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Mechanistic Studies Regarding the Oxidation of Alcohols by Silver Carbonate on Celite

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The mechanism of the oxidation of alcohols by silver carbonate on Celite was thoroughly investigated to ascertain the nature of the transition state and the possible intervention of reaction intermediates. Kinetic, stereochemical, and isotopic labeling techniques were used to differentiate among the various theoretically plausible mechanistic alternatives. The effects of surface adsorption and solvent composition on the outcome of the reaction were also studied. The data were consistent with a concerted process for which a model is proposed.

Although silver carbonate precipitated on Celite is a relatively new[1] oxidizing agent, it has already gained wide acceptance. The chief advantages of this reagent lie in its selectivity, the mild conditions necessary to carry out the oxidation, and the ease with which the products can be isolated. These factors have been extensively reviewed in a recent report.[2] It can be seen from this review that silver carbonate is an efficient and convenient reagent for the oxidation of not only alcohols but a variety of other substrates.

In view of the wide scope of this reaction and its ever-increasing applications in organic synthesis, we thought that it would be of considerable theoretical as well as practical interest to undertake a comprehensive study of the mechanism of the oxidation of alcohols. Some preliminary findings of this investigation were reported in an earlier communication.[3] We now wish to present the final data which bear on the mechanism. For convenience we have chosen to present and discuss our findings under seven different headings: stoichiometry, intermediates, surface phenomena, isotope effects, steric effects, kinetics, and postulated models.

Results and Discussion

I. Stoichiometry. Since the usual procedure for carrying out silver carbonate oxidations utilizes a large excess of silver carbonate, the mole ratios of reactants and products are not immediately apparent. To ascertain the exact stoichiometry of the reaction we have conducted two independent experiments. The first was a gravimetric method which consisted of trapping the carbon dioxide produced during the course of the reaction in a suitable absorption tube. It was found that the moles of carbon dioxide produced were approximately equal to the moles of alcohol oxidized and independent of the amount of silver carbonate used. The second experiment involved the oxidation of standard solutions of benzhydrol with varying amounts of silver carbonate which had been previously analyzed to obtain its exact composition. Quantitative analyses of the product (benzophenone) were carried out by comparing the ultraviolet absorption of the mixtures against a standard Beer's law curve. These data are summarized in Tables I and II. It was generally found that the mole ratio of alcohol to silver carbonate was 1:1.

The above data allowed us to establish the exact stoichiometry of the reaction, which can be summarized by the following equation.

$$R_2CHOH + Ag_2CO_3 \longrightarrow R_2C{=}O + H_2O + 2Ag + CO_2$$

The stoichiometric relationships defined by the above equation are consistent with the mechanistic model proposed in the last section.[4]

II. Intermediates. The oxidation of alcohols to carbonyl compounds necessarily involves the removal of two hydrogens. In principle, unless the process is concerted, each of these hydrogens may come off as a free radical, a hydrogen ion, or a hydride ion. This leads to six theoretically possible reaction intermediates.

$$\underset{|}{-\dot{C}}-OH \quad \underset{|}{-\ddot{C}}-OH \quad \underset{|}{-\overset{+}{C}}-OH \quad \underset{|}{-CH}-O\cdot \quad \underset{|}{-CH}-O^- \quad \underset{|}{-CH}-O^+$$

1 2 3 4 5 6

Table I
Data[a] from the Gravimetric Analysis of the Carbon Dioxide Evolved during Oxidation of Benzhydrol by Silver Carbonate on Celite

Net wt of CO_2, mg	Mol of CO_2	Mol of benzhydrol	Mol of CO_2 / Mol of alc
83.3	1.9×10^{-3}	1.7×10^{-3}	1.1

[a] Average of four experiments.

General considerations render a number of these intermediates highly unlikely. For example, an intermediate such as 6 would be very unstable and thus not easily formed. Oxidations of primary alcohols proceeding *via* a type 1 intermediate should lead, at least in part, to carboxylic acids, whereas type 4 intermediates are known[5] to yield cyclization products as well as functionalization of nonactive methylene groups. No such products have ever been observed in silver carbonate oxidations of alcohols. Nevertheless, to obtain direct experimental evidence the following experiments were conducted.

A. Oxidation of Cyclopropylcarbinols. The oxidations of cyclopropylcarbinol, methylcyclopropylcarbinol, and dicyclopropylcarbinol were carried out in the usual way.[1] The products were isolated and identified by infrared and nmr spectroscopy and by syntheses of crystalline derivatives. In each case it was found that the alcohols were converted smoothly to the corresponding carbonyl compound without rearrangement or ring opening. These results are in agreement with the findings of other investigators.[6-8]

In view of the well-known[9] tendency of cyclopropylcarbinyl, carbonium ions, carbanions, and radicals to undergo ring opening or rearrangement, we interpret the lack of such products as evidence for the absence of these intermediates in the reaction studied.

