The Chromic Acid Oxidation of Cyclohexanone. Reaction Products[1]

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The products formed in the chromic acid oxidation of cyclohexanone were investigated using both isotopic dilution analysis and gas–liquid partition chromatography. All oxygen introduced into the reaction in the form of chromic acid could be accounted for. It is demonstrated that the first step in the reaction is an α oxidation leading to 2-hydroxycyclohexanone. Less than 3% of the reaction proceeds by dehydrogenation *via* 2-cyclohexen-1-one. 2-Hydroxycyclohexanone is oxidized further to 1,2-cyclohexanedione (78% yield) and cleaved to adipic acid, oxidation being faster than enolization. Besides adipic acid, glutaric acid and succinic acid are formed. The last is formed with 50% loss of the carbon-14 label originally present in the carbonyl group. Degradative oxidation of adipaldehydic acid and (in part) induced oxidation of adipic acid are suggested as the main reactions leading to the formation of glutaric acid without loss and with 50% loss of the radioactive label, respectively. Induced oxidation of adipic acid is responsible for the formation of succinic acid. An explanation of the effect of concentration of the reactants on the ratio of reaction products is offered.

Although several kinetic studies of the chromic acid oxidation of ketones have been reported in the literature,[3-6] no detailed study of reaction products is available. As we believe that no meaningful discussion of the reaction mechanism is possible without the detailed knowledge of the reaction products formed, we felt it necessary to undertake such a study. We selected cyclohexanone because its particularly high reactivity[4] should make the detection of reaction intermediates much easier. Also, a cyclic ketone has the advantage of yielding fewer and simpler reaction products.

Experimental Section

Materials.—Cyclohexanone (Eastman Reagent Grade) was purified by distillation, bp 157–160°, lit. 156.7°. For kinetic work, it was purified further by vapor phase chromatography immediately before use (Carbowax column, 175°).

A stock solution of cyclohexanone-1-C^{14} was prepared by diluting 0.10 millicurie (4.0 mg) of cyclohexanone-1-C^{14} (New England Nuclear Corp.) with 96.1 mg of unlabeled cyclohexanone and dissolving in water (51.515 g).

Chromic acid (Fisher Certified, 99.8% pure) was used without further purification.

(perchloric acid 70%, Allied Chemical, reagent grade) was standardized against standard sodium hydroxide and diluted to a 5 *M* stock solution.

The hyamine solution utilized was hyamine hydroxide (Packard Instrument Company) (*p*-diisobutyl-cresoxethoxyethyl)-dimethyl-benzylammonium hydroxide at a concentration of 1 *M* in methanol.

The internal standard utilized was toluene-C^{14} (Nuclear Chicago) with an activity of $4.43 \times 10^5 \pm 5\%$ dpm/ml diluted with unlabeled toluene (Fisher Certified) to give a standard of 52.0 dpm/mg for high-counting samples and 4.08 dpm/mg for low-counting samples.

An ether solution of diazomethane was prepared from "Diazald" (*p*-tolysulfonyl methyl nitrosamide, Aldrich Chemical Co.) according to De Boer and Backer.[7]

Glutaric acid (Aldrich Chemical Co.) was recrystallized from benzene, mp 97–99°.

Adipic acid (Eastman), mp 152–154°, and succinic acid (Baker Analyzed Reagent), mp 188–188.5°, were used without further purification.

2-Cyclohexen-1-one (Aldrich Chemical Co.) was purified by glpc on a Carbowax column at 150°.

1,2-Cyclohexanedione (Columbia Organic) was purified by sublimation, mp 35°, lit. 35–38°.

Isotopic Dilution Analysis of the Products of Chromic Acid Oxidation of Cyclohexanone-1-C^{14}.—Perchloric acid (0.20 ml, 5.0 *M*) and chromic acid (0.50 ml, 0.010 *M*) were placed in one leg of a two-legged reaction flask. About 0.3 ml of an exactly weighed stock solution of cyclohexanone-1-C^{14} was added into the other leg and the reaction vessel closed and degassed by repeated evacuation of the Dry Ice–acetone cooled flask. After reaching room temperature the contents of the flask were thoroughly mixed and immersed in a water bath kept at 50 ± 1° for about 16 hr in darkness. After this time the reduction of chromic acid was completed. The bottom of the reaction flask was cooled in Dry Ice–acetone to avoid the loss of volatile products; the flask was opened, and the acid was neutralized by the addition of sodium hydroxide (0.20 ml, 5.0 *M*). A precisely weighed amount (about one gram) of the particular product to be determined was added and thoroughly mixed until a homogeneous solution was obtained (if necessary, more water was added). The added compound was then isolated and purified by one of the following procedures.

A. The Isolation of Cyclohexanone.—The solution was extracted with ether and dried over magnesium sulfate; the major part of the solvent was removed by distillation through a 10-cm, Heli-Pak filled column. The crude ketone was then purified by preparative glpc on a 6-ft Carbowax column until a constant C^{14} activity had been reached. This required two purifications.

B. 2-Cyclohexen-1-one was isolated by the same procedure as cyclohexanone. However, because of the special importance of this compound, the experiment was repeated using a larger amount of cyclohexanone-1-C^{14} than in the standard procedure. The unsaturated ketone was purified seven times by glpc, converted into the dinitrophenylhydrazone, and the derivative was recrystallized five times from ethanol. The C^{14} content was determined directly by liquid scintillation counting (lsc) after each glpc purification and by combustion analysis followed by lsc after the final purification of the dinitrophenylhydrazone (NEN Assay Corp., Boston, Mass.). The C^{14} content from the combustion analysis agreed well with the last value from the direct determination of the free ketone.

C. Adipic, Glutaric, Succinic, and Oxalic Acids.—The solution was evaporated to dryness and the crude acids were recrystallized (adipic, succinic, and oxalic acids from water, glutaric acid from benzene), dried, and esterified by an ether solution of diazomethane. The resulting dimethyl esters were purified by glpc on a cross-linked diethylene glycol adipate column at 200°.

