



solution was neutralized with aqueous sodium hydroxide and 70 cc. of liquid distilled from the mixture. (Subsequently, 2.7 g. (33% yield) of benzoic acid was isolated from the alkaline solution.) The distillate, which contained water, pivalophenone and *t*-butyl alcohol, was heated on a steam-bath for 18 hours with 10 cc. of concd. hydrochloric acid and 3.2 g. of thioglycolic acid. The mixture was extracted with ether; the ether layer was washed with water, and then extracted with 5% sodium hydroxide solution. Pivalophenone was isolated from the ethereal residue and identified as its oxime. The aqueous sodium hydroxide solution, containing the anion of *S-t*-butylthioglycolic acid, was converted, *via* the acid, to the corresponding anilide,<sup>9,10</sup> m.p. 80–80.9°. The melting point was not depressed when the sample was mixed with authentic anilide of *S-t*-butylthioglycolic acid.

**Deuterobenzaldehyde.**—A 0.50-g. sample of the deuterocarbinol was oxidized with 0.30 g. of  $\text{CrO}_3$  in 20 cc. of 86.5% acetic acid plus 2.3 g. of sodium acetate. The resulting solution was diluted with 100 cc. of water, saturated with salt and extracted with ether. The ether layer was washed with bicarbonate solution, dried and the ether evaporated. The residue, which contained unreacted carbinol as well as the oxidation and cleavage products, was heated on a steam-bath for 5 minutes with a drop of piperidine and a solution of 0.42 g. of methone in 8 cc. of 50% ethanol. The mixture was cooled and filtered; the solid filter-cake was extracted with petroleum ether to remove ketone and unreacted carbinol from the benzaldehyde-methone. The crude derivative was recrystallized from aqueous methanol to yield pure benzaldehyde-methone, m.p. 191.5–193° (lit.<sup>11</sup> m.p. 194–195°).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{17}\text{DO}_4$ : atom % D, 3.57. Found: atom % D, 3.50.

#### Determination of Cleavage Yield

**High Chromic Acid Concentrations.**—An excess of chromic acid was used to oxidize all the benzaldehyde to benzoic acid. Control experiments showed that pivalophenone is stable under the experimental conditions employed. The reaction mixture was made up in accordance with the concentrations shown in Table III, and with a total of 3 g. of carbinol. After the oxidation was complete, the solutions were diluted with about five volumes of water, saturated with salt and extracted with ether. The ether layer was then extracted with aqueous bicarbonate solution, and dried. Pivalophenone was isolated from the ether as its oxime. The aqueous bicarbonate extract was acidified, saturated with salt and extracted with ether. The ether was washed several times with ice-water to remove residual acetic acid and then evaporated; the resulting benzoic acid was recrystallized from hot water, filtered, dried and weighed. The yield of benzoic acid varied from a few milligrams to about a gram. When comparable amounts of benzoic acid were subjected to this isolation procedure, the recovery was about 95%.

**Low Chromic Acid Concentrations.**—A large excess of carbinol was used to suppress the oxidation of benzaldehyde to benzoic acid. The amount of benzaldehyde formed was estimated by an isotopic dilution technique, and the fraction cleavage calculated on the basis of the stoichiometry of equations 1a and 1b.

For example, in experiment E<sub>3</sub>, 40 cc. of a reaction mixture was prepared containing 0.05 *M* deuterocarbinol, 0.02 *M*  $\text{HClO}_4$ , 0.005 *M*  $\text{CrO}_3$  and 0.100 *M* sodium perchlorate. After the mixture had stood for 72 hours at 25°, 0.85 cc. of an 0.883 *M* solution of benzaldehyde in 86.5% acetic acid was added to 19 cc. of the reaction mixture, which was then diluted with 100 cc. of water, saturated with salt and extracted with ether. The methone derivative of benzaldehyde was prepared from the ethereal solution and purified in the manner already described in the section on "Deuterobenzaldehyde." After two recrystallizations from methanol, the methone derivative melted at 193.5–194.5°. On analysis, it was found to contain 0.342 atom % deuterium. This value has already been corrected by 0.026 atom % for the background value, or "natural abundance" of deuterium. Since the methone derivative contains 28 hydrogen atoms

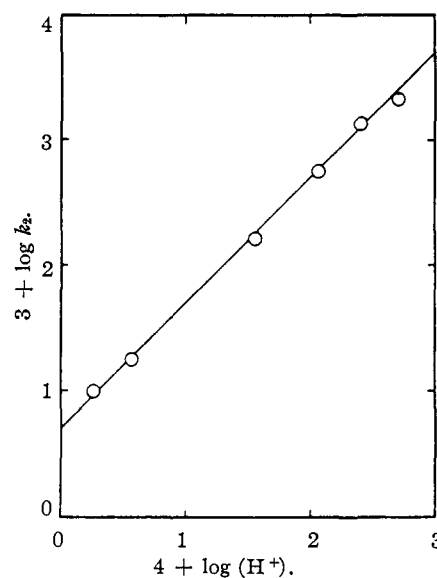


Fig. 1.—Second-order rate constant ( $\text{l. mole}^{-1} \text{ min.}^{-1}$ ) for the oxidation of phenyl-*t*-butylcarbinol as a function of hydrogen ion concentration (mole/l.).