B. Free-Radical Catalysis and Inhibition. Exploring further the possibility of free-radical intermediates, we have carried out two parallel oxidations of benzhydrol under identical conditions except that one of the reaction mixtures was treated with a catalytic amount of azobisisobutyronitrile, a well-known[10] free-radical initiator. The reaction was stopped before completion and the yield of the product (benzophenone) was determined by ultraviolet spectroscopy with the aid of a standard Beer's law curve. It was found that the free-radical initiator had in fact inhibited rather than catalyzed the reaction. Furthermore, it was found that the reaction rate was unaffected by the presence of oxygen, which is known to inhibit free-radical processes. Finally, the usual coupling products observed in many free-radical reactions were totally absent, not only from the benzhydrol oxidation but also from any other silver carbonate oxidation of alcohols.

These findings provide additional evidence against the intervention of any kind of free-radical intermediates in the reaction studied.

C. Stereochemical Evidence. A sample of optically active 1,2,2-triphenylethanol was partially oxidized with silver carbonate on Celite and the unchanged starting material was isolated and examined for optical activity. It was found that there was no change in the optical rotation. This compound was selected as the model because of the well-known[11-16] tendency of this system toward rearrangement even under conditions which do not normally produce carbonium ions.

The complete lack of racemization which we have observed is therefore inconsistent with the existence of free carbonium ion intermediates in the present system. However, a "carbonium ion like" transition state which goes irreversibly to products cannot be ruled out on the basis of this experiment alone.

D. Solvent Effects. The role of the solvent in heterogeneous reactions is not easy to assess because there are several other factors which are superimposed on the normal solvation effects. Among other things the polarity of the solvent influences the degree of self adsorption, the rate of adsorption of the reactants, and the rate of desorption of the products. Nevertheless, we have attempted to gain some further insight as to the nature of this process by carrying out several comparative oxidations of alcohols in solvents of varying polarities.

To eliminate temperature effects, solvents and solvent mixtures with approximately the same boiling points were chosen and the oxidations were carried out in such a manner as to ensure that all other reaction conditions were as closely identical as possible. The details of these oxidations are given in Table III. It was generally found that the polar solvents severely inhibited the reaction.

III. Surface Effects. In view of the heterogeneous nature of our reaction, adsorption undoubtedly plays an important role. To investigate the catalytic effect of the increased surface afforded by Celite, a series of concurrent oxidations of benzhydrol but with oxidizing reagents containing varying amounts of Celite was carried out. The oxidant samples were analyzed prior to use and appropriate weights were taken to ensure that the same number of equivalents of silver carbonate were used in each case. As before, the product formation was followed by ultraviolet absorption measurements. The results are summarized in Table IV.

It was generally found that the increase in the amount of Celite on which the silver carbonate is precipitated causes an increase in the rate of oxidation until a maximum value is reached. On further increasing the Celite content of the oxidant a decrease in the rate is observed.

The observed increase in the rate of oxidation with increasing surface supports the postulated importance of the adsorption on the outcome of the oxidation. The decrease in the rate after the maximum value was reached is simply a dilution effect.

These results also showed that the addition of free Celite to the standard reagent does not influence the rate of oxidation, *i.e.*, the effective oxidizing agent is not simply a mixture of silver carbonate and Celite.

Table II
Uv Data and Calculated Results for the Oxidation of Benzhydrol with Varying Amounts of Silver Carbonate on Celite

Wt of Ag_2CO_3, mg	Mmol of Ag_2CO_3[a]	Mmol of benzhydrol	Equiv of Ag_2CO_3	A (λ_{max} 278 mμ)	Ph_2CO, mmol/l.	% oxidn
120.4	0.20	0.20	1	1.74	0.82	100
90.0	0.15	0.20	0.75	1.37	0.65	79
60.5	0.10	0.20	0.50	0.96	0.44	54
30.0	0.05	0.20	0.25	0.455	0.21	26

[a] A quantitative analysis of the silver carbonate/Celite reagent used in these experiments showed that it contained 1 mmol of silver carbonate per 0.60 g of reagent.

Table III
Comparative Oxidations of Alcohols in Various Solvents

Solvent	ϵ, D	Bp, °C	Time of reflux, hr: 1-Heptanol	Benzhydrol	5α-Androstan-3β-ol	% oxidation: 1-Heptanol	Benzhydrol	5α-Androstan-3β-ol
Hexane (35%) + Heptane (65%)	1.9	80	6.5	0.75		100	50	
Benzene	2.27	80.1	6.5	0.75	0.33	90	2	100
Ethyl acetate	6.02	77.1	6.5			<1		
tert-Butyl alcohol	12.47	82.5	6.5		300	<1		90
Methyl ethyl ketone	18.51	77–80	15			<1		
Acetonitrile	37.50	81.6	7			<1		

Table IV
Results of the Oxidation of Benzhydrol by Silver Carbonate Containing Various Amounts of Celite[a]

Wt of Celite/mol of silver carbonate, g	Wt of silver carbonate/Celite used, mg	% Ag_2CO_3 in each reagent[c]	Equiv of silver carbonate	Wt of free Celite, mg	% oxidation[b]	Relative rate[b]
300	117.0	49.24	5		5	1
600	184.3	31.18	5		12.5	2.5
900	231.7	24.85	5		35	7
1200	298.8	19.27	5		30	6
600	369.2	31.18	10		81	2.5
300	234.0	49.24	10	135.2	32	1

[a] Average of several experiments. [b] ±10%. [c] These values vary somewhat from the theoretical because they were based on the silver content of each sample found by actual analysis.

