sample of IIIa and to Dr. R. B. Morin for cladinose. This investigation was supported by a research grant (RG-5474) of the National Institutes of Health, Public Health Service.

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On the Mechanism of the Oxidative Cleavage of Phenyl-*t*-butylcarbinol with Chromic Acid[1]

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Chromic acid partially oxidizes phenyl-*t*-butylcarbinol to pivalophenone and partially cleaves it to benzaldehyde and *t*-butyl alcohol. The present work was designed to decide whether the oxidative cleavage occurs directly (to produce a *t*-butyl cation) or indirectly, by way of a rearrangement to form the oxonium ion A, $C_6H_5-CH=\overset{+}{O}-C(CH_3)_3$; subsequent hydrolysis of A would yield benzaldehyde and *t*-butyl alcohol. The latter pathway has now been ruled out by experiments in which the alcohol has been labeled with ^{18}O. The oxidative cleavage of labeled carbinol in ordinary water leads exclusively to the production of unlabeled *t*-butyl alcohol. Prior work had shown that the hydrolysis of the *t*-butyl oxoniun salt of benzaldehyde, A, proceeds without rupture of the alkyl–oxygen bond. Therefore, if the cation A were an intermediate in the oxidation–reduction process, the label would have been found in the *t*-butyl alcohol. Confirmatory experiments were conducted with excess ^{18}O in the solvent rather than in the carbinol, and with anisyl-*t*-butylcarbinol rather than phenyl-*t*-butylcarbinol.

The chromic acid oxidation of alcohols has now been shown to proceed by way of a chromic acid ester of the alcohol as intermediate.[2-4] The ester undergoes internal oxidation–reduction to produce ketone and a chromium compound of valence IV.[5] A possible pathway for the subsequent reduction of the derivative of tetravalent chromium, applied to a particular example, is shown in eq. 1–3 below.

In 1948, Mosher and Whitmore[6] discovered that chromic acid oxidizes methyl-*t*-amylcarbinol in part with cleavage to acetaldehyde and (presumably) *t*-amyl alcohol. Mosher has further postulated that, in this and similar reactions,[7] the alcohol is oxidized by chromic acid to an intermediate with a positively charged electron-deficient oxygen atom; the intermediate is assumed to cleave spontaneously to form a tertiary carbonium ion.

In a further investigation of the problem, it was discovered that the cleavage of phenyl-*t*-butylcarbinol is caused by a derivative of tetravalent or pentavalent chromium[8]; that fraction of the oxidation which is caused by hexavalent chromium yields pivalophenone.

$$C_6H_5-CHOH-R + Cr^{VI} \longrightarrow C_6H_5CO-R + Cr^{IV} \quad (1)$$

$$Cr^{VI} + Cr^{IV} \longrightarrow 2Cr^{V} \quad (2)$$

$$C_6H_5-CHOH-R + Cr^{V} \longrightarrow C_6H_5CHO + ROH + Cr^{III} \quad (R = t\text{-butyl}) \quad (3)$$

The evidence for this pathway rests both on the primary deuterium isotope effects observed in the oxidation,[8] and on the effect of manganous ion on the reaction. The chromic acid oxidation of alcohols "induces" the oxidation of manganous ion[5] to manganese dioxide; kinetic analysis shows that the active oxidant for Mn^{++} is Cr^{IV}, which is thereby swept from solution by the process

$$Mn^{++} + Cr^{IV} \longrightarrow Mn^{III} + Cr^{III} \quad (4)$$

Cr^{V} arises from Cr^{IV}, so that reaction 4 eliminates both of the intermediate valence states of chromium from solution. Since manganous ion diminishes or suppresses[8] the cleavage of phenyl-*t*-butylcarbinol, the cleavage must be caused by the oxidation of the alcohol by a compound of pentavalent or possibly tetravalent chromium.