(or rather hydrogen plus deuterium atoms), the isotopically mixed methone must have been formed from 0.75 mmole  $\text{C}_6\text{H}_5\text{CHO}$  (added) and 0.0794 mmole  $\text{C}_6\text{H}_5\text{CDO}$ . Assuming the stoichiometry of equation 1a and 1b, 0.142 mmole of oxidation products was formed from 19 cc. of 0.005 *M* chromic acid; the yield of deuterobenzaldehyde was thus 56%. The other calculations were carried out in a similar fashion.

In experiment G<sub>3</sub>, 100 cc. of a reaction mixture was prepared containing 0.100 *M* ordinary phenyl-*t*-butylcarbinol, 0.050 *M* sodium acetate, 0.010 *M* chromic acid and 0.065 *M* sodium perchlorate. After 61 hours, 8.0 cc. of reaction mixture E<sub>3</sub> (containing 0.0334 mmole of deuterobenzaldehyde) was added, and the methone derivative of benzaldehyde was isolated and purified as before. The atom % deuterium found in the methone derivative was 0.155; the cleavage yield was calculated as 49%. When the entire extraction procedure was carried through, approximately 6 mg. of benzoic acid was isolated. Accordingly, the total cleavage was approximately 53%.

**Competitive Experiments.**—A solution of 20 mmoles of phenyl-*t*-butylcarbinol, 1.33 mmoles of the deuterocarbinol and 25.7 mmoles of sodium acetate in 80 cc. of 86.5% acetic acid was oxidized with 1.0 mmole of chromic acid at 0° for 50 hours. The benzaldehyde methone derivative was isolated as before, and showed on analysis 0.252 atom % deuterium. If benzaldehyde and deuterobenzaldehyde had been formed in the same ratio as that of the initial concentrations of the carbinols, the deuterium content of the methone derivative would have been 0.223 atom %. When the extraction procedure was carried through on this solution, about 8 mg. of benzoic acid was obtained. Apparently very little, if any, isotopic fractionation occurs in a competitive oxidation. When an appropriate correction is made for the benzoic acid formed by the oxidation of benzaldehyde (assuming a  $k_H/k_D$  factor of 7), even the slight difference in isotopic composition between starting materials and products can be accounted for.

**Deuterium analyses** were conducted by burning the samples to water, converting the water to a mixture of  $\text{H}_2$  and HD, and analyzing the gas with a Consolidated-Nier Isotope Ratio Mass Spectrometer.<sup>12</sup>

#### Rate Determinations

**Spectrophotometric Method.**—The chromic acid concentration, as a function of time, was usually obtained spectrophotometrically<sup>4\*</sup> at 3500 Å. with a Beckman model DU quartz spectrophotometer. The spectrophotometric readings were corrected for the small optical absorption at 3500

(9) N. Hellstrom and T. Lauritzon, *Ber.*, **69**, 2003 (1936).

(10) M. S. Kharasch, F. S. Arimoto and W. Nudenberg, *J. Org. Chem.*, **16**, 1556 (1951).

(11) E. C. Horning and M. G. Horning, *ibid.*, **11**, 95 (1946).

(12) R. B. Alfin-Slater, S. Rock and M. Swislocki, *Anal. Chem.*, **22**, 421 (1950); J. Graff and D. Rittenberg, *ibid.*, **24**, 878 (1952).

Å. of the Cr<sup>+++</sup> formed during the reaction. In some of the slow reactions, the entire absorption curve from 3500 to 6250 Å. was followed as a function of time. The family of curves so obtained passed through a single point at 5200 Å. The results at this wave length then supply no evidence for any appreciable quantity of a metastable intermediate. The rate constants were reproducible to about ±2%.

**Titrimetric Method.**—The chromic acid concentration was followed by titration.<sup>4b</sup> In contrast to the spectrophotometric method, titration could also be employed in the presence of cerous and ceric ions.

TABLE I  
VALUES OF  $H_0$  IN 86.5% ACETIC ACID AT 0°  
 $\mu = 0.125$  (with sodium perchlorate)

HClO <sub>4</sub> added, mole/l.	NaOAc added, mole/l.	$H_0$	H <sup>+</sup> , <sup>a</sup> mole/l.	Indicator <sup>b</sup>
0.100	...	0.17	0.100	A
.075	...	.30	.075	A
.050	...	.49	.0502	A
.025	...	.79	.0254	A
.010	...	1.13	.0109	A
.005	...	1.36	.00643	A
.005	...	1.32	.00643	B
...	...	1.66	.00303	A
...	...	1.68	.00303	B
...	0.005	2.02	.00143	B
...	.010	2.26	$8.45 \times 10^{-4}$	B
...	.025	2.65	$3.62 \times 10^{-4}$	B
...	.050	3.01	$1.83 \times 10^{-4}$	B
...	.075	3.26	$1.23 \times 10^{-4}$	B
...	.100	3.48	$0.92 \times 10^{-4}$	B

<sup>a</sup> Calculated from  $K = (H^+)(-OAc) = 0.92 \times 10^{-5}$  (mole/l.)<sup>2</sup> in approximate agreement with the experimental values of  $H_0$ . <sup>b</sup> A = *p*-nitroaniline; B = benzeneazodiphenylamine.