D. 2-Hydroxycyclohexanone.—After evaporation to dryness, the hydroxy ketone was esterified by acetic anhydride. The resulting 2-acetoxycyclohexanone was purified first by distillation and then by glpc on a cross-linked diethylene glycol adipate column at 175°.

E. 1,2-Cyclohexanedione.—After the addition of the monoenol form of the diketone, the reaction mixture was heated at 80° for 15 min to allow the ketone and enol forms of the compound to reach an equilibrium. The required time was calcu-

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[2] To whom all correspondence should be addressed at the Department of Chemistry, University of Illinois, Chicago, Illinois 60680.

[3] G. Petit, *Bull. Soc. Chim. France*, **12**, 568 (1945).

[4] F. Mareš, J. Roček, and J. Sicher, *Collection Czech. Chem. Commun.*, **26**, 2355 (1961).

[5] P. A. Best, J. S. Littler, and W. A. Waters, *J. Chem. Soc.*, 822 (1962).

[6] K. Umeda and K. Tarama, *Nippon Kagaku Zasshi*, **83**, 1216 (1964).

[7] T. J. De Boer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

lated from the data of Long and Bakule.[8] The cooled mixture was then extracted with chloroform and the 1,2-cyclohexanedione was isolated and purified by glpc, SE 30 column at 130°.

Determination of the Ratio of Dicarboxylic Acids Formed in the Oxidation of Cyclohexanone, 2-Hydroxycyclohexanone, 2-Cyclohexen-1-one, 1,2-Cyclohexanedione, and 1,3-Cyclohexanedione.—Chromic acid (0.38 g, 0.0038 mole) was weighed into a 25-ml flask and dissolved in 3.6 g of water. After the addition of cyclohexanone (0.40 g, 0.004 mole), the solution was frozen by immersion of the flask in a Dry Ice–acetone bath. Perchloric acid (1 ml, 5.0 *M*) was added; the flask was closed and evacuated. The contents were allowed to melt and were then mixed and placed in a water bath kept at 50 ± 1° for 15–18 hours, the reaction being protected from light. The concentration of the residual chromic acid was determined spectrophotometrically. Sodium ethylenediamine tetracetate (EDTA, 1.41 g, 0.0038 mole) was added and the reaction mixture heated on a steam bath for about 15 min until it had the dark purple color of the chromium complex. The resulting solution was adsorbed in silica gel (5 g, 28–200 mesh, Fisher) and placed on top of a chromatographic column (10 g of silica gel to which 3.5 g of water had been added, prepared in chloroform). The dicarboxylic acids were then eluted completely with ether, converted to dimethyl esters by diazomethane, and analyzed by glpc on a diethylene glycol adipate column at 200° on a F & M Model 500 chromatograph with a thermal conductivity detector and integrator. The analytical method was checked by using a synthetic mixture of adipic, glutaric, and succinic acids.

The procedure requiring the removal of chromium(III) as a complex with EDTA was adopted after a number of preliminary experiments had shown than the dicarboxylic acids formed rather strong complexes with the chromium ion and could not be recovered unless a stronger complexing agent was supplied.

The experiments in which larger quantities of cyclohexanone-1-C^{14} were oxidized in order to determine the isotopic activity of the dicarboxylic acids were carried out in a very similar way, except that quantities about 20 times larger were used. The final mixture of dimethyl esters was then separated by glpc and the individual fractions were collected in a cooled (Dry Ice–acetone) receiver. In the second of these experiments, chromic acid was added in small portions every 5 min over a period of 3.5 hr in order to keep the chromic acid concentration low and to obtain higher yields of glutaric acid.

Oxidation of 2-Hydroxycyclohexanone.—A solution of 2-hydroxycyclohexanone (105.80 mg, 0.93 mmole) and potassium dichromate (45.70 mg, 0.465 mmole available oxygen) in 10 ml of 1 *M* perchloric acid was heated for 1.5 hr at 50°. After this time the oxidation was completed. The resulting solution was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2 *M* hydrochloric acid. The dinitrophenylhydrazones were isolated by filtration and continuous extraction of the filtrate with ether. The combined dinitrophenylhydrazones were extracted with aqueous sodium bicarbonate solution. From this extract the dinitrophenylhydrazone of adipaldehydic acid was isolated in a 21.0% yield (based on available oxygen) and identified by comparing its melting point, infrared spectrum, and behavior in tlc with those of an authentic sample which was prepared according to Baer.[9] The nonacidic dinitrophenylhydrazones were separated by column chromatography on acid-washed alumina (Merck) into the dinitrophenylhydrazones of 2-hydroxycyclohexanone and of 1,2-cyclohexanonedione and identified by comparison with authentic samples. 1,2-Cyclohexanedione was obtained in a 77.6% yield; hence, 98.6% of the oxygen introduced into the reaction as potassium dichromate was accounted for.

Kinetic Measurements.—The oxidation rates were followed spectrophotometrically in a thermostated cellholder of a Carl Zeiss PMQ II spectrophotometer at 350 mμ. First-order rate constants were determined graphically; second-order rate constants were obtained by dividing the former by substrate concentration. The rate of hydration of 2-cyclohexen-1-one was followed at 308 mμ.

Determination of Radioactivity.—About 30 to 50 mg of a precisely weighed sample were dissolved in 15 ml of the scintillation fluid (PPO and POPOP in toluene) and counted on a Model 701 Nuclear Chicago liquid scintillation counter. Compounds with a low solubility in toluene (*e.g.*, dicarboxylic acids) were first dissolved in a small amount (0.5 to 1 ml) of absolute ethanol. The counting time was always long enough to allow for at least 10,000 counts to be registered.[10] Averages of at least two countings were used in the calculation. In order to correct for quenching, about 0.5 ml of an exactly weighed sample of toluene-C^{14} was added as internal standard and the counting was repeated. For the determination of $C^{14}O_2$, the reaction flask, at the conclusion of the reaction, was cooled by liquid nitrogen for about 1 hr in order to condense all carbon dioxide at the bottom of the flask. The flask was then opened and immediately connected to an apparatus in which, after allowing the contents of the flask to come to room temperature, the carbon dioxide was distilled from the reaction flask into 1 ml of a solution of hyamine hydroxide by a slow stream of pure nitrogen. The gases were passed through a flask of concentrated sulfuric acid in order to remove all organic vapors, particularly cyclohexanone-1-C^{14}. The hyamine solution was counted in the liquid scintillation counter only after being allowed to stand in the dark for at least 1 hr to eliminate the disturbing effects of chemiluminescence. The procedure was tested by using $NaHC^{14}O_3$ solutions of known carbon content. Also, in blank experiments using cyclohexanone-C^{14}, it was demonstrated that the vapors of the ketone are completely removed by washing with sulfuric acid and that they do not pass into the hyamine solution.

