclobutanol and found a k_5/k_6 value of 0.127 corresponding to a deuterium isotope effect k_H/k_D = 4.96.

These results support the conclusion that chromium(V) closely resembles chromium(VI) and acts as a two-electron oxidant. By analogy to chromium(VI) oxidations one thus can propose the following mechanism (Scheme IV) for the chromium(V) oxidation of primary and secondary alcohols.

Scheme IV

$$R_2CHOH + H_3CrO_4 \rightleftharpoons R_2CHCrO_3H_2 \qquad (16)$$



$$\longrightarrow R_2CO + Cr(III) \qquad (17)$$

Cooxidation of Cyclobutanol and Oxalic Acid in the Presence of Acrylonitrile. Table II shows the effect of the addition of acrylonitrile on the cooxidation rate. It will be noted that with the increasing concentration of acrylonitrile, the value of k_{obsd} decreases to about one-half of its original value.

Table II. Effect of Acrylonitrile on the Rate of Chromic Acid Cooxidation of Cyclobutanol and Oxalic Acid[a]

Acrylonitrile, M	k_{obsd}, sec^{-1}
0	2.89×10^{-3}
2.30×10^{-4}	2.54×10^{-3}
2.30×10^{-3}	1.89×10^{-3}
2.30×10^{-2}	1.66×10^{-3}
2.30×10^{-1}	1.54×10^{-3}

[a] Cyclobutanol = 0.0139 M, oxalic acid = 0.023 M, perchloric acid = 0.0628 M, and chromium(VI) = 5.6×10^{-4} M.

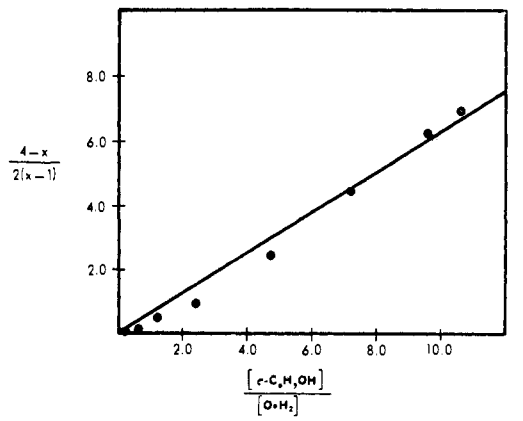


Figure 2. Determination of the relative rates of chromium(V) oxidation of cyclobutanol and oxalic acid. Perchloric acid = 0.126 M.

The compositions of the reaction product in the presence of acrylonitrile are given in Table III. Although the ratio of cyclobutanol to oxalic acid was varied by a factor of 20, the yield of cyclobutanone and of carbon dioxide remains at a constant 1:1 ratio; the total yield of oxidation products accounts for all chromic acid reduced. These results can be interpreted using Scheme V in which the reactions up to the rate-limiting step (reaction 7) are identical with Scheme II, but the free radical formed in the three-electron oxidation instead of reacting with another molecule of chromic acid (and thus doubling the observed oxidation rate) reacts with acrylonitrile (reaction 18) to initiate a radical chain reaction. The termination step must consist of a bimolecular reaction between two radicals, leading either to dimerization or disproportionation. It should be noted that the polymer radical in this case is obviously relatively unreactive toward oxidation, and thus can be accumulated in high enough concentrations to react by a bimolecular termination step.

Table III. Effect of Cyclobutanol Concentration on the Yield of Cyclobutanone and Carbon Dioxide in Presence of Acrylonitrile[a]

[Cyclobutanol], M	Cyclobutanol/oxalic acid	Cyclobutanone, mmol	Cyclobutanone/chromium(VI)
A. Chromium(VI) = 0.025 mmol			
0.0278	13.90	0.026	1.08
0.0139	6.95	0.027	1.12
0.0028	1.40	0.025	1.00
0.0014	0.70	0.024	0.98
B. Chromium(VI) = 0.0025 mmol			
[Cyclobutanol], M	Cyclobutanol oxalic acid	Carbon dioxide, mmol	Carbon dioxide/chromium(VI)
0.0278	13.90	0.0025	1.00
0.0139	6.95	0.0024	0.96
0.0028	1.40	0.0024	0.96
0.0014	0.70	0.0027	1.08

[a] Acrylonitrile = 0.230 M, oxalic acid = 0.002 M, and perchloric acid = 0.126 M.