## Results

The yields<sup>13</sup> of cleavage products from the ordinary and from the deuterated carbinol are recorded in Table II. The experiments where the chromic acid was added slowly to a solution of carbinol in 86.5% acetic acid are shown in Table III. A con-

TABLE III  
CLEAVAGE OF PHENYL-*t*-BUTYL CARBINOL IN 86.5% ACETIC ACID BY SLOW ADDITION OF A SOLUTION OF CrO<sub>3</sub>

Carbinol, mole/l.	Pivalophenone, mole/l.	T, °C.	CrO <sub>3</sub> , mole/l. total	HClO <sub>4</sub> , mole/l.	NaOAc, mole/l.	Mn-(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup> or Ce-(ClO <sub>4</sub> ) <sub>3</sub> <sup>b</sup> , mole/l.	% Cleavage (C <sub>6</sub> H <sub>5</sub> -CO <sub>2</sub> H)
0.550	...	0	0.654	...	...	...	22.4
.589	...	0	.881	...	0.809	...	22.4
.229	...	0	.620	...	...	0.370 <sup>a</sup>	3 <sup>c</sup>
.397	...	0	.595	...	...	.184 <sup>b</sup>	3.5
.167	...	50-55	.260	0.25	...	...	19.7
.905	...	50-55	1.61	...	...	...	33 <sup>d</sup>
.606	...	50-55	0.795	...	...	...	30.5
.435	0.309	50-55	.917	...	...	...	29.5 <sup>e</sup>
.567	...	50-55	.945	.750	...	...	22.2
.339	...	50-55	.790	...	...	.514 <sup>a</sup>	46 <sup>f</sup>
...	.175	50-55	.686	...	...	.575 <sup>a</sup>	18.8 <sup>g</sup>
...	.249	50-55	.479	...	...	...	0.5 <sup>h</sup>

<sup>a</sup> Mn(ClO<sub>4</sub>)<sub>2</sub>. <sup>b</sup> Ce(ClO<sub>4</sub>)<sub>3</sub>. <sup>c</sup> An 88% yield of pivalophenone was isolated as the 2,4-dinitrophenylhydrazone. <sup>d</sup> A 25% yield of *t*-butyl alcohol was isolated as *S*-*t*-butylthioglycolic acid anilide. <sup>e</sup> Based on carbinol. <sup>f</sup> A 39% yield of pivalophenone was isolated as the 2,4-dinitrophenylhydrazone. <sup>g</sup> Based on ketone.

sideration of the rate of the reaction (Table IV) and the rate of addition suggested that the average chromic acid concentration, during "slow addition" was around 0.002 *M*, despite the fact that a large

TABLE II

CLEAVAGE OF PHENYL-*t*-BUTYL CARBINOL WITH CrO<sub>3</sub> IN 86.5% ACETIC ACID<sup>13</sup>

Carbinol, mole/l.	Isotope	T, °C.	CrO <sub>3</sub> , mole/l.	HClO <sub>4</sub> , mole/l.	NaOAc, mole/l.	Mn(ClO <sub>4</sub> ) <sub>2</sub> , mole/l.	% Cleavage		Total
							Benzaldehyde	Benzoic acid	
0.443	H	0	0.88	...	...	...	...	3.0	3.0
.231	H	0	.276	...	...	...	...	8.0	8.0
.378	H	0	.348	...	...	...	...	14.8 <sup>a</sup>	14.8
.262	H	0	.402	...	...	0.23	...	Trace <sup>b</sup>	..
.170	H	0	.364	...	...	.605	...	None detected	
.215	H	0	.314	...	0.572	...	...	22.8 <sup>c</sup>	22.8
.100	H	25	.200	...	.20	...	...	22.3	22.3
.100	H	25	.0100	0.050	...	...	32 <sup>d</sup>	...	32
.100	H	25	.0100	...	.050	...	49	ca. 4	53
.100	D	0	.0050	.020	...	...	58	...	58
.050	D	0	.0050	.020	...	...	56.6 <sup>e</sup>	...	56.6
.100	D	0	.0050	.020	...	.030	8.5 <sup>f</sup>	...	8.5
.100	D	0	.0050	.020	...	.030	12 <sup>g</sup>	...	12
.100	D	25	.200	.20	...	...	0.3	5.0	5.3
.100	D	25	.200	...	.20	...	29.9	9.1	39
.050	D	25	.0050	.050	...	...	53	...	53
.050	D	25	.0050	...	.020	...	70.6	...	70.6

<sup>a</sup> A 77% yield of pivalophenone was isolated as the 2,4-dinitrophenylhydrazone. <sup>b</sup> An approximately 90% yield of pivalophenone was isolated as the 2,4-dinitrophenylhydrazone. <sup>c</sup> A 52% yield of pivalophenone was isolated as the 2,4-dinitrophenylhydrazone. <sup>d</sup> The chromic acid was added at such a rate as to keep the average Cr<sup>6</sup> concentration at 0.0015 *M*. <sup>e</sup> These experiments were conducted *in vacuo*. <sup>f</sup> The cleavage fraction was determined by estimating the amount of benzaldehyde formed and dividing by the initial amount of chromic acid. For these calculations it was assumed that all of the Cr<sup>4</sup> formed oxidized Mn<sup>2</sup> to Mn<sup>3</sup>.

**Acidity.**—The acidity of solutions of perchloric acid and of sodium acetate in 86.5% acetic acid was determined by an indicator method with *p*-nitroaniline and benzeneazodiphenylamine.<sup>4e</sup> The data are presented in Table I. Neither added manganous perchlorate nor added cerous perchlorate had a marked effect on the acidity, even in the presence of added sodium acetate.

amount of the oxidizing agent was eventually introduced into a small volume. The experiments with added perchloric acid were conducted at approximately constant hydrogen ion concentration by

(13) For additional data, see J. Hampton, Dissertation, University of Chicago, 1955.