Table V
Oxidative Data and Intramolecular Isotope Effects for Primary Alcohols

Alcohol[a]	Products of the oxidation	Equiv of Ag_2CO_3	Reaction conditions: Support	Solvent	Reaction time, hr	% D	K_H/K_D
PhCDHOH[c]	PhCHO + PhCDO	6	None	Benzene	72	86.8[b]	6.4
PhCHDOH	PhCHO + PhCDO	6	Celite	Heptane	10	83.0	5.06
PhCHDOH	PhCHO + PhCDO	6	Celite	Benzene	18	83.4	5.00
PhCHDOH	PhCHO + PhCDO	6	Celite	$CHCl_3$	48	82.8	4.80
PhCHDOH	PhCHO + PhCDO	6	Silica gel	Benzene	15	83.0	4.88
o-MeOPhCHDOH	*o*-MeOPhCHO + *o*-MeOPhCDO	6	None	Benzene	72	86.8	6.57
p-MeOPhCHDOH	*p*-MeOPhCHO + *p*-MeOPhCDO	6	Celite	Benzene	24	83.5	5.06
m-NO_2PhCHDOH	*m*-NO_2PhCHO + *m*-NO_2PhCDO	6	Celite	Benzene	24	82.6	4.75
$CH_2{=}CHCHDOH$[c]	$CH_2{=}CHCHO$ + $CH_2{=}CHCDO$	4	Celite	Chlorobenzene	10	82.4	4.7
Geraniol[c] (CHDOH)	Citral + citral-*d*	4	Celite	Benzene	24	83.7	5.1
Heptanol-d_1	Heptanal + heptanal-*d*	20	Celite	Benzene	72	82.5	4.71
Heptanol-d_1	Heptanal + heptanal-*d*	20	Celite	Heptane	48	83.2	5.0

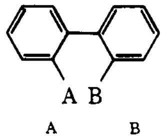
[a] Ten millimoles. [b] Average of four experiments. [c] These reactions were performed under nitrogen.

The role of adsorption on the course of this reaction was further studied by performing several competitive partial oxidations of equimolar amounts of various primary or secondary alcohols. The oxidations were carried out in the same reaction vessel and the mixtures were analyzed by gas chromatography before and after the reaction. The details of these experiments are shown in Tables IX and X and discussed in section V.

IV. Kinetic Isotope Effects. Both the intramolecular and intermolecular primary deuterium kinetic isotope effects were investigated. A variety of primary and secondary alcohols, deuterated and undeuterated, were oxidized with silver carbonate and the relative rates of oxidation were ascertained by careful product analysis utilizing nuclear magnetic resonance and mass spectrometry. The results are summarized in Tables V–VIII. The average primary intermolecular deuterium isotope effect for primary alcohols was found to be 1.9 and for the secondary alcohols 3.2. These values are consistent with those reported by other investigators.[17,18]

The average intramolecular isotope effects involving the oxidation of alcohols of the type RCHDOH were 4.9 except in the two instances in which the Celite support was omitted. For those cases the isotope effect was found to be 6.5. In all of the above oxidations there was no significant change in the isotope effect with the solvent composition. Additional isotope effect data were obtained from the oxidation of *o,o′*-bis(hydroxymethyl)biphenyl (7–9).

Two types of experiments were performed with this compound. The first involved the oxidation of 7 and the second the oxidation of a 1:1 mixture of 8 and 9. In the



	A	B
7	CH_2OH	CD_2OH
8	CH_2OH	CH_2OH
9	CD_2OH	CD_2OH

first instance the average value of the kinetic isotope effect was 6.1 (slightly higher when the Celite support was omitted, *ca.* 6.8).

The second set of experiments gave a kinetic isotope effect value of 2.0 with or without Celite.

Table VI
Oxidative Data and Intermolecular Isotope Effects for Primary Alcohols

		Reaction conditions			
Alcohol[a]	Ratio	Support	Solvent	Reaction time	K_H/K_D
PhCH$_2$OH, PhCD$_2$OH	1:1	Celite	Benzene	1 hr	1.90
PhCH$_2$OH, PhCD$_2$OH	1:1	Celite	Heptane	30 min	2.0
o-MeOPhCH$_2$OH, *o*-MeOPhCD$_2$OH	1:1	Celite	Benzene	90 min	1.82
o-MeOPhCH$_2$ H, *o*-MeOPhCD$_2$OH	1:1	Silica gel	Benzene	40 min	1.74
o-MeOPhCH$_2$OH, *o*-MeOPhCD$_2$OH	1:1	Cellulose	Benzene	90 min	2.0
o-MeOPhCH$_2$OH, *o*-MeOPhCD$_2$OH	1:1	Alumina	Benzene	55 min	1.80
o-MeOPhCH$_2$OH, *o*-MeOPhCD$_2$OH	1:1	Celite	CHCl$_3$	7 hr	1.70
o-MeOPhCH$_2$OH, *o*-MeOPhCD$_2$OH	1:1	None	Heptane	48 hr	1.75
CH$_3$(CH$_2$)$_8$CH$_2$OH, CH$_3$(CH$_2$)$_8$CD$_2$OH	1:1	Celite	Heptane	2 hr	2.03
CH$_3$(CH$_2$)$_8$CH$_2$OH, CH$_3$(CH$_2$)$_8$CD$_2$OH	1:1	Celite	Benzene	3 hr	1.98