The present paper shows that the cleavage does not occur by way of a rearrangement of phenyl-*t*-butylcarbinol to the cation A. The hypothetical reactions may be formulated as occurring by way of an ester of an acid of pentavalent chromium, as

$$C_6H_5-\underset{\displaystyle OH}{\underset{|}{CH}}-C(CH_3)_3 + Cr^{V} \rightleftarrows \quad (5)$$

$$C_6H_5-\underset{\displaystyle O\\ \displaystyle CrO_2H_2}{\underset{|}{CH}}-C(CH_3)_3 \not\longrightarrow C_6H_5-\overset{\displaystyle H}{\overset{|}{C}}=\overset{+}{O}-C(CH_3)_3 + Cr^{III}$$

A

This scheme was initially not without merit, since Winstein[9] has discovered that when migration of a group, R, to oxygen takes place during the acetolysis of compounds of the type $(CH_3)_2\underset{\displaystyle R}{\underset{|}{C}}-O-O-COC_6H_4NO_2$, *t*-butyl migrates more rapidly than does phenyl.

The proof that the mechanism outlined in eq. 5 does not apply to the oxidative cleavage depends on labeling the oxygen atom of phenyl-*t*-butylcarbinol with ^{18}O. Proper control experiments show that if the cation A were involved, the reaction sequence would transfer the oxygen atom to the *t*-butyl alcohol; the label is not in fact so recovered.

The conclusions drawn from these experiments are in accord with those of Lansbury, *et al.*,[10] who inferred that the oxidative cleavage must occur by the direct production of a carbonium ion. They observed that phenyl apocamphylcarbinol is oxidized without accompanying cleavage and correlated this finding with the difficulty of establishing a positive charge at a bridgehead.[11] The rearrangement is also ruled out by their experiments, since the apocamphyl group rearranges, in the Baeyer–Villiger reaction, in preference to phenyl.[12]

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TABLE I

CONTROL EXPERIMENTS: EXCHANGE IN 86.5% ACETIC ACID AT 0°

Compound studied	Compound measured	Time, hours	Experimental conditions	Excess ^{18}O in solvent	% excess ^{18}O Before	% excess ^{18}O After	Exchange, %
PBC[a]	CO_2[b]	45	0.05 *M* NaOAc	1.469	0.000	0.007[c]	0.5
PBC-^{18}O	CO_2[b]	60	0.05 *M* NaOAc		.581	.573	1.4
PBC-^{18}O	CO_2	13	1 *M* NaOAc		.607	.604	0.5
t-$C_4H_9{}^{18}OH$	*t*-C_4H_9OH	13	1 *M* NaOAc		1.254	1.216	3.0
ABC[d]	CO_2	5	1 *M* NaOAc	1.469	0.000	0.012	0.8
ABC-^{18}O	CO_2	5	1 *M* NaOAc		0.596	0.594	0.3
$H_2{}^{18}O$	CO_2	5	1 *M* NaOAc	1.166	1.166	1.066	8.6[e]

[a] Phenyl-*t*-butylcarbinol. [b] Isotope-ratio spectrometer used. [c] Average deviation of duplicate determinations throughout Table I is about 0.005 atom % ^{18}O. [d] Anisyl-*t*-butylcarbinol. [e] Per cent of ^{18}O lost by water and presumably incorporated into acetic acid

Experimental

Materials. Benzaldehyde-^{18}O.—One mole of freshly distilled benzaldehyde, one mole of water enriched in ^{18}O and a few drops of concentrated sulfuric acid were refluxed under nitrogen for 48 hours. The layers were separated, the aldehyde diluted with ether and dried, and then purified by distillation. Anisaldehyde-^{18}O was similarly prepared. Phenyl-*t*-butylcarbinol (labeled or unlabeled) was prepared from the *t*-butyl Grignard reagent and the (labeled or unlabeled) aldehyde[13] and purified through the acid phthalate.[14] The alcohol, analyzed by the method of Anbar, *et al.*,[15] contained 0.796 atom % ^{18}O. The product melted at 44–45° (lit.[14] 45°). Anisyl-*t*-butylcarbinol (labeled or unlabeled) was prepared similarly from anisaldehyde.[16] The alcohol contained 0.800 atom % ^{18}O. Labeled *t*-butyl alcohol, prepared by the method of Anbar and Dostrovsky,[17] contained 1.084 atom % excess ^{18}O.