TABLE IV  
RATES OF CHROMIC ACID OXIDATION OF PHENYL-*t*-BUTYLCARBINOL IN 86.5% ACETIC ACID

Carbinol, <sup>a</sup> mole/l.	Isotope	T, °C.	CrO <sub>3</sub> , mole/l.	HClO <sub>4</sub> , mole/l.	NaOAc, mole/l.	Initial H <sup>+</sup> , mole/l.	μ	$\frac{k_2}{\text{min.}^{-1}}$	$\frac{k_3}{\text{min.}^{-1}}$	$k_H/k_D$
0.0060	H	0	0.0020	0.050	...	0.0521	0.125	2.14	41.1	
.0500	H	0	.0010	.025	...	.0264	.125	1.37	52	
.0250	H	0	.00050	.025	...	.0258	.125	1.42	55	
.0250	H	0	.0010	.025	...	.0264	.125	1.31	49.6	
.0500	H	0	.0010	.010	...	.0118	.125	0.55	46.6	
.0500	H	0	.0010	...	...	.00358	.125	.166	46.5	
.1330	H	0	.0010	...	...	.00358	.125	.159	44.5	
.3320	H	0	.0020	...	...	.00369	.125	.154	41.8	
.1330	H	0	.0010	...	0.025	.000377	.125	.0178	47.2	
.1330	H	0	.0010	...	.050	.000187	.125	.00966	51.7	
.025	H	0	.0010	.025	...	.0264	.026	3.04	115	
.025	H	0	.0010	.025	...	.0264	.063	1.98	75	
.025	H	0	.0010	.025	...	.0264	.125	1.31	50	
.025	H	0	.0010	.025	...	.0264	.250	0.995	38	
.050	D	0	.0010	.050	...	.0521	.125	.252	4.84	8.5
.050	D	0	.0010	.025	...	.0264	.125	.120	4.54	11.5
.050	D	0	.0010	.025	...	.0264	.125	.118	4.48	
.050	D	0	.0010	...	...	.00358	.125	.0114	3.18	14
.087	D	0	.0010	...	.025	.000377	.125	.00124	3.29	14.4
.025	H	25	.0010	.050	...	.0510 <sup>d</sup>	.125	17.5	343	
.025	H	25	.0010	.050	...	.0510	.125	16.5 <sup>b</sup>	323	
.050	H	25	.0010	...	...	.00358	.125	1.00	279	
.100	H	25	.0010	...	...	.00358	.125	1.078 <sup>c</sup>	301	
.400	H	25	.0010	...	...	.00358	.125	0.898 <sup>c</sup>	250	

<sup>a</sup> Carbinol purified through the acid phthalate and sublimed except where otherwise noted. <sup>b</sup> Carbinol prepared by LiAlH<sub>4</sub> reduction and recrystallization from petroleum ether. <sup>c</sup> Carbinol prepared by LiAlH<sub>4</sub> reduction. <sup>d</sup> Approximate hydrogen ion concentration at 25°, calculated using spectrophotometric data obtained at 0°.

adding perchloric acid in 86.5% acetic acid simultaneously with the addition of the chromic acid and at such a rate that about 4 moles of perchloric acid was added for each mole of oxidizing agent. M. Cohen<sup>14</sup> had previously shown that this stoichiometry is correct where the concentration of added acid exceeds 0.1 *M*; in less strongly acid solution, less hydrogen ion is consumed during the oxidation process. Pivalophenone is unaffected by chromic acid at 0° or at 25°, in the presence or the absence of Mn<sup>++</sup> or Ce<sup>+++</sup>. However, at 50–55° the ketone is slowly attacked by the oxidizing agent in the absence of these ions, and rapidly attacked in the presence of Mn<sup>++</sup>. The high yield of cleavage products in the presence of Mn<sup>++</sup> at 50–55° is therefore an artifact, and does not contradict the generalization that Mn<sup>++</sup> and Ce<sup>+++</sup> sharply decrease the cleavage yield.

The rates<sup>13</sup> of the chromic acid oxidation of the ordinary and of the deuterated carbinol are recorded in Table IV. Under the experimental conditions here recorded, the carbinol was always present in large excess, so first-order constants were obtained. The values of  $k_2$  recorded in Table IV are the quotients of the first-order constants by the (initial) carbinol concentrations. The third-order constants,  $k_3$ , obtained by dividing  $k_2$  by the hydrogen ion concentrations, show no trend over a 1000-fold change in acidity; the reaction rate, like that for the oxidation of isopropyl alcohol<sup>14</sup> in 86.5% acetic acid, can be expressed by the equation

$$-d(\text{CrO}_3)/dt = k_3(\text{Carbinol})(\text{HCrO}_4^-)(\text{H}^+) \quad (3)$$

(14) M. Cohen, Dissertation, University of Chicago, 1951.

Chromic acid is largely ionized in 86.5% acetic acid,<sup>15</sup> so that equation 3 is correct as written. The observed decrease in rate with increasing ionic strength is consistent with a reaction between oppositely charged ions. In view of the equilibria which obtain prior to the rate controlling step, the temperature coefficient (2.3 per 10°) cannot yet be interpreted. All the rates recorded in Table IV were determined spectrophotometrically; similar experiments conducted by titration gave the same rate constants within a few per cent.