Calculation of the Tracer Experiments.—The yields were expressed in per cent of cyclohexanone-1-C^{14} and in per cent of available oxygen as calculated from the following equations

$$\%\ (\text{cyclohexanone-1-}C^{14}) = \frac{100 \times F}{S}$$

$$\%\ (\text{oxygen}) = \frac{100 \times F \times E}{O}$$

where *S* and *O* are the initial amounts (in millimoles) of the substrate (cyclohexanone) and of available oxygen. *E* is the number of oxygen atoms required for the formation of the product (*e.g.*, three for adipic acid, six for glutaric acid, etc.). *F* is the amount (millimoles) of the product present and is calculated from the relationship

$$F = \frac{B \times I}{A}$$

where *A* is the activity of the substrate, *I* the amount (millimoles) of unlabeled product added for dilution, and *B* the activity of the product expressed in decompositions per minute (dpm) per millimole of the product. *B* was determined in the usual way using an internal standard and correcting for background counts.

Results

Reaction Products.—The results of the isotopic dilution analysis of the products formed in the oxidation of cyclohexanone-1-C^{14} are given in Table I. In column A the results are expressed directly for the distribution of C^{14} in the reaction products. All determinations are averages of at least two measurements. The relative standard deviation of the individual measurements was less than 2% of the average values.

The results in column A give only the yields of products formed without loss of the radioactive label. In order to calculate the total yield of compounds in which one or more carbon atoms were lost, the specific activities were determined in a larger scale experiment without dilution with a nonactive sample. The results of this study are given in Table II.

Using the values of specific activities, 84% for glutaric[11] and 50% for succinic acid, we could then cal-

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[8] F. A. Long and R. Bakule, *J. Am. Chem. Soc.*, **85**, 2313 (1963).

[9] E. Baer, *ibid.*, **64**, 1419 (1962).

[10] R. T. Overman and H. M. Clark, "Radioisotope Techniques," McGraw-Hill Book Co., New York, N. Y., 1960, p 116.

[11] We preferred to use 0.84 as the average value for the specific activity for glutaric acid rather than the average value (0.83) because of the larger amount of the available sample and, consequently, higher degree of purity of the isolated glutaric ester in expt II.

culate the actual amounts of the dicarboxylic acids formed and from them the yields based on both cyclohexanone (Table I, column B) and on the amount of available oxygen introduced into the reaction in the form of chromic acid (Table I, column C).

Table I
Isotope Dilution Analysis of Products in the Oxidation of Cyclohexanone-1-C^{14} in 1 M Aqueous Perchloric Acid at 50°[a]

Product	Yield, % A C^{14}	B Cyclohexanone	C Oxygen
Cyclohexanone (recovered)	61.25	61.25	...
Adipic acid	25.93	25.93	67.2
Glutaric acid	2.90	3.46	17.5
Succinic acid	0.76	1.52	10.6
Oxalic acid	0.17	c	c
Carbon dioxide	1.04	c	c
2-Hydroxycyclohexanone	2.38	2.38	2.34
1,2-Cyclohexanedione	1.62	1.62	2.86
2-Cyclohexen-1-one[b]	0.15	0.15	0.12
Total	96.20	96.31	100.62

[a] The concentration of cyclohexanone-1-C^{14} was 0.0058 M (average) and that of CrO_3 was 0.0050 M. [b] Estimated from the result 0.17% of C^{14} and 0.38% O obtained using 0.0029 M CrO_3 and 0.0098 M cyclohexanone. [c] Included in corrected values of glutaric and succinic acid.

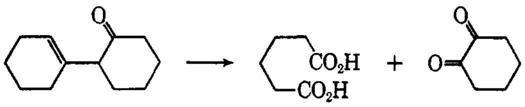
Table II
Specific Activities of the Dicarboxylic Acids Formed in the Oxidation of Cyclohexanone by Chromic Acid[a]

	Activity, dpm/mmole Expt I	Activity, dpm/mmole Expt II	C^{14}, % Expt I	C^{14}, % Expt II
Cyclohexanone[b]	1.22×10^5	6.17×10^4	...	...
Adipic acid	1.12×10^5	6.12×10^4	100	100
Glutaric acid	0.92×10^5	5.12×10^4	82	84
Succinic acid	0.55×10^5	3.13×10^4	49	51

[a] Concentrations used were 1 M $HClO_4$, 0.75 M CrO_3, and 0.81 M cyclohexanone; at 50°. [b] Calculated starting activity.

The amount of radiocarbon lost in the oxidation of cyclohexanone to glutaric and succinic acid should therefore amount to 1.32% and should be present among the final reaction products as oxalic acid and carbon dioxide. It can be seen from Table I that the total amount of these two products (1.21%) approaches the calculated figure fairly well. As the amount of labeled carbon dioxide is considerably higher than that of oxalic acid, the formation of the latter was neglected in the computation of the amount of oxygen used in the formation of succinic acid (Table I, column C).

The losses in C^{14} (column A) are due to condensation reactions of cyclohexanone.[12-14] This was demonstrated in an experiment in which cyclohexanone-1-C^{14} was subjected to the same reaction conditions used during the oxidation experiments except for the absence of chromic acid. A loss of 19% of cyclohexanone has been observed. This amount is actually greater than the deficiency observed in Table I. In the presence of chromic acid the condensation product, 2-cyclohexen-1-ylcyclohexanone, will react with chromic acid (eq 1) to yield products (*e.g.*, adipic acid, 1,2-cyclohexanedione) which have been determined. The portion of cyclohexanone which undergoes condensation at the time when still enough chromic acid is present is therefore not lost, but will be registered in one form or another. Only the condensation products formed after most of the chromic acid has been used up, will actually be responsible for the deficiency in C^{14}.