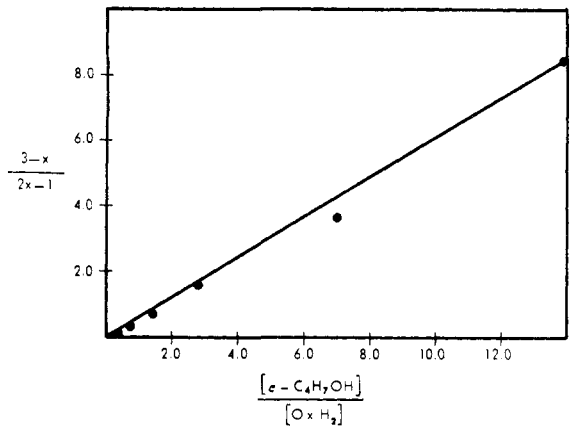


Figure 3. Determination of the relative rates of chromium(V) oxidation of cyclobutanol and oxalic acid in the presence of 0.189 *M* acrylamide. Perchloric acid = 0.126 *M*.

Scheme V

$$\cdot CO_2H + CH_2{=}CHCN \longrightarrow HO_2CCH_2\dot{C}HCN \quad (18)$$

$$HO_2CH_2\dot{C}HCN + nCH_2{=}CHCN \longrightarrow HO_2CCH_2[CHCH_2]_n\dot{C}HCN \quad (19)$$
(CN)

$$2HO_2CCH_2[CHCH_2]_n\dot{C}HCN \longrightarrow$$
(CN)

$$HO_2C[CH_2CH]_{n+1}[CHCH_2]_{n+1}CO_2H \quad (20)$$
(CN) (CN)

or

$$HO_2C[CH_2CH]_nCH{=}CHCN + HO_2C[CH_2CH]_nCH_2CH_2CN \quad (21)$$
(CN) (CN)

Cooxidation of Cyclobutanol and Oxalic Acid in the Presence of Acrylamide. Although acrylamide and acrylonitrile are closely related, and both have the ability to react with the free radicals generated in the reaction and undergo free-radical polymerization, the two monomers differ quite significantly.

Acrylamide has no effect on the rate of the chromic acid oxidation of a cyclobutanol–oxalic acid mixture (Table IV), but composition of the reaction products

Table IV. Effect of Acrylamide on the Chromic Acid Cooxidation of Cyclobutanol and Oxalic Acid[a]

Acrylamide, *M*	k_{obsd}, sec^{-1}
0	2.67×10^{-3}
9.90×10^{-3}	2.48×10^{-3}
9.90×10^{-2}	2.56×10^{-3}
4.50×10^{-1}	2.60×10^{-3}

[a] Cyclobutanol = 0.0131 *M*, oxalic acid = 0.0234 *M*, perchloric acid = 0.0628 *M*, and chromium(VI) = 2.8×10^{-4} *M*.

varies quite significantly as a function of the ratio of the two substrates (Table V). The yield of cyclobutanone varies from 0.5 to 1.0 mol per each mol of chromium(VI) reduced, whereas the yield of carbon dioxide changed from about 1.5 to 0.5. The overall ratio of CO_2 to cyclobutanone thus changes from 3.0 to 0.5 (Figure 1), which differs considerably from the range of 4.0–1.0 observed in the absence of a monomer and

Table V. Effect of Cyclobutanol Concentration on the Yields of Cyclobutanone and Carbon Dioxide in Presence of Acrylamide[a]

A. Chromium(VI) = 0.025 mmol

[Cyclobutanol], *M*	Cyclobutanol/oxalic acid	Cyclobutanone, mmol	Cyclobutanone/chromium(VI)
0.0556	27.80	0.025	1.00
0.0278	13.90	0.024	0.96
0.0139	6.95	0.023	0.92
0.0056	2.80	0.020	0.80
0.0028	1.40	0.017	0.68
0.0014	0.70	0.015	0.60
0.0010	0.50	0.012	0.48
0.0006	0.30	0.012	0.48
0.0003	0.15	0.012	0.48

B. Chromium(VI) = 0.0025 mmol

[Cyclobutanol], *M*	Cyclobutanol/oxalic acid	Carbon dioxide, mmol	Carbon dioxide/chromium(VI)
0.0556	27.80	0.0012	0.48
0.0278	13.90	0.0015	0.60
0.0139	6.95	0.0018	0.72
0.0056	2.80	0.0024	0.96
0.0028	1.40	0.0025	1.00
0.0014	0.70	0.0032	1.28
0.0010	0.50	0.0032	1.28
0.0006	0.30	0.0035	1.50
0.0003	0.15	0.0036	1.44

[a] Acrylamide = 0.189 *M*, oxalic acid = 0.002 *M*, and perchloric acid = 0.126 *M*.

from the constant 1:1 ratio obtained in the presence of acrylonitrile. Moreover, it will be noted that the total yield of both products accounts for only 83.3%, or 5/6, of the amount of chromium(VI) reduced.