Deuterioacetic acid was made by refluxing purified acetic anhydride with an equivalent quantity of D_2O. Water enriched with ^{18}O was purchased from the Weizmann Institute, Rehovoth, Israel, and deuterium oxide obtained from the Atomic Energy Commission. Other chemicals were of reagent grade.

Cleavage.—The oxidation of phenyl-*t*-butylcarbinol and of anisyl-*t*-butylcarbinol were conducted according to the procedure of Hampton,[8,18] by the slow addition of chromic acid to a solution of the carbinol in 86.5% aqueous acetic acid. The work-up followed Leo's procedures,[8,19] except that the proportions of non-acidic materials were estimated by infrared spectroscopy.

A weighed amount of chromium trioxide (0.00963 mole) was dissolved in 4 ml. of 86.5% aqueous acetic acid and added from a microburet at a rate of 6 drops per minute to the stirred carbinol solution at 0° or room temperature. The time of addition averaged 4–5 hours. Then the mixture was stirred for an hour more at the temperature of the addition, and overnight at room temperature.

The reaction mixture was diluted with five volumes of water, saturated with sodium chloride, and extracted with two 25-ml. portions of ether. The ether layer was exhaustively extracted with sodium bicarbonate solution, from which benzoic or anisic acid was later isolated. The ether layer was dried, and the solvent removed on a rotary evaporator. The residue was dissolved in carbon tetrachloride and subjected to quantitative infrared analysis with a Perkin–Elmer model 21 infrared spectrophotometer. The carbonyl bands for aldehyde and ketone are separable, and about 0.1 micron apart. (For example, those of anisaldehyde and methyl anisyl ketone are at 5.86 and 5.97 μ, respectively.) When, however, the amount of aldehyde was less than 6% of the total carbonyl compounds present, the accuracy of the measurements fell. Under these circumstances, after determination of the quantity of ketone by infrared analysis, the carbon tetrachloride solution was extracted with aqueous sodium bisulfite solution. The bisulfite solution was decomposed with sodium carbonate solution by heating for 5 minutes on the steam-bath. The resulting suspension was extracted with carbon tetrachloride and the aldehyde determined by ultraviolet spectroscopy. Control experiments showed that 85% of benzaldehyde could be recovered by this procedure.

For the isolation of *t*-butyl alcohol, the acidic oxidation mixture was poured into excess sodium hydroxide solution, and the azeotrope of *t*-butyl alcohol and water was distilled through a vacuum-jacketed distilling column (1 × 30 cm.). The fraction boiling at 80.5 ± 0.5° was collected and analyzed for ^{18}O, either directly or after drying to the anhydrous alcohol. The latter, after final drying with calcium hydride, melted at 25°.

^{18}O Analyses.—Most of the measurements here recorded were performed with a Consolidated Engineering Corporation model 21-103C mass spectrometer. When carbon dioxide was measured, the parent peak (mass 44) predominated, and the ratio of masses 46/44 was measured. However, for *t*-butyl alcohol, with an ionizing current of 10 μamperes the parent peak of mass 74 was almost absent, and the largest peak corresponded to mass 59, which is presumably $(CH_3)_2C^+{-}OH$. The ratio of masses 61/59 was used to calculate the atom % ^{18}O. The normal abundance, found with stock samples of *t*-butyl alcohol, varied from 0.00238 to 0.00246; the calculated ratio (taking into account the natural abundances of ^{13}C, ^{17}O and ^{2}H, as well as the natural abundance of ^{18}O as 0.00206) is 0.00246. In addition to measuring the ratios of isotopic abundances carefully, tracings of the region from mass 20 to 70 were taken at the fastest scan rate and were used for the identification of products and the detection of impurities.