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Reaction Intermediates.—To obtain more information about the way in which the final products are formed, we subjected cyclohexanone and a selected number of possible reaction intermediates to oxidation by chromic acid under comparable conditions and analyzed the reaction products. In this part of the study we used unlabeled compounds, isolated the dicarboxylic acids, and determined their ratio by integration of the glpc curves of their respective esters. The results are given in Table III.

Table III
Products of the Chromic Acid Oxidation of Possible Intermediates[a]

Substrate	Major product	Composition of dicarboxylic acids formed, % Adipic	Glutaric	Succinic
Cyclohexanone	Adipic acid	92.9	4.3	2.8
2-Cyclohexen-1-one	Glutaric acid	1.5	93.7	4.9
1,2-Cyclohexanedione[b]	Glutaric acid	6.8	55.2	38.1
1,3-Cyclohexanedione	Glutaric acid	0.0	74.6	25.4
2-Hydroxycyclohexanone	Adipic acid	95.4	3.4	1.2
		94.2	4.4	1.3

[a] Reaction conditions were 1 M $HClO_4$, 0.75 M CrO_3, and 0.40 M substrate at 50°. [b] Monoenol form.

Inspection of Table III will show that only 2-hydroxycyclohexanone gives a composition of reaction products similar enough to those from cyclohexanone to be considered a common reaction intermediate. The other two compounds of the same oxidation level, 2-cyclohexen-1-one and 3-hydroxycyclohexanone (investigated indirectly by using 1,3-cyclohexanedione), formed at most only small amounts of adipic acid and yielded glutaric acid as the main reaction product.

Effect of Concentration on the Composition of Reaction Products.—Comparison of Table I with Table III will reveal that the ratio of dicarboxylic acids formed in the two sets of experiments is not exactly the same. The amounts of the lower dicarboxylic acids formed in the isotopic dilution experiments (Table I) are clearly higher than those obtained by glpc analysis of the large scale experiments (Table III). The conditions for both sets of experiments (temperature, acidity, ratio of oxidant to substrate) were essentially identical. The only difference was in the much higher concentrations used in the second set of experiments. In order to check to what extent the results might be influenced by the method of analysis, we used the isotopic dilution method at high concentration of substrate and chromic acid. The results summarized in Table IV clearly demonstrate that the difference is

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(12) J. Resse, *Ber.*, **75**, 384 (1942).

(13) J. Plešek, *Collection Czech. Chem. Commun.*, **21**, 375 (1956).

(14) J. Mleziva, *Chem. Listy*, **47**, 1031 (1953); *Chem. Abstr.*, **48**, 13642 (1954).

TABLE IV

COMPOSITION OF THE DICARBOXYLIC ACIDS FORMED IN THE OXIDATION OF CYCLOHEXANONE IN 1 M PERCHLORIC ACID AT 50°

CrO_3, M	Cyclohexanone, M	Method of analysis	Composition of dicarboxylic acids, % — Adipic	Glutaric	Succinic
0.0050	0.0058	Isotopic dilution[a]	83.9	11.2	4.9
0.75	0.40	Glpc of esters	92.9	4.3	2.8
0.763	0.823	Isotopic dilution[a]	92.6	5.0	2.4

[a] In calculating the yields of glutaric and succinic acid it was assumed that they retain 84 and 50%, respectively, of the C^{14} originally present in the substrate.

real and not affected by the analytical method. Table V shows the dependence of the yield of glutaric acid as a function of concentration of the reactants. This finding also makes it easier to understand why none of the previous workers noticed the formation of the lower dicarboxylic acids, the formation of which is less noticeable the more one approaches conditions for preparative work.

TABLE V

DEPENDENCE OF THE YIELD OF GLUTARIC ACID ON THE CONCENTRATION OF THE REACTANTS 1 M PERCHLORIC ACID AT 50°

CrO_3, M	Cyclohexanone, M	C^{14} found as glutaric acid, %
0.0050	0.0058	2.90
0.255	0.275	1.88
0.763	0.823	1.26

Oxidation Rates.—Only those products which are not too reactive towards chromic acid can be expected to be found in detectable amounts among the reaction products. It was therefore essential for our purposes to determine the rates of oxidation of a number of possible reaction intermediates and reaction products. The data are given in Table VI, together with rate measurements for some other related compounds of interest.

TABLE VI

THE SECOND-ORDER RATE CONSTANTS FOR THE CrO_3 OXIDATION OF SEVERAL KETONES AND RELATED COMPOUNDS[a]

Substrate	k_2, M^{-1} min^{-1}
Cyclohexanone	0.151
Cyclohexanol	1.43
2-Hydroxycyclohexanone	4.53
2-Cyclohexen-1-one	2.10
1,2-Cyclohexanedione	
keto form	4.8[b]
monoenol	2000[c]
1,3-Cyclohexanedione	78[d]
Oxalic acid	0.445
Acetone	0.0021
Methyl ethyl ketone	0.0071
3-Methyl-2-butanone	0.238
3-Hydroxy-3-methyl-2-butanone	3.40

[a] Reaction conditions were 1.0 M $HClO_4$ and 5.4×10^{-4} M CrO_3 at 30°. [b] Estimated value; *cf.* Discussion. [c] Extrapolated from $k_2 = 200$ M^{-1} min^{-1} in 0.10 M $HClO_4$. [d] Approximate value.

Some of the rate data in Table VI deserve comments. 1,2-Cyclohexanedione exists predominantly in its monoenol form.[15] It is the oxidation rate of this enol which is given in the table. The keto form of the dione has never been prepared in a pure enough form to make it possible to measure its oxidation rate directly. An estimate of the rate will, however, be made in the discussion.

Similarly, the highly enolized[16] 1,3-cyclohexanedione undergoes a very rapid oxidation.

A rather surprising finding is the high oxidation rate of 2-hydroxycyclohexanone. Generally, it is found[17] that electronegative groups retard the oxidation of a hydroxyl group very considerably. In this case, however, the hydroxy ketone is oxidized faster than cyclohexanol. Even though the rate acceleration is not large in itself, the size of the increase becomes more significant when one realizes that a strongly electronegative group like the carbonyl would be expected to slow down the oxidation by about a factor of 10.