These results can be understood on the basis of the mechanism given in Scheme VI. The free radical

Scheme VI

$$\cdot CO_2H + CH_2{=}CHCONH_2 \longrightarrow HO_2CCH_2\dot{C}HCONH_2 \quad (22)$$

$$HO_2CCH_2\dot{C}HCONH_2 + nCH_2{=}CHCONH_2 \longrightarrow HO_2CCH_2\left[CHCH_2\right]_n\dot{C}HCONH_2 \quad (23)$$
(CONH2)

$$HO_2CCH_2\left[CHCH_2\right]_n\dot{C}HCONH_2 + Cr(VI) \longrightarrow$$
(CONH2)

$$HO_2CCH_2\left[CHCH_2\right]_nCHCONH_2 + Cr(V) \quad (24)$$
(CONH2)

formed in the three-electron oxidation again initiates a polymerization reaction (reactions 22 and 23). However, the polymer radical in this case is oxidized by chromium(VI) (reaction 24). The chromium(V) species formed in this reaction then can react either with oxalic acid (reaction 10) or with cyclobutanol (reaction 4). If all chromium(V) formed in this reaction reacted with cyclobutanol, one molecule of carbon dioxide and two molecules of cyclobutanone would be formed for each two molecules of chromium(VI) reduced. If, on the other hand, chromium(V) reacted only with oxalic acid, three molecules of carbon dioxide and only one molecule of cyclobutanone would be obtained per two molecules of chromic acid.

We have shown earlier[13] that a quantitative relationship between the substrate and product composition can be derived and utilized to determine relative oxida-

tion rates for chromium(V). The same type of expression (eq 25), with appropriately modified constants, can be derived for the oxidation in the presence of acrylamide. Figure 3 shows that a good straight line plot can be obtained if the data given in Table V are plotted according to eq 25. It is gratifying to find an excellent agreement between the relative rates for the chromic acid oxidation of cyclobutanol with respect to oxalic acid determined from eq 25 in the presence of acrylamide ($k_5/k_6 = 0.61$) and those determined from eq 16 in the absence of acrylamide ($k_5/k_6 = 0.63$).

$$\frac{3 - x}{2x - 1} = \frac{k_5}{k_6}\frac{[\mathrm{ROH}]}{[(\mathrm{CO_2H})_2]} \qquad (25)$$

The striking difference between the behavior of acrylonitrile and acrylamide is most likely the result of the considerably higher electronegativity of the $-CN$ group as compared with the $-CONH_2$ group. The different behavior of the two polymer radicals could be caused either by the change in reactivity of the radical toward oxidation or toward dimerization. However, as the activation energy for the dimerization reaction is expected to be quite low, it is more plausible to assume that the difference in the behavior of the two radicals is a result of a considerably reduced reactivity toward oxidation resulting from the introduction of the strongly electronegative cyano group. It thus seems that the decrease in oxidation rates with increasing electronegativity of substituents observed in alcohols,[18,19] aldehydes[20] or carboxylic acids[21] also holds in the oxidation of free radicals.

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On the Conformation and Synthesis of Diketopiperazines. 3,4-Dehydroproline Anhydride

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Abstract: The amino acid 3,4-dehydro-D,L-proline was prepared from pyrrole-2-carboxylic acid and converted to the hydrochloride of the methyl ester with thionyl chloride in methanol. Liberation of the amino group with triethylamine resulted in the spontaneous formation of the diketopiperazine. Crystal structure analysis by X-ray diffraction showed that both halves of the molecule have the same configuration; *i.e.*, the dimerization occurred between two L molecules or two D molecules rather than between an L and a D molecule. The diketopiperazine ring occurs in a folded conformation with a dihedral angle of 139°. Hydrogen atoms on the two C^{α} atoms are axial and cis to each other. The space group is $P4_12_12$ with $a = 5.607 \pm 0.003$ Å, $c = 28.753 \pm 0.009$ Å, and four molecules in the unit cell.

Cyclic dipeptides with (modified) prolyl constituents occur in a number of natural products, such as the toxic principle prolyl-2(1′,1′-dimethylallyl)tryptophyldiketopiperazine[4] extracted from moldy maize meal, the therapeutic agent zizyphin,[5] and also in the epidithiodiketopiperazine systems of sporidesmin,[6] gliotoxin,[7] and chaetoxin,[8] for example.[9] The interest in 3,4-dehydroproline anhydride (IV) is twofold: first, as a possible intermediate suitable for the synthesis of natural products containing an epidithiodiketopiperazine system (I), the anhydride of 3,4-dehydroproline (IV) was synthesized. It was expected that replacement of the allylic hydrogens in the α positions by halogen would lead to intermediates which could then be converted to V by sulfur nucleophiles.[10] In the course of this work it was necessary to determine the exact structure of IV, in particular the stereorelationship of the two α-hydrogen atoms, since a disulfide bridge could be introduced only with the two α hydrogens in a cis relationship. X-Ray diffraction analysis of a single crystal of 3,4-dehydroproline anhydride established that both prolyl groups have identical configurations; or in other words, that the two hydrogen atoms in the diketopiperazine ring are on the same rather than on opposite sides as would be the case in a molecule composed of a D- and an L-prolyl group.

Our second interest is the conformation of the diketopiperazine ring in cyclic dipeptides as a function of

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