The rate of the chromic acid oxidation of the carbinol in the presence of Mn<sup>++</sup> is very hard to measure spectrophotometrically, since the product of induced oxidation of Mn<sup>++</sup> is dark brown. Titration methods were unsuccessful, since the various manganous salts obscured the end-point of an iodometric titration (perhaps by catalyzing the air oxidation of I<sup>-</sup>). A further complication is introduced by the slow direct oxidation of Mn<sup>++</sup> by chromic acid in the presence of sodium acetate (but not in the presence of perchloric acid). Mn<sup>++</sup> is not oxidized by chromic acid in water solution; presumably Mn<sup>IV</sup> is tightly complexed by acetate ion. However, whatever the reason for the direct oxidation, it effectively obscures the induced reaction. The best estimate<sup>13</sup> suggests that Mn<sup>++</sup> has a small but positive effect on the reaction rate.

Experiments with Ce<sup>+++</sup> were more successful; reasonable rate constants, recorded in Table V, were obtained by the titration procedure. In the presence of Ce(ClO<sub>4</sub>)<sub>3</sub> and sodium acetate, the oxidation of the carbinol led to a red solution which had about 1/3 of the oxidizing power of the original

(15) W. Watanabe, Dissertation, University of Chicago, 1948.

chromic acid solution; clearly, cerous ion had been oxidized to ceric ion with an induction factor of  $1/2$ . (Compare the induced oxidation of  $Mn^{++}$  in the reaction of isopropyl alcohol with chromic acid in water.<sup>4b</sup>) In the presence of added perchloric acid, however, the ceric ion does not accumulate, but (presumably) oxidizes carbinol; the oxidizing titer of the solution finally fell to zero. The solution, however, darkened perceptibly during the oxidation process, so that a small concentration of  $Ce^{++++}$  was, in fact, present during the reaction.

TABLE V

EFFECT OF CEROUS NITRATE ON THE RATE OF OXIDATION OF PHENYL-*t*-BUTYL-CARBINOL<sup>a</sup> IN 86.5% ACETIC ACID AT 0°

$Ce(NO_3)_3$ , mole/l.	$\mu$	$\frac{k_H}{k_D}$ , (mole/l.) <sup>-1</sup> min. <sup>-1</sup>	$k_D$ , (mole/l.) <sup>-1</sup> min. <sup>-1</sup>	$k_H/k_D$
0.00	0.125	1.22 <sup>b</sup>	0.105 <sup>b</sup>	11.6
.00	.250	0.935	.0775	12.1
.015	.125	.85	.796	10.7
.030	.250	.712	.075 <sup>b</sup>	9.5

<sup>a</sup> 0.025 *M* carbinol (normal or deuterated), 0.025 *M*  $HClO_4$  and 0.0020 *M*  $CrO_3$ . <sup>b</sup> Average of two "runs."

### Discussion

As a result of these kinetic studies, considerable control has been obtained over the preparation of ketones by the action of chromic acid on secondary alcohols. In particular, high yields of ketone can be obtained by carrying out the reaction in the presence of manganous ion, or by using concentrated chromic acid solutions; alternatively, moderately high yields of cleavage products can be obtained in the absence of manganous salts by carrying out the oxidation with very dilute solutions of chromic acid. The work has also provided data which contribute toward an understanding of the mechanism of the cleavage process.

**Experimental Facts.**—Any mechanism for the chromic acid oxidation of phenyl-*t*-butylcarbinol in 86.5% acetic acid must account for the following experimental facts:

- (A) The reaction kinetics accord with equation 3.  
 (B) The oxidation of the carbinol is accompanied by cleavage to benzaldehyde and *t*-butyl alcohol; 1-deutero-1-phenyl-2,2-dimethylpropanol-1 yields monodeuterobenzaldehyde.  
 (C) The maximum yield of cleavage products is about 67%; the yield is sharply reduced by increasing the chromic acid concentration or by adding  $Ce^{+++}$  or  $Mn^{++}$ ; the yield is somewhat greater with deuterocarbinol than with ordinary phenyl-*t*-butylcarbinol.  
 (D) No isotopic fractionation occurs in the benzaldehyde (plus deuterobenzaldehyde) formed in a competitive oxidation of phenyl-*t*-butylcarbinol and the deuterocarbinol.

(E) In the presence of  $Ce^{+++}$  and sodium acetate, one  $Ce^{IV}$  is produced for each molecule of chromic acid reduced; the rate of reduction of chromic acid is slightly decreased by  $Ce^{+++}$ .

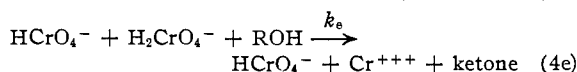
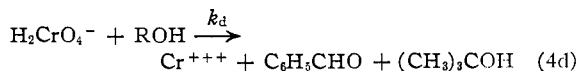
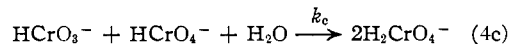
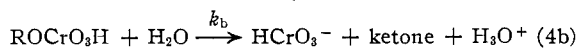
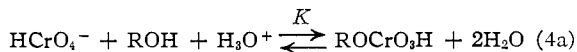
(F) The  $k_H/k_D$  ratio is about 12 at 0° and about 9 at 25° (*i.e.*, a C-H (or C-D) bond is broken in the rate-controlling step of the oxidation-reduction process, but the ratios are higher than those ordinarily observed).