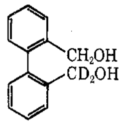
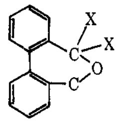
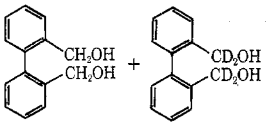
[a] The isotopic purity of these mixtures was checked before the reaction and found to be 50 ± 2%.

Table VII
Oxidative Data and Intermolecular Isotope Effects for Secondary Alcohols

		Oxidation conditions			
Alcohol[a]	Ratio	Support	Solvent	Reaction time	K_H/K_D
CH$_3$CH(OH)(CH$_2$)$_7$CH$_3$, CH$_3$CD(OH)(CH$_2$)$_7$ CH$_3$	1:1	Celite	Benzene	1 hr	3.5
CH$_3$CH(OH)(CH$_2$)$_7$CH$_3$, CH$_3$CD(OH)(CH$_2$)$_7$CH$_3$	1:1	Silica gel	Benzene	2 hr	3.5
CH$_3$CH(OH)(CH$_2$)$_7$CH$_3$, CH$_3$CD(OH)(CH$_2$)$_7$CH$_3$	1:1	Silica gel	Benzene	30 min	3.45
CH$_3$CH(OH)(CH$_2$)$_7$CH$_3$, CH$_3$CD(OH)(CH$_2$)$_7$CH$_3$	1:1	Celite	Toluene	45 min	3.53
PhCHOHCH$_3$, PhCDOHCH$_3$	1:1	None	Benzene	30 min	2.95
PhCHOHCH$_3$, PhCDOHCH$_3$	1:1	Celite	Benzene	15 min	3.2
PhCHOHCH$_3$, PhCDOHCH$_3$	1:1	Celite	Heptane	1 hr	3.6
o-MeOPhCHOHCH$_3$, -PhCDOHCH$_3$	1:1	None	Heptane	10 hr	3.0

[a] The isotopic purity of these mixtures was checked before the reaction and found to be 50 ± 2%.

Table VIII
Isotope Effects and Oxidative Data for the Reaction of *o,o'*-Bis(hydroxymethyl)biphenyl

		Reaction conditions			K(CH$_2$OH)/
Substrate	Product	Support	Solvent	Reaction time	K(CD$_2$OH)
	 X = H or D	Celite	Benzene	5 days	6.15[a]
		None	Benzene	1 day	6.8
					K_H/K_D
[b]  1:1 mixture		Celite	Benzene	2 hr	1.98
		Celite	Heptane	1 hr	2.02

[a] Average of four experiments. [b] Partial oxidation.

From observed values of the kinetic isotope effects the following conclusions may be drawn.

(1) Theoretical considerations[19,20] for homogeneous systems predict a maximum isotope effect for symmetrical transition states. The isotope effects we have measured, although significant, fall somewhat short of the predicted maxima. However, we feel that the theoretical arguments mentioned are not entirely applicable to our heterogeneous system. The isotope effect observed in our study is most likely a combination of differential adsorption with elimination. To separate the two effects we have designed experiments which minimized the adsorption step. This was accomplished by conducting some of the oxidations without Celite.[21] The consequence of omitting the Celite was an increase in the observed isotope effect. Similar results were obtained in all of our experiments, *i.e.*, the kinetic isotope effect decreased with increasing adsorption. Thus we feel that the kinetic isotope effect values obtained from the oxidations without Celite can serve as a more valid criterion of the nature of the transition state because they can be attributed almost exclusively to the breaking of the carbon-hydrogen bond.

In view of the above we interpret the rather high values of the kinetic isotope effect (>6) obtained from the silver carbonate oxidations without Celite as indicative of a symmetrical transition state.

(2) The intramolecular kinetic isotope effects we have measured were larger than the intermolecular effects by a factor of three. Usually the reverse is found, *i.e.*, the intermolecular effects are higher because of the contribution of the secondary isotope effect.[22,23] Inverse isotope effects have been previously reported[24] for silver ion-olefin complexes where deuteration has led to an increase in complex stability. However, the difference we have observed is much too high to be solely attributed to secondary effects of this type. Therefore what we have measured must be principally a primary effect stemming from hydrogen *vs.* deuterium adsorption. These data indicate that the adsorption of the hydrogen which is attached to the carbon bearing the hydroxyl group precedes elimination. The steric effects, which will be discussed in section VI, lend support to this hypothesis by dramatically demonstrating the necessity of having this hydrogen oriented toward the surface of the solid prior to oxidation.