Hydration of 2-Cyclohexen-1-one and Dehydration of 2-Hydroxycyclohexanone.—The rate and equilibrium for the hydration of 2-cyclohexen-1-one under the conditions used in our oxidation experiments (1 M $HClO_4$, 50°) were measured spectrophotometrically using the absorption maximum of the unsaturated ketone at 308 mμ. Calculated in the usual way for reversible processes, the following constants were obtained.

$$K_{\text{hydration}} = \frac{[\text{3-hydroxycyclohexanone}]}{[\text{2-cyclohexen-1-one}]} = 0.22$$

$$k_{\text{hydration}} = 1.06 \times 10^{-2}\ \text{min}^{-1}$$

$$k_{\text{dehydration}} = 4.8 \times 10^{-2}\ \text{min}^{-1}$$

Once the equilibrium between 3-hydroxycyclohexanone and 2-cyclohexen-1-one was reached, no further change in the spectrum could be observed, indicating that the equilibrium mixture is stable and no condensation reactions are taking place. The spectrum of the equilibrium mixture is that expected for a mixture of an unsaturated and a saturated ketone.

For 2-hydroxycyclohexanone a completely different picture was observed. When followed by measuring the absorbance at 308 mμ a very slow steady increase could be noticed. However, when the complete spectrum was measured after 15 hr, only a continuously increasing absorption towards the shorter wavelengths was observed. The dehydration to 2-cyclohexen-1-one if taking place at all, is clearly not the only process. The principal reaction is probably a condensation process leading to a complex mixture of product. Even though the rate of formation of cyclohexen-3-one from 2-hydroxycyclohexanone cannot be determined, an upper limit for the reaction rate can be calculated if one assumes that all the absorption at 308 mμ is due to the formation of the unsaturated ketone. The actual rate of dehydration of the 2-hydroxycyclohexan-

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[15] R. Bakule and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2309 (1963).

[16] C. Tamm and R. Albert, *Helv. Chim. Acta*, **43**, 768 (1960).

[17] J. Roček, *Collection Czech. Chem. Commun.*, **25**, 1052 (1960).

one then can be anywhere between this value and zero. The value found for this upper limit is ~10^{-4} min^{-1} at 50°.

Discussion

A. The First Oxidation Product, 2-Hydroxycyclohexanone.—Of the various oxidation products which could be formed from cyclohexanone and the equivalent of one oxygen atom only one, namely 2-hydroxycyclohexanone, yields the same oxidation products as cyclohexanone (Table III) and must, therefore, be considered as the major reaction intermediate. Furthermore, its presence among the reaction products was directly demonstrated (Table I).

More quantitatively, the role of 2-hydroxycyclohexanone as a reaction intermediate was assessed by comparison of the experimentally determined yields with those calculated for a sequence of consecutive reactions (see Appendix). The results given in Table VII show an excellent agreement between the two values, indicating clearly that the hydroxyketone must be either the major or sole reaction intermediate and is produced as a free molecule and does not undergo further oxidation while still complexed with the chromium(IV) species.

Table VII

2-Hydroxycyclohexanone as Intermediate in the Oxidation of Cyclohexanone in 1 *M* Perchloric Acid at 50°

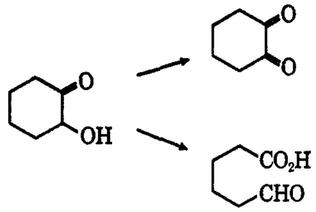
Cyclohexanone, *M*	CrO_3, *M*	2-Hydroxycyclohexanone yield, % Calcd	2-Hydroxycyclohexanone yield, % Found
0.0058	0.0050	2.24	2.38
0.035	0.0050	2.87	2.71

B. 2-Cyclohexen-1-one.—As this ketone is oxidized mostly to glutaric acid, it obviously cannot be an important intermediate in the oxidation of cyclohexanone. Nevertheless, in the isotopic dilution analysis even most careful purification and conversion of the unsaturated ketone into a derivative followed by further purification could not completely remove its radioactivity. We are therefore forced to assume that a small amount of the unsaturated ketone is indeed formed. Unfortunately, the question whether it is formed as a direct oxidation product from cyclohexanone or indirectly from another intermediate cannot be decided at the present time.

Using the equations for consecutive reactions given in the appendix, it is possible to estimate from the known oxidation rates and yields of the intermediate (*i.e.*, cyclohexenone) which fraction of cyclohexanone could undergo oxidation *via* this particular intermediate. This calculation shows that about 2.8% of the total amount of cyclohexanone could be oxidized by way of the unsaturated ketone. However, as cyclohexenone is oxidized predominantly to glutaric acid, we should then assume that the yield of glutaric acid in the oxidation of cyclohexanone should be by about this amount higher than that obtained in the oxidation of hydroxycyclohexanone. As this is obviously not the case (Table III), the formation of cyclohexenone by oxidation of cyclohexanone is doubtful.

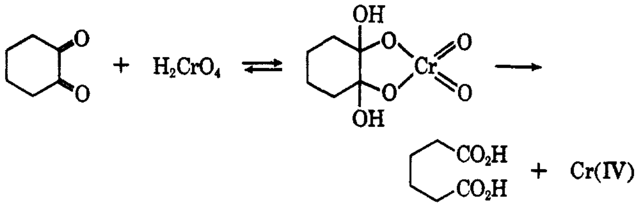
Another possibility is that cyclohexenone is formed from 2-hydroxycyclohexanone by dehydration. This reaction is very slow if it takes place at all. However, the upper limit of 10^{-4} min^{-1} which we placed on the rate of dehydration of 2-hydroxycyclohexanone is still high enough to allow the formation of the very small amounts of the unsaturated ketone found among the reaction products.

The Formation of Adipic Acid.—Adipic acid, as the major product of the oxidation, must clearly be formed through the intermediacy of 2-hydroxycyclohexanone. From there on two different routes for the formation of adipic acid have to be considered, oxidation to 1,2-cyclohexanedione or ring cleavage to yield the monoaldehyde of adipic acid.