(G) The  $k_H/k_D$  ratio is somewhat smaller at higher acidities, or in the presence of  $Ce^{+++}$ .

**Cleavage.**—The cleavage cannot be caused by a direct attack of chromic acid on phenyl-*t*-butylcarbinol, but must result from the action of some unstable intermediate containing chromium in an unusual valence state. The evidence for this statement is threefold: First, the rate ratio  $k_H/k_D$  is about 10 (item F above). But, in dilute solution, cleavage (which does not break the C-H or C-D bond) accounts for almost  $2/3$  of the chromic acid consumed (item C). If chromic acid itself were responsible for the cleavage, the value of  $k_H/k_D$  would be only about 1.4. (This ratio was calculated by assuming that the rates of the cleavage reactions, 1b and 2b, are unaffected by isotopic substitution but the rates of direct oxidation, 1a and 2a, are decreased 10-fold.) Second, although isotopic substitution somewhat increases the cleavage yield (item C above), the increase is much smaller than that which would be calculated if cleavage took place in the first step. Third, the cleavage products are almost eliminated by the addition of  $Mn^{++}$  or  $Ce^{+++}$ . Under the experimental conditions used, these ions are not rapidly oxidized by chromic acid itself. On the other hand, earlier work<sup>4b</sup> showed that these ions react rapidly according to equations 5a and 5b with the unstable intermediate containing tetravalent chromium which arises during chromic acid oxidations. Furthermore, an unstable intermediate containing pentavalent chromium also occurs during chromic acid oxidations,<sup>4b</sup> but arises only from tetravalent chromium, probably by way of equation 4c. Therefore when  $Mn^{++}$  or  $Ce^{+++}$  sweeps tetravalent chromium from solution, it removes pentavalent chromium as well. Since each of these metal ions almost eliminates cleavage, the cause of cleavage reaction probably lies in pentavalent chromium, or tetravalent chromium, or both.

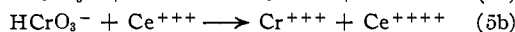
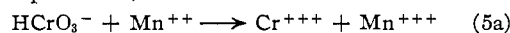
Although this argument fails to identify the particular ion responsible for cleavage, the fact that the maximum cleavage for phenyl-*t*-butylcarbinol in 86.5% acetic acid approaches 67% suggests that pentavalent and not tetravalent, chromium is the active oxidant (*i.e.*, two-thirds of the oxidizing power of hexavalent chromium is needed for cleavage).

**Partial Mechanism.**—Until the detailed chemical mechanism and the stereochemistry for the cleavage are understood, any prediction from kinetics alone is necessarily tentative. A mechanism which ascribes the cleavage to pentavalent chromium is consistent with the facts now known; it is represented by equations 4a-4e, and 5a and 5b below.



Here ROH represents phenyl-*t*-butylcarbinol, "ketone" represents pivalophenone, and  $\text{HCrO}_3^-$  and  $\text{H}_2\text{CrO}_4^-$  are postulated, for the sake of definiteness, as the intermediates containing tetravalent and pentavalent chromium, respectively.

In the presence of  $\text{Mn}^{++}$  or  $\text{Ce}^{+++}$ , reaction 5a or 5b replaces 4c, 4d and 4e.



Reactions 4a, 4b and 4c are the same as those previously<sup>4</sup> found for the chromic acid oxidation of isopropyl alcohol. Reaction 4d, like the reaction of  $\text{Cr}^5$  with isopropyl alcohol, represents a two-electron change, but the reaction has here been assumed to be cleavage rather than simple oxidation. Reaction 4e is new; it probably should be regarded as a reaction between a  $\text{Cr}^5$ - $\text{Cr}^6$  complex and the carbinol. Such a complex previously<sup>4,6</sup> has been postulated to account for the kinetics of the chromic acid oxidation of ferrous ion.<sup>16</sup>

**Kinetics.**—Application of the usual steady-state assumption to the set of reactions 4a-4e leads to equation 6

$$v = -d(\text{Cr}^6)/dt = 2k_b K (\text{HCrO}_4^-)(\text{Carbinol})(\text{H}^+) \quad (6)$$

The mechanism is therefore in accord with equation 3 and with (A) above.

The effects of  $\text{Mn}^{++}$  and  $\text{Ce}^{+++}$  on the reaction rate have not yet been fully explained. The rates with  $\text{Mn}^{++}$  are highly uncertain experimentally, but in acid solution  $\text{Ce}^{+++}$  decreases the rate, probably by about 20%. The sequence of steps 4a, 4b, 4d leads to the prediction that the rate should drop by 50%; a decrease almost as large as predicted was actually observed<sup>4b</sup> for the effect of  $\text{Mn}^{++}$  on the rate of the chromic acid oxidation of isopropyl alcohol. Qualitatively, the decrease should occur because the sequence 4a-4e is a chain of length 2; the chain is cut in half when  $\text{Ce}^{+++}$  (or  $\text{Mn}^{++}$ ) sweeps  $\text{Cr}^{\text{IV}}$  from solution. But in 86.5% acetic acid solution, with added  $\text{HClO}_4$ ,  $\text{Ce}^{\text{IV}}$  is produced and then reacts with the carbinol; since the mechanism of this secondary reaction is unknown, no firm prediction of rate effect can be made. The yield of  $\text{Ce}^{\text{IV}}$  obtained in the presence of sodium acetate agrees with that predicted from the sequence 4a, 4b, 5b.