A few measurements were made on carbon dioxide with the Consolidated–Nier model 21-201 isotope ratio mass spectrometer. Here the ion accelerating voltage was 1175 volts and the ionizing current was 50 μamperes. The peak 46 was focused on selector 2; peaks 44 and 45 were then recorded together on selector 1. The small differences involved in going from one machine to the other were negligible in comparison with the magnitude of the enrichments used.

Results

Control Experiments. Oxygen-18.—Under the experimental conditions for these reactions, the starting alcohols (phenyl-*t*-butylcarbinol and anisyl-*t*-butylcarbinol) and the product alcohol (*t*-butyl alcohol) do not exchange their oxygen atoms rapidly with those of the solvent. The appropriate control data are found in Table I. Acetic acid does exchange slowly with $H_2{}^{18}O$, but approximately 91% of the label remains in the water during an exchange experiment.

Oxidative Cleavage. Oxygen-18.—The results of the studies of oxidative cleavage are presented in Table II. Essentially no oxygen from the carbinol-^{18}O is found in the *t*-butyl alcohol produced. When the solvent, rather than the organic starting material, carries the label, the *t*-butyl alcohol produced has approximately one atom of ^{18}O per molecule, although the agreement between the percentage in the solvent and final alcohol leaves something to be desired. Under the experimental conditions of these experiments, the

TABLE II

OXIDATIVE CLEAVAGE OF CARBINOLS IN 86.5% ACETIC ACID AT 0°

Compound oxidized	Time, hours	Experimental conditions	Excess ^{18}O, % Reactant	Excess ^{18}O, % Reaction medium	Excess ^{18}O, % Product
PBC-^{18}O[a]	7	Standard	0.607	0.000	0.005[b]
PBC-^{18}O	5	Standard	.607	.000	.011
PBC-^{18}O	5	Twice usual amt. of CrO_3	.000	.415	.430
ABC-^{18}O[c]	5	Standard	.596	.000	.005
ABC-^{18}O	5	Standard	.596	.000	.006
ABC	5	Twice usual amt. of CrO_3	.000	.429	.512
ABC-^{18}O	4	Mn^{++} added[d]	.596	.000	.007

[a] Phenyl-*t*-butylcarbinol. [b] Average deviation of duplicate determinations throughout Table II is about 0.005 atom % ^{18}O. [c] Anisyl-*t*-butylcarbinol. [d] Ratio of Mn^{++} to CrO_3 = 1.8.

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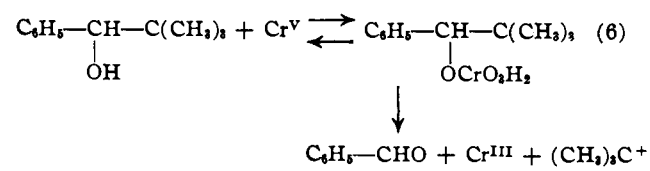
pivalophenone produced is reasonably stable; about 6% of it may be oxidized to the corresponding acid, but the rest survives. Cleavage, then, accompanies the oxidation of the alcohol and is not a subsequent process.

A few oxidations were carried out with deuterioacetic acid and D_2O. The *t*-butyl alcohol produced was analyzed mass-spectrometrically and contained very little, if any, deuterium. When isobutylene was hydrated under these experimental conditions, the ratio of the mass peaks 60/59 was 1.5; in the oxidative experiments it was about 0. Thus the *t*-butyl alcohol found is not formed from isobutylene.