Table IX
Kinetic Data[a] and Calculated Results for the Oxidation of Alcohols by Silver Carbonate/Celite

Alcohol(s)	Equiv of Ag_2CO_3 for the mixture	Equiv of Ag_2CO_3 for each alcohol	Rate constants × 10^6, sec^{-1}
1-Octanol	5	5	19
	10	10	24
	40	40	132
1-Hexanol		10	1.7
+	5		
1-Octanol		10	2.6
1-Hexanol		15	0.6
+			
1-Octanol	5	15	0.8
+			
1-Decanol		15	1.3
1-Hexanol		60	82
+			
1-Octanol	20	60	82
+			
1-Decanol		60	82
2-Hexanol		15	8.8
+			
2-Octanol	5	15	8.8
+			
2-Decanol		15	8.8
1-Octanol		20	86
+	10		
2-Octanol		20	16

[a] Average of three experiments. Average deviation 10%.

In all cases where steric and conformational factors prevented the adsorption of the CH hydrogen, the reaction was severely inhibited.

(3) The above discrepancy in the observed values of intramolecular and intermolecular isotope effects points out the obvious dissimilarity in the mechanism of alcohol oxidations by manganese dioxide[22] and those by silver carbonate on Celite.

In addition, the kinetic isotope effect values obtained[22] for manganese dioxide oxidations were significantly higher than our own.

(4) The isotope effects measured during the oxidation of *o,o'*-bis(hydroxymethyl)biphenyl are particularly illuminating. The oxidation of this diol leads to an ε-lactone. There are two significant observations to be made regarding this reaction. First, the abstraction of single hydrogen dictates and fixes the particular hydroxymethyl group which is oxidized. The isotope effect is therefore equivalent to that of a primary alcohol. Second, the two hydroxymethyl groups, being part of the same molecule, are probably adsorbed at the same time, a fact which for the diol **7** results in an intramolecular type kinetic isotope effect. This effect is the sum of a primary and secondary effect.[22] Thus the data obtained from the oxidation of the diols permit us to calculate a secondary isotope effect for this reaction using the relation

$$k_{\mathrm{sec}} \cong \frac{k_{\mathrm{diol}}}{k_{\mathrm{intra}}} = \frac{6.1}{4.8} \cong 1.3$$

This value is consistent with that reported by Goldman.[22] The simultaneous adsorption of the two alcohol functions was verified by oxidizing a 1:1 mixture of **8** and **9**. The measured isotope effect (2.0), which is intermolecular, agrees with that obtained for the intermolecular oxidation of ordinary primary alcohols.

The above results can only be explained in terms of a two-step oxidation for the diol studied: a slow step leading to the aldehyde which cyclizes to the lactol, followed by the rapid oxidation of the lactol to the ε-lactone. Any other alternative would have given much higher values for the isotope effect. A previously reported[25] silver carbonate oxidation of 1,6-hexanediol has also resulted in the isolation of an ε-lactone. These findings are significant, since it is well known[26] that seven-membered-ring ketones form with difficulty. It is noteworthy, however, that the mechanistic model we propose (*cf.* section VII) invokes protonated carbonyl structures which are known to undergo rapid cyclization. Thus the isolation of seven-membered-ring ketones from the oxidation of diols by silver carbonate provides additional, be it indirect, evidence for the correctness of the postulated mechanism.

Table X
Results from the Competitive Oxidation of an Equimolar Mixture of Primary Alcohols

Alcohol	1-Butanol	1-Hexanol	1-Octanol	1-Decanol
Per cent oxidation[a] after 7.5 days	2	7	10	15
Per cent oxidation[a] after 18.5 days	17	16	18	23

[a] ±1%.

V. Kinetics. General. The difficulties associated with the study of kinetics of heterogeneous reactions are well known.[22,27] In our particular system there are some important reaction parameters which are impossible to control. To begin with, it has been reported that silver carbonate[28] can exist in two distinct forms, and that the proportion of the two is a function of the mode of preparation. Second, it is not possible to achieve absolute uniformity in the size and shape of the adsorbent particles. Such variations are known to affect significantly the course of heterogeneous reactions. Third, we have established by means of many trials that the rate of agitation greatly influences the rate of oxidation. Again it is difficult to maintain absolutely identical rates of agitation. Finally, in our experiments we have always utilized predried silver carbonate/Celite reagent, and, although we have carefully followed the same drying procedure, there is no way of assessing quantitatively the amount of moisture which was retained by the samples in each case.

In view of the above we felt that it would be meaningless to attempt to obtain absolute rates for these oxidations. The only meaningful experiments, therefore, were competitive oxidations which take place in the same reaction vessel and therefore can give good values for the relatives rates. All other types of measurements give answers which are not very reproducible. Thus it can only be used in a qualitative way, *i.e.*, to reveal general trends.

Specific. The rates of oxidation of 1-octanol as well as mixtures (1-hexanol and 1-octanol; 1-hexanol, 1-octanol and 1-decanol; 2-hexanol, 2-octanol and 2-decanol; and 1-octanol and 2-octanol) in heptane were determined by gas chromatography. In each case an excess of silver carbonate/Celite reagent was used. The details on these experiments are summarized in Table IX. It was generally found that after an initial induction period good pseudo-first-order rate constants can be obtained. The rate was also found to be roughly proportional to the amount of silver carbonate/Celite used in each case. In another experiment we have oxidized an equimolar mixture of 1-butanol, 1-hexanol, 1-octanol, and 1-decanol, but rather than performing detailed kinetic measurements we have examined the reaction mixture after 7.5 days and again after 18.5 days by gas chromatography to ascertain the per cent oxidation of each alcohol. These results are summarized in Table X.