An experiment in which an excess of the hydroxyketone was oxidized showed that the dione is formed in a 77% yield whereas not more than 21% of the aldehydoacid could be detected.

It has been shown in Table III that the stable monoenol form of the dione gives almost only glutaric and succinic acids and almost no adipic acid at all. The oxidation of the dione must therefore clearly proceed as a direct oxidation of the keto form without the intervention of an enol intermediate. In analogy with the previously studied oxidation of ditertiary glycols,[18,19] we may assume that the reaction may proceed through a cyclic ester intermediate.



It has been mentioned in a previous section that the rate of oxidation of the diketone cannot be measured directly because of the inaccessibility of the pure keto form. However, the oxidation rate cannot be much higher than that of the hydroxy ketone, because otherwise a good yield of the diketone could not have been isolated in the oxidation of the hydroxy ketone. On the other hand, were the oxidation rate slower or about the same as that of the cyclohexanone, most of the diketone would accumulate as a reaction product and very little adipic acid would be found in the oxidation of cyclohexanone where the substrate is present in excess. As 2-hydroxy ketone is only about 40 times more reactive toward chromic acid than cyclohexanone the oxidation rate of 1,2-cyclohexanedione has to fit into these rather narrowly defined limits. Using again the expression for the yield of an intermediate in a series of consecutive reactions together with the known oxidation rate of 2-hydroxycyclohexanone, the yield of cyclohexanedione formed in the oxidation of

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[18] Y. W. Chang and F. H. Westheimer, *J. Am. Chem. Soc.*, **82**, 1401 (1960).

[19] J. Roček and F. H. Westheimer, *ibid.*, **84**, 2241 (1962).

the hydroxy ketone, and the yield of the diketone formed in the oxidation of cyclohexanone (Table I), we can calculate an approximate value of 4.8 M^{-1} min^{-1} for the rate constant for the oxidation of the keto form of 1,2-cyclohexanedione. Comparison of this value with the rate constant for the oxidation of the monoenol form reveals that the enol is more reactive than the diketone by a factor of about 400.

The Origin of Succinic Acid in the Oxidation of Cyclohexanone. Induced Oxidation of Adipic Acid.—Succinic acid is a product of extensive degradation (the equivalent of nine oxygen atoms is needed to convert cyclohexanone to succinic acid and two molecules of carbon dioxide). It could be formed either by an independent path starting with the attack of cyclohexanone in the 4 position or, alternatively, by a further oxidation of one of the other oxidation products. Adipic acid would certainly serve as a suitable candidate for the latter alternative, as it is formed in rather large amounts and could, at least in principle, yield succinic acid by a sequence of reactions starting with the oxidative attack on the more reactive[20] β-methylene group.

However, there is one obvious difficulty for using this interpretation; the reactivity of adipic acid towards chromium(VI) is so low[20,21] that a degradation of adipic acid by chromic acid, *i.e.*, by a hexavalent chromium species, can be definitely ruled out. From our previous measurements[4,20] we can estimate that cyclohexanone would react with chromium(VI) at least 10,000 times faster than adipic acid.

On the other hand, it is known[22,23] that reactive chromium(IV) and chromium(V) intermediates are formed during oxidation with chromic acid and further that these compounds are often capable of oxidizing compounds unreactive toward chromium(VI). As a result, some compounds unreactive to chromium(VI) itself can undergo oxidation if subjected to the action of chromic acid in the presence of a substrate capable of reducing chromium(VI) to the intermediate valence states. This "induced oxidation" has been observed in the past for some inorganic species, *e.g.*, manganous, cerous, or iodide ions; however, no clearly demonstrated induced oxidation of an otherwise unreactive organic substrate has been recorded in the literature.

Therefore, even though the formation of succinic acid cannot be explained in terms of oxidation of adipic acid by chromium(VI), the possibility exists that such a degradation can take place at a fast enough rate by the intermediate chromium valences. To check this possibility, we have analyzed the dicarboxylic acids formed in the oxidation of a model ketone in the presence of adipic acid. As the ketone we selected 3-methyl-2-butanone which has a reactivity toward chromic acid comparable with that of cyclohexanone (3-methyl-2-butanone reacts 1.58 times faster than cyclohexanone) and which is definitely not expected to yield any succinic acid upon oxidation. Table VIII gives a comparison of the ratios of dicarboxylic acid obtained in the direct oxidation of cyclohexanone with those formed in the induced oxidation of adipic acid using 3-methyl-2-butanone as the inductor. Both glutaric acid and succinic acid are formed in the reaction. The amount of succinic acid is high enough to account for all the succinic acid found in the oxidation products of cyclohexanone. Even though other ways of formation of succinic acid are possible, it seems likely that the major part of this product was indeed formed through adipic acid as an intermediate. As in adipic acid the radioactive label residing originally in the carbonyl group must be equally divided between the carbonyl groups, one half of the radioactivity must be lost in the formation of succinic acid from adipic acid. Although this is in full agreement with the experimentally determined specific activity of succinic acid (Table II), it cannot be applied as proof for the suggested mechanism of formation of succinic acid as any other route proceeding through a symmetrical intermediate would lead to the same prediction. The induced oxidation of adipic acid is discussed in more detail elsewhere.[24]

TABLE VIII

COMPARISON OF THE AMOUNTS OF GLUTARIC AND SUCCINIC ACID FORMED IN THE OXIDATION OF CYCLOHEXANONE AND IN THE INDUCED OXIDATION OF ADIPIC ACID IN 1.0 M PERCHLORIC ACID AT 50°

Reactants	Concn, mole/l.	Composition of dicarboxylic acids in reaction products, % Adipic	Glutaric	Succinic
Cyclohexanone	0.40	92.9	4.3	2.8
H_2CrO_4	0.75			
$(CH_3)_2CHCOCH_3$	1.5	94.2	2.3	3.5
H_2CrO_4	0.75			
$HO_2C(CH_2)_4CO_2H$	0.137			

The Formation of Glutaric Acid.—The rather surprising finding that glutaric acid is formed with 84% retention of the C^{14} label leads to the conclusion that this product must be formed in at least two different ways, by one route in which no label is lost or by another which would occur with either complete or 50% loss of the radiocarbon. Assuming the latter alternative to be the more probable one, we suppose that about one-third of the glutaric acid is formed through a symmetrical intermediate with loss of half of the radiocarbon label, whereas two-thirds originate from a process in which no carbon-14 is lost.