Discussion

t-Butyl alcohol, obtained as the product of the chromic acid oxidation of isotopically labeled phenyl-*t*-butylcarbinol and of anisyl-*t*-butylcarbinol, shows no enrichment in ^{18}O (Table II). Conversely, *t*-butyl alcohol, obtained as the product of oxidation of these carbinols in aqueous solution of acetic acid, initially labeled with oxygen-18 only in the water, shows an isotropic enrichment about equal to that calculated for the solvent. These data are consistent with the following partial mechanism where the cleavage is performed (as explained in the Introduction) by pentavalent chromium.

The argument that reaction scheme 5 is excluded depends on the prior demonstration that the hydrolysis of the di-*t*-butyl acetal of benzaldehyde occurs according



(6)

to eq. 7, without exchange between the solvent and the oxygen atoms originally present in the acetal.[20]

$$C_6H_5CH(OR)_2 + H_2O^* \xrightarrow{H^+} C_6H_5CHO^* + 2ROH \qquad (7)$$

This hydrolysis almost certainly proceeds by way of the same cation, A, $C_6H_5CH{=}O^+{-}C(CH_3)_3$, which is required for the oxidative rearrangement. Therefore, if this intermediate were formed, the oxygen atom originally present in the carbinol would appear in the *t*-butyl alcohol. None does. Therefore the rearrangement does not occur.

On the basis of the present work alone, no distinction can be made between an oxidative process producing a carbonium ion and one producing a radical. The work of Lansbury, *et al.*,[10] coupled with that here reported, makes the carbonium ion sequence of eq. 6 quite probable.

Acknowledgment.—This work was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

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The Hydrolysis of Methyl Ethylene Phosphate: Steric Hindrance in General Base Catalysis

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The general base catalysis of the mutarotation of glucose and the general acid catalysis of the inversion of menthone are subject to steric hindrance; 2,6-lutidine is a poorer catalyst than would be expected considering its ionization constant by factors of 25 and about 10, respectively. The hydrolysis of methyl ethylene phosphate is catalyzed by heterocyclic bases with a solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, of about 2; 2,6-lutidine is again a poorer catalyst than anticipated by a factor of ten. These data suggest: (1) that the hydrolysis of methyl ethylene phosphate is subject to general base, rather than to nucleophilic, catalysis; and (2) that general base and general acid catalysis are moderately sensitive to steric hindrance.

One of the criteria which might be considered to characterize nucleophilic, as opposed to general base, catalysis is that the former is subject to steric hindrance. Thus Butler and Gold[2] found that pyridine catalyzes the solvolysis of acetic anhydride, whereas 2-picoline and 2,6-lutidine, which are stronger bases, have no effect on the reaction rate. The pyridine catalysis is diminished by acetate ions, and on this evidence they concluded that, despite the large deuterium solvent isotope effect,[2,3] the reaction proceeds by way of acetylpyridinium ions, *i.e.*, that it represents an example of nucleophilic catalysis.[4] The low rates with 2-picoline and 2,6-lutidine were ascribed to steric hindrance of nucleophilic attack by the bases on the anhydride. Similarly, 2,4-lutidine and 2,6-lutidine (in contrast to pyridine) fail to catalyze the hydrolysis of tetramethylphorphorodiamidic chloride[5]; this reaction presumably occurs by way of nucleophilic attack by the heterocyclic base on the phosphorous atom.

Implicit, however, in the use of steric hindrance as a criterion for nucleophilic attack is the assumption that general base (and general acid) catalysis is not subject to such hindrance. The Brönsted equation[6] connects base strength and catalytic activity

$$k_B = GK_B^x$$

where k_B is the catalytic constant for any base, B, and K_B is its ionization constant; G is a constant for a series of similar bases, and $0 < x < 1$. This relationship might seem already to take into account steric hindrance of the base toward a proton, *i.e.*, such hindrance might already be included in a diminished basicity of B. Recently, however, Gutsche[7] and his co-workers have found that the aldol condensation is promoted by some tertiary amines, including pyridine but that 2,6-lutidine is not very effective. It is here shown that three other reactions which proceed by

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