The kinetic behavior observed during all of these competitive oxidations above deserves further comment.

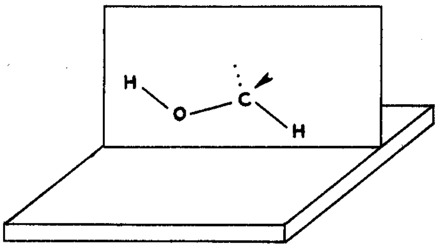


Figure 1.

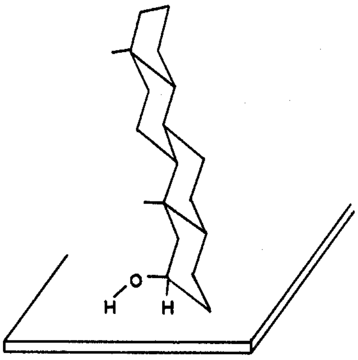


Figure 2. 5α-Androstan-2β-ol (**10**).

(1) The specific rate constant obtained for the oxidation of 1-octanol in the presence of 1-hexanol is significantly lower than that obtained for the oxidation of the 1-octanol by itself, even though in each case the same equivalents of silver carbonate were used and identical reaction conditions were maintained. A further decrease was observed when a mixture containing a third alcohol (1-decanol) was oxidized under the same conditions. It is clear, therefore, that the presence of one alcohol inhibits the oxidation of the others.

(2) When equimolar mixtures of alcohols (either all primary or secondary) were oxidized, and there was competition for the oxidizing agent, the increase in the rate of oxidation coincided with increased molecular weight, *i.e.*, the heavier alcohols oxidized faster than the lighter ones. Since all of the alcohols were oxidized in the same vessel, this difference can only be due to differential adsorption,[29] which underscores the significance of this phenomenon in silver carbonate/Celite oxidations.

(3) An inspection of Tables IX and X reveals that the difference in the rate of oxidation of the various alcohols in the mixtures becomes smaller as the quantity of silver carbonate increases. Thus, when a large excess of oxidant is used, the oxidations proceed essentially at the same rate. Even in this case, however, one can observe differences by making measurements in the very early stages of the reactions where the difference in the rate of oxidation is more pronounced. These results are consistent with our postulated differential adsorption of heavy and light alcohols.

(4) Our measurements confirmed the previously reported general tendency of secondary alcohols to oxidize faster than primary alcohols under the same conditions.[30] In the presence of significant steric interactions this general trend may be reversed (*e.g.*, dicyclopropylcarbinol oxidized slower than cyclopropylcarbinol).

VI. Steric Effects. A. Steroid Alcohols. To establish the steric and conformational parameters associated with this oxidation, several competitive oxidations of binary mixtures of steroidal epimeric secondary alcohols were carried out. These studies provided us with significant further insights as to the mechanism of the oxidation. The results of these experiments were presented in our preliminary communication.[3]

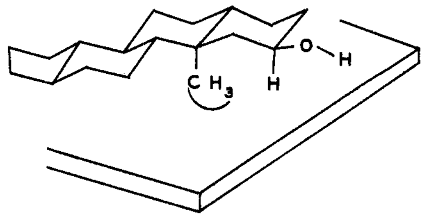


Figure 3. 5α-Androstan-2α-ol (**11**).

It was generally found that the oxidations were first order with respect to the alcohol. Furthermore, the necessity of proper orientation toward the adsorbent surface of not only the hydroxyl group but also the hydrogen attached to the carbon bearing the hydroxyl group was dramatically demonstrated.

Our results can best be explained in terms of a coplanar configuration of all the groups undergoing bond change, which is perpendicular to the plane of the solid surface of the oxidizing reagent.[31]

The necessary three-dimensional arrangement of the various groups is depicted in Figure 1.

In all cases where steric and conformational factors did not permit the described orientation toward the surface, the oxidation was found to proceed much slower than that involving isomers which could more easily attain the required orientation. In severely restricted cases the oxidation was totally inhibited.

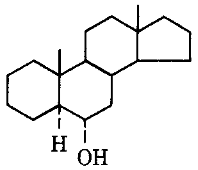
The significance of these steric effects may be illustrated by means of the following example.

The oxidation of 5α-androstan-2β-ol (**10**) proceeds 25 times faster than the oxidation of the 2α isomer (**11**). An examination of the models reveals that in the case of the 2β alcohol (**10**, hydroxyl axial) there is no interaction whatsoever between the rest of the molecule and the solid surface of the oxidant (Figure 2).

In contrast, the adsorption of the epimeric 2α alcohol (**11**, hydroxyl equatorial) is sterically hindered by the C-19 methyl group (Figure 3).