A. Formation with Loss of Carbon-14.—It has been shown in the previous paragraph that adipic acid undergoes induced oxidation in the presence of cyclohexanone acting as an inductor. Table VIII shows that besides succinic acid, which is the major reaction product, a considerable amount of glutaric acid is also produced. Being formed through a symmetrical intermediate, this glutaric acid would, of course, have lost 50% of the radiocarbon originally present. The amount of glutaric acid formed in the induced oxidation is large enough to account for the required one-third of the total amount. We assume therefore that induced oxidation of adipic acid is the major or only source of glutaric acid formed with loss of radiocarbon at high concentrations of the reactants.

However, as has been shown in Table IV and V, the relative amount of glutaric acid formed depends on the

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(20) F. Mareš and J. Roček, *Collection Czech. Chem. Communs.*, **26**, 2389 (1961).

(21) H. C. S. Snethlage, *Rec. Trav. Chim.*, **56**, 873 (1937); **59**, 111 (1940); **60**, 710 (1941).

(22) For an excellent review, see F. H. Westheimer, *Chem. Rev.*, **45**, 419 (1949), and Errata, June 1950.

(23) K. B. Wiberg and H. Schäfer, *J. Am. Chem. Soc.*, **89**, 455 (1967).

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

concentration of the reactants and increases considerably with increasing dilution. Unfortunately, we are unable to determine whether this additional amount of glutaric acid is formed with or without loss of the radiocarbon label (because the determination of specific activity could be carried out only using larger amounts and hence high concentrations). Nevertheless, one mode of formation of glutaric acid, which seems to us particularly interesting and likely, would lead to the formation of additional amounts of this acid with loss of half of the label, and we will therefore discuss it in this section.

In an earlier section it was shown that 1,2-cyclohexanedione is a reaction intermediate in the formation of adipic acid. It has further been demonstrated that the more stable monoenol form of the dione is oxidized predominantly to glutaric acid.

The rate of enolization of the dione has been studied by Long and Bakule.[8] From their data it is possible to estimate that, under the conditions which we used in our studies, the rate of enolization would be about 4.6×10^{-4} min^{-1}. On the other hand, we estimated the rate of oxidation to be 4.8 M^{-1} min^{-1}. Assuming the rate laws of the enolization and oxidation of the dione to be

$$v_{\text{enolization}} = k_1\,[\text{dione}]\,[\text{H}^+]$$
$$v_{\text{oxidation}} = k_2\,[\text{dione}]\,[\text{CrO}_3]\,[\text{H}^+]$$

the ratio of glutaric to adipic acid should be indirectly proportional to the concentration of chromic acid

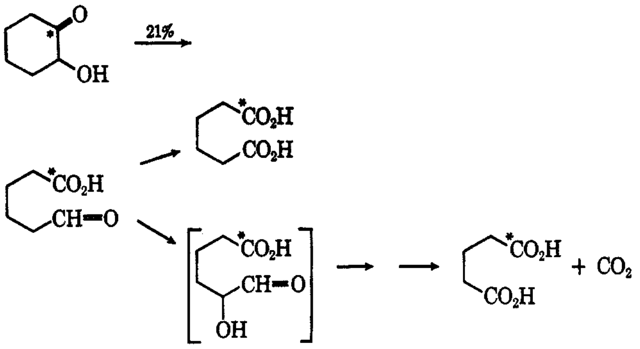
$$\frac{[\text{glutaric acid}]}{[\text{adipic acid}]} = \frac{v_{\text{enolization}}}{v_{\text{oxidation}}} = \frac{k_1}{k_2\,[\text{CrO}_3]}$$

with k_1/k_2 having the approximate value of 10^{-4} M^{-1}. It follows then that at very low concentration of chromic acid some glutaric acid should indeed be formed by way of oxidation of the cyclohexanedione enol, whereas this route will be unimportant at higher chromic acid concentrations. We consider it therefore quite likely that it is this enolization of the diketone intermediate which is primarily responsible for the variation of the yield of the lower dicarboxylic acids with the concentration of the reactants[25] (Tables IV and V).

B. Formation of Glutaric Acid without the Loss of Carbon-14.—As has been discussed in a previous section, a certain small amount of the oxidation possibly proceeds through 2-cyclohexen-1-one. We have also shown that cyclohexenone is oxidized to glutaric acid as the main oxidation product. As there is little doubt that this oxidation would proceed with the loss of the carbon α to the carbonyl group, no loss of the radioactive label could be expected. This process could therefore explain the formation of some glutaric acid with fully preserved activity.

We have, however, shown that the yields of glutaric acid are almost the same from cyclohexanone and from 2-hydroxycyclohexanone. As the dehydration of the hydroxyketone to the unsaturated ketone is too slow (if it occurs at all) to compete with the oxidation at least at higher concentrations of chromic acid,[26] another route to glutaric acid is required.

2-Hydroxycyclohexanone yields, on oxidation, adipaldehydic acid (21%). In this compound all the carbon-14 label will be in the carboxyl group. The aldehydo-acid will undergo further oxidation in the aldehydic group to yield adipic acid as the major product. If, however, a part of the oxidation would proceed in the α position to the aldehydic carbonyl group, then a degradation to glutaric acid without the loss of label would result.



The degradation of the carbon chain in the oxidation of aldehydes has indeed been observed by Bernard and Karayannis,[27] who found considerable amounts of propionic acid besides butyric acid and small amounts of acetic acids among the oxidation products of butyraldehyde. From their results it can be estimated that about 70% of the aldehydic group is oxidized directly to the carboxyl group, whereas about 30% undergoes degradation to the lower homolog. Assuming the same proportion to hold approximately for the monoaldehyde of adipic acid, we would expect the formation of about 6% of glutaric acid. This is obviously in excess of the amount of glutaric acid which is formed without loss of label. This means that even if the α oxidation in adipaldehydic acid should be less important than in butyraldehyde, we can still explain the formation of glutaric acid by this process without difficulty.