Quantitatively, the cleavage yield,  $f$ , calculated from equations 4a-4e above and from the stoichiometry of equations 1a and 1b, is given by equation 7

$$f = \frac{2}{3} \left[ \frac{1}{1 + r(\text{Cr}^6)} \right] \quad (7)$$

where  $r = k_e/k_d$ . The values of  $r$  can be calculated from the cleavage yields or, conversely, values of  $r$  can be assumed, and used to calculate the yields. The value of  $r$  must of course be constant for any particular acidity, but depends on the isotope used;  $r_{\text{H}}$  should be about  $7r_{\text{D}}$  (or perhaps  $10r_{\text{D}}$ , see below) since  $k_e$  should be sensitive to isotopic substitution, whereas  $k_d$  is not. But  $r$  need not be (and is not) independent of acidity. Equation 7 is qualitatively correct, in that it predicts a maximum cleavage yield for phenyl-*t*-butylcarbinol of

(16) C. Benson, *J. Phys. Chem.*, **7**, 356 (1903); R. Gortner, *ibid.*, **12**, 632 (1908); C. Wagner and W. Preiss, *Z. anorg. Chem.*, **168**, 265 (1928).

67% at low chromic acid concentrations, and accounts for the fact that the cleavage yield is diminished as the chromic acid concentration is increased. For each acidity, the value of  $r$  for the ordinary (hydrogen) carbinol is a parameter, chosen to fit the data at one particular chromic acid concentration. The calculated and observed yields, recorded in Table VI, show that equation 7 then predicts, with reasonable precision, the variation in  $f$  (the cleavage fraction) with chromic acid concentration and with isotopic substitution, but at constant acidity.

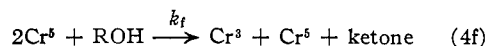
TABLE VI

Approximate acidity	$r_{\text{H}}$ or $r_{\text{D}}$	$T$ , °C.	Av. $\text{Cr}^6$ , mole/l.	Isotope	$f$		
					Calcd.	Obsd.	
0.1 M $\text{H}^+$	(30) <sup>a</sup>	0	0.74	H	0.03	0.03	
		30	0	.53	H	.04	.066
		30	0	.34	H	.06	.036
		30	0	.195	H	.097	.08
"Neutral" solvent	(20) <sup>a</sup>	0	.285	H	.10	.096	
		20	0	.195	H	.136	.127
		20	0	.22	H	.123	.148
0.3 M $\text{AcO}^-$	(10) <sup>a</sup>	0	.24	H	.196	.228	
0.1 M $\text{H}^+$	(350) <sup>a</sup>	25	.167	H	.011	.011	
		350	25	.167	H	.011	.014
		350	25	.333	H	.006	.023
0.05 M $\text{AcO}^-$	(20) <sup>a</sup>	25	.167	H	.44	.32	
		20	25	.0015	H	.155	.22
		20	25	.005	H	.61	.53
0.1 M $\text{H}^+$	50 <sup>b</sup>	25	.167	D	.072	.073	
		50	25	.167	D	.072	.053
		50	25	.0025	D	.59	.53
		50	25	.0025	D	.59	.56
		50	25	.0025	D	.59	.60
0.05 M $\text{AcO}^-$	3 <sup>b</sup>	25	.167	D	.44	.39	
		3	25	.0025	D	.67	.68
		3	25	.0025	D	.67	.71
	3	25	.0025	D	.67	.67	

<sup>a</sup> Assumed. <sup>b</sup> Calculated as  $1/7$  of  $r_{\text{H}}$ .

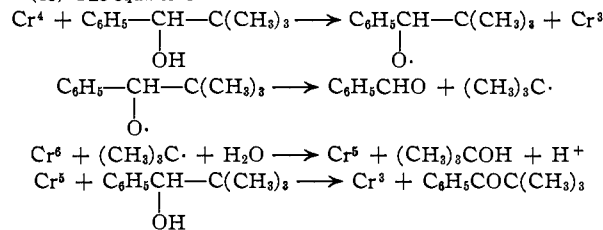
Alternative but less satisfactory mechanisms have been formulated which also involve pentavalent chromium as the cleavage intermediate.<sup>17</sup> No completely satisfactory mechanism has been found which ascribes the cleavage exclusively to tetravalent chromium, although a suitable mechanism<sup>18</sup> is available which will account for the observed facts

(17) Reaction 4e is certainly somewhat arbitrary, and can be replaced by at least one other termolecular reaction, 4f.



At low chromic acid concentrations, the combination of 4a, 4b, 4c, 4d and 4f leads to the correct reaction kinetics, and the calculated cleavage yields agree with experimental about as well as those from equation 7.

(18) The equations



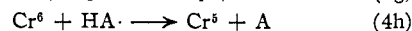
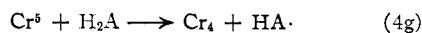
account qualitatively for all the facts except the cleavage yields which exceed 33%.

under those experimental conditions where the fraction cleavage does not exceed 33%. The validity of this mechanism, as a partial explanation of the facts, has not yet been determined.