A similar analysis can be used to explain the virtual lack of reactivity toward silver carbonate of 5α-androstan-6α-ol (**12**) and 5α-androstan-7α-ol (**13**). The adsorption of compound **12** is sterically hindered by both the C-19 methyl and the C-4 methylene groups, whereas the adsorption of compound **13** is hindered by the C-15 methylene group. The corresponding 6β and 7β epimeric alcohols **14** and **15**, whose adsorption is not sterically hindered, were readily oxidized.

As we have pointed out in our preliminary communication,[3] steric acceleration apparently plays only a minor role in the reaction under study, since, in contrast to chromic acid oxidations,[32] we have found that 5α-androstan-2β-ol (hydroxyl axial) does not oxidize appreciably faster than 5α-androstan-3β-ol (hydroxyl equatorial).



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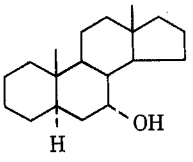

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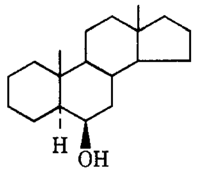

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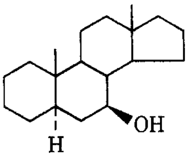

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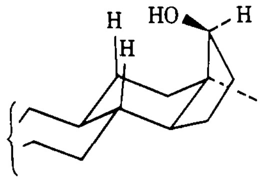
Another type of steric interaction, one which involves the degree of accessibility of the hydrogen which is attached to the carbon bearing the hydroxyl group, is exemplified by the relative rates of oxidation of 13α,5α-androstan-17β-ol (**16**) and 13α,5α-androstan-17α-ol (**17**). Inspection of the structures below shows that the hydrogen of the 17β isomer (**16**) is more accessible than the hydrogen of the 17α isomer (**17**). **16** was found to oxidize six times faster than **17**.



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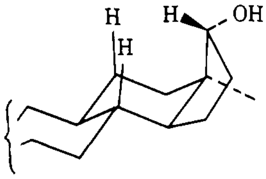

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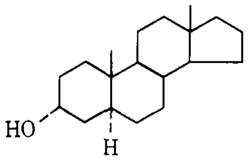
A similar result was reported by Eckert, *et al.*,[16] who found that the silver carbonate oxidation of *endo*-norbornanol proceeds much faster than that of *exo*-norbornanol.

The fact that 5α-androstan-3α-ol (**18**) and 5α-androstan-3β-ol (**19**) were found to oxidize at the same rate may be compared with the results of Venkatasubranian, *et al.*[33,34] These authors effected the oxidation of 3α and 3β cholestanols by *N*-bromosuccinimide in the presence of mercuric acetate[35] and found that the two isomers oxidized at the same rate. The results were interpreted in terms of a cyclic transition state which involved simultaneously the hydroxyl group of the alcohols and hydrogen which is attached to the carbon bearing the hydroxyl group. Our data lead to postulate a similar transition state (*cf.* section VI).



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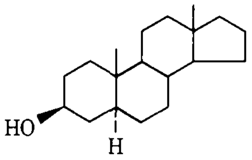

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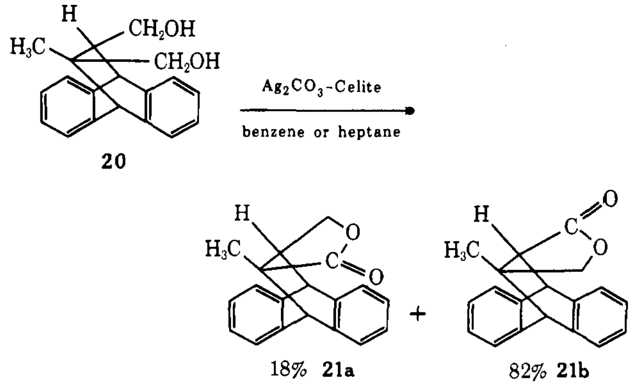
B. 11-Methyl-11,12-dihydroxymethyl-9,10-dihydro-9,10-ethanoanthracene (20). The effect of steric hindrance on the outcome of silver carbonate oxidations of alcohols was further verified by means of the oxidation of the disymmetric diol **20**. The oxidation of this compound can lead to two different lactones (**21a** and **21b**). In the absence of steric interactions the two products should form in equal amounts. We have found, however, that the major product was **21b**, *i.e.*, that resulting from the oxidation of the least hindered 12-hydroxymethyl group of **20**. The oxidation of the 11-hydroxymethyl group is hindered by the presence of the methyl group, thus leading to the minor product **21a**.



VII. Postulated Models. A. Kinetic. The data from the rate studies discussed above permit us to postulate a kinetic model to explain the behavior of alcohols when they are oxidized by silver carbonate on Celite. This model is based on the assumption that there is no significant reaction except with adsorbed molecules, and that the silver ions in the solid phase constitute "active sites" for the chemisorption of the alcohol oxygen.[36]

The reaction under investigation bears an interesting similarity to one-substrate enzymatic reactions, a thorough theoretical treatment of which has been recently published.[37] Thus, if we let A represent a free alcohol molecule in solution, P a molecule of the product, and F_o and F_r the oxidized and reduced forms of the silver carbonate reagent, respectively, the overall process can be represented by two reversible and one irreversible steps

$$A + F_o \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A{-}F_o \xrightarrow{k_2} P{-}F_r \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} P + F_r$$

where $A{-}F_o$ represents the adsorbed alcohol[39] on the oxidized form of the reagent and $P{-}F_r$ the adsorbed product on the reduced form of the reagent.