Registry No.—2-Hydroxycyclohexanone, 533-60-8; adipic acid, 124-04-9; succinic acid, 110-15-6; glutaric acid, 110-94-1; oxalic acid, 144-62-7; carbon dioxide, 124-38-9; 1,2-cyclohexanedione, 765-87-7; 2-cyclohexen-1-one, 930-68-7; chromic acid, 10553-72-7; cyclohexanone, 108-94-1; cyclohexanone-1-C^{14}, 13952-89-1; 1,3-cyclohexanedione, 504-02-9; 3-methyl-2-butanone, 563-80-4.

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Appendix

Quantitative evaluation of a compound as a reaction intermediate is expressed in the following manner.

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(25) Actually, if our interpretation is correct, then the difference between the yields at the low and at the high concentration of chromic acid should be even higher than is indicated by the data in Table IV. As we assume that the difference between the lower and higher yield of glutaric acid is due to the oxidation of the 1,2-cyclohexanonedione *via* its monoenol form then we have to assume that all the additional glutaric acid is formed with a loss of 50% radioactive label.

(26) The slow dehydration of the hydroxyketone might be another concentration-dependent route to glutaric acid.

(27) J. A. Barnard and N. Karayannis, *Anal. Chim. Acta*, **26**, 253 (1962).

For a reaction of the type

$$A + B \rightarrow C$$
$$A + C \rightarrow \text{products}$$

rate eq 1 and 2 can be written

$$dB/dt = -k_1[A][B] \qquad (1)$$
$$dC/dt = k_1[A][B] - k_2[A][C] \qquad (2)$$

Combination of eq 1 and 2 and integration leads to expression 3[28]

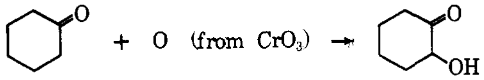
$$[C] = \alpha[B]\left[1 - \left(\frac{[B]}{[B]_0}\right)^{1/\alpha}\right] \qquad (3)$$

which expresses the concentration of the reaction intermediate C as a function of the initial and residual concentration of the starting material. In eq 3 the constant $\alpha = k_1/(k_2 - k_1)$.

From eq 3 the final concentration of the intermediate C can be calculated if the final concentration of the substrate B is known and the rate constants k_1 and k_2 are available.

The final concentration of the substrate can be either determined directly (as in Table I) or estimated from the initial concentration $[B_0]$, the amount of oxidant introduced into the reaction, and the over-all stoichiometry of the reaction. In the oxidation of cyclohexanone, where adipic acid is formed as the major product, we assume that approximately one molecule of substrate is consumed per two molecules of CrO_3.

Oxidation rates for the substrate and the intermediate can usually be measured directly, but are most commonly expressed in terms of concentration changes of the oxidant rather than of the substrate and intermediate. In order to calculate k_1 and k_2 the stoichiometry under the conditions of the kinetic runs is needed. The calculation can be demonstrated for the example of 2-hydroxycyclohexanone. This intermediate is oxidized about 30 times faster than cyclohexanone. However, in the kinetic runs, cyclohexanone is used in a 100:1 ratio to oxygen available (in the form of chromic acid). When about 10% of the reaction is over, the ratio of cyclohexanone to the hydroxyketone will be 1000:1, and about 97% of the oxidant will react with the ketone and only about 3% will react with the reaction intermediate. As the reaction rates are determined from extrapolation to zero time when any curvature is observed, the experimental rate constant refers clearly to the reaction



and k_1 will therefore be equal to the experimentally determined rate constant. If, on the other hand, the intermediate is more reactive than the substrate by several orders of magnitude, the rate of disappearance of the substrate may be several times lower than the observed rate constant.

The whole treatment, although very useful and informative in evaluating the importance of different routes *via* alternative reaction intermediates, has an inherent limitation to its accuracy even if all the constants needed in eq 3 can be determined precisely. The constants k_1 and k_2 are measures of the reactivity of the substrate and intermediate toward Cr(VI). Actually, however, two-thirds of the oxidation is carried out by intermediate valence states, Cr(V) and/or Cr(IV). The present treatment would be exactly valid only if the relative reactivities of the substrate and intermediate remained the same for all valence states of chromium. We know, however, that this condition is not fulfilled precisely, even though we may accept it as a first approximation. Within the limitations and uncertainties just discussed, the treatment proved to be a valuable tool and gives at least very useful semiquantitative results.

Equation 3 is also useful in finding the optimal conditions for the detection and quantitative determination of a reaction intermediate. The maximum yield of C calculated from the condition $dC/dB = 0$, will be obtained when

$$\log [B]_0/[B] = \alpha \log k_1/k_2 \qquad (4)$$

In the experiments in which we tried to verify the formation of a reactive compound and to determine its importance as an intermediate we have always used reaction conditions close to those required by eq 4.

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[28] Z. Cihla, *Collection Czech. Chem. Commun.*, **26**, 2367 (1961).

Conformational Effects in Cyclic Olefins. The Relative Rates of Iodomethylzinc Iodide Addition[1]

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The relative rates of cyclopropane formation using iodomethylzinc iodide have been determined for a number of cyclic olefins. The normal sequence cyclopentene > cycloheptene > cyclohexene is followed. The unusually low rate factors associated with alky and aryl substitution suggest a balance between small inductive and steric effects for this reaction. Norbornene reacts only 70% faster than cyclohexene. The slightly diminished rates exhibited by 4-alkylcyclohexenes are shown to be due to steric rather than inductive effects.

We have previously reported[2] the results of a kinetic study of epoxidation of a number of alkyl- and dialkylcyclohexenes. The values obtained were used in conjunction with stereochemical data to evaluate the conformational preference of 4-methylcyclohexene (equatorial conformer preferred by ~1 kcal/mole). Intrinsic in this evaluation were two assumptions: first, that the conformation of the six-membered ring,

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[1] Support by the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation is gratefully acknowledged.

[2] B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).