**Detailed Chemistry.**—The kinetic analysis presented above does not permit a complete determination of the mechanism for the cleavage reaction. However, equations 4a-4e suggest that the cleavage results from the oxidation of the carbinol to a real or potential oxygen cation, which then undergoes cleavage. The kinetic study must be supplemented by stereochemical and other investigations before a detailed mechanism can be presented.

**Isotope Effects.**—Although the set of reactions in equations 4a-4e explains the kinetics and the cleavage yields satisfactorily, and accounts for the effect of deuterium substitution on the reaction rate, it nevertheless is true that the isotope effect is somewhat larger than usual.<sup>19</sup> Deuterium substitution decreases the rate of the oxidation of isopropyl alcohol by a factor of 8 at 0° in 86.5% acetic acid<sup>4e</sup> and by a factor of 6.9 in water<sup>20</sup> at 25°. Large and unusual isotope effects have, however, occasionally been reported.<sup>21</sup> The usual  $k_H/k_D$  ratio is the result of the zero-point energy difference which arises when a C-H vibration, in the reacting molecule, is converted, in the transition state, to transla-

tional motion. Possibly in the present example the C-H bending vibrations have considerably lower frequencies in the transition state than in the carbinol; if so, the zero-point energy difference between the hydrogen and the deuterium compounds will be exceptionally large. Tunnelling also has been suggested<sup>22</sup> as a possible cause for large  $k_H/k_D$  ratios. But although these explanations may be correct, an alternative explanation is embodied in the schematic equations 4g and 4h below.



Here HA· represents the free radical  $\text{C}_6\text{H}_5\dot{\text{C}}(\text{OH})\text{C}(\text{CH}_3)_3$  and A represents  $\text{C}_6\text{H}_5\text{COC}(\text{CH}_3)_3$ .

These equations, together with the set of reactions 4a-4e, lead by way of the usual steady-state assumption to a kinetic equation which predicts more chain branching for the hydrogen than for the deuterium compound, and hence an abnormally high  $k_H/k_D$  ratio. Although this mechanism is highly speculative, it appears worthwhile to point out that the high isotopic rate ratio here observed may be caused by chemistry rather than physics.

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(22) R. P. Bell, *Proc. Roy. Soc. (London)*, **A139**, 446 (1933).

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(19) W. F. K. Wynne-Jones, *J. Chem. Phys.*, **2**, 381 (1934); C. Reitz, *Z. physik. Chem.*, **A176**, 363 (1936); C. Reitz and J. Kopp, *ibid.*, **A184**, 429 (1939); L. Melander, *Arkiv Kemi*, **2**, 211 (1950); K. Wiberg, *This Journal*, **76**, 5371 (1954); K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

(20) A. Leo, Dissertation, University of Chicago, 1951.

(21) W. H. Urry, Twelfth National Organic Chemistry Symposium, Denver, June, 1951, p. 30; H. C. Urey and D. Price, *J. Chem. Phys.*, **2**, 300 (1934).

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## Physical Chemical Studies of Soluble Antigen-Antibody Complexes. VII. Thermodynamics of the Reaction between Benzenearsonic Acid-Azo-bovine Serum Albumin and Rabbit Antibodies to Benzenearsonic Acid<sup>1,2</sup>

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Solutions of antigen (Ag)-antibody (Ab) complexes formed between benzenearsonic acid-azo-bovine serum albumin as Ag and antibodies to benzenearsonic acid, have been subjected to electrophoresis and ultracentrifugation. Two different Ab preparations exhibited some differences in behavior, but for one of these the following thermodynamic data have been obtained. For the reaction  $\text{Ag} + \text{AgAb} \rightleftharpoons (\text{Ag})_2\text{Ab}$ , in veronal-NaCl buffer, pH 8.5,  $\Gamma/2$  0.3, at 0°:  $K = (7 \pm 3) \times 10^3$  liters/mole,  $\Delta F^\circ = -4.8 \pm 0.2$  kcal./mole;  $\Delta H^\circ = 0 \pm 2$  kcal./mole;  $\Delta S^\circ = +18 \pm 8$  e.u. These data are very similar to those obtained with natural protein antigen-antibody systems and their significance is discussed. A preliminary study of the effect of pH on the Ag-Ab equilibria is described.

In previous papers of this series,<sup>4</sup> general methods were developed which permit, for the first

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(2) From the thesis submitted by Melvin C. Baker in partial fulfillment of the requirements for the Ph.D. degree at Yale University, June, 1955.

(3) Du Pont Predoctoral Fellow, 1954-1955.

(4) (a) S. J. Singer and D. H. Campbell, *This Journal*, **74**, 1794 (1952); (b) **76**, 5577 (1953); (c) **77**, 3499 (1955); (d) **77**, 3504 (1955); (e) **77**, 4851 (1955); (f) S. J. Singer, L. Eggman and D. H. Campbell, *ibid.*, **77**, 4855 (1955).

time, thermodynamic data to be obtained for the reactions of natural protein antigens (Ag) and their antibodies (Ab). The systems containing rabbit antibodies to bovine serum albumin<sup>4c</sup> (BSA) and ovalbumin<sup>4e</sup> (OA) have been studied. We have now investigated a system containing an artificial antigen, benzenearsonic acid-*p*-azo-bovine serum albumin (RBSA) and antibodies to benzenearsonic acid (anti-R). This investigation has several purposes. Current concepts of the nature of the antigen-antibody reaction have largely been derived from studies with artificial antigens (usually pre-