The irreversible step can be broken down further

$$A{-}F_o \rightleftharpoons (A{-}F)^* \longrightarrow P{-}F_r$$

where $(A{-}F)^*$ represents the activated complex.

In theory[36] any one of these three steps can be rate determining. In the initial stages of the reaction the concentration of the chemisorbed alcohol is very small; therefore, the overall rate of the forward reaction is too slow to be perceptible. This would account for the observed induction periods. Subsequently, as the concentration of the chemisorbed alcohol acquires a finite value the forward reaction begins at a measurable rate.

However, since the kinetics were followed by sampling the solution, there was in heptane a sharp decrease in the concentration of the alcohol in the very beginning of the reaction because of its rapid physical adsorption on the virgin solid phase. This accounts for the apparent rate acceleration observed during the initial stages of the reaction.

It is noteworthy that this trend was reversed when benzene was used as a solvent instead of heptane. In that instance, the solid surface was not "free," but covered with benzene molecules which formed π complexes with the silver ions in the reagent.[38] Consequently, the alcohol had to displace the benzene molecules from the adsorption sites before it could be bound; hence an apparent lowering of the initial rate resulted. The actual oxidation begins after the concentration of the chemisorbed alcohol has reached a finite value and it is this concentration which governs the rate.

The factors affecting this concentration are as follows: (1) the concentration of the alcohol, (2) the temperature, (3) the polarity of the solvent, (4) the number of "active sites" in the solid reagent, (5) the available surface, (6) the presence of other polar or mobile electron groups in the molecule, (7) the amount of contact between the alcohol molecules and the surface, *i.e.*, the rate of mixing, and (8) the pressure.

The effects of concentration and temperature on the rate are well known. It must be noted, however, that an increase in the temperature in this system may have two opposing effects: an increase in the rate of oxidation but also an increase in the rate of desorption of the alcohol and its oxidation products from the surface.

It is well known[39] that for polar solids the temperature effect on the adsorption is minimal if one component is more polar than the other. It has been reported,[40] for example, that the extent of adsorption of ethyl alcohol on silica gel from a benzene solution was not significantly affected by temperature variations. These results were later confirmed[41] and attributed to chemisorption of the alcohol by the silica gel. If our model (which also postulates a chemisorbed alcohol) is correct, an increase in temperature should increase the rate of oxidation and desorption of products, leaving the concentration of chemisorbed alcohol virtually unaffected. Thus, an increase in the oxidation rate is predicted. This prediction has been well authenticated experimentally.[42]

Our experiments and those of other investigators[17] have shown that an increase in the polarity of the solvent deactivates the reaction. This we believe is due to the combination of several effects. First, an increase in the polarity of the solvent facilitates desorption, thereby decreasing the effective concentration of the bound substrate. Second, the polar solvent molecules occupy adsorption sites on the surface of the solid phase in competition with the substrate molecules. Thus a lowering of the reaction rate results similar to the well-known "competitive inhibitions" observed in enzymatic systems. Finally, adsorption of polar solvents alter the nature and polarity of the surface,[36,39] deactivating the adsorption of the substrate. It is for the same reason that mixtures of alcohols were found to oxidize slower than the individual species under the same conditions. In these cases each alcohol inhibited the reaction of the others. As we have already stated, this effect is minimized as the amount of available solid surface increases.

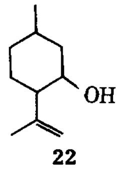
The number of "active sites" in the solid is dependent upon the nature of the solid (*i.e.*, its crystal structure) and the mode of the preparation of the reagent. We have found (section III) that the simple addition of Celite to silver carbonate does not catalyze the reaction. The silver carbonate must be precipitated in the presence of Celite. We feel that this method is responsible for increasing the number of active sites on the surface.

The fact that the other silver salts (acetate, formate, oxalate, benzoate, etc.) similarly precipitated are totally ineffective as oxidizing agents for alcohols could be due to the dependence of the oxidation on the interatomic distances in the crystal. The observed differences in reactivity cannot be explained on the basis of oxidation potentials, since silver oxalate has the same potential as silver carbonate (−0.47 V), and silver acetate has a higher oxidation potential than silver carbonate (−0.64 V).[43]

We have postulated that oxidation begins with the chemisorption of the hydroxyl group on the silver ions of the oxidant. Thus, if a molecule in addition to the hydroxyl function also contains other π electron systems offering alternative modes of adsorption on the solid surface, a lowering of the rate is predicted.

On the other hand, if those π systems are so situated as to facilitate the adsorption and proper orientation of the substrate molecule, an increase in the rate of oxidation is predicted. Both of these theoretical predictions have been authenticated experimentally, thus lending support to the validity of the model.

For example, *endo*-2-norbornanol has been found to oxidize over 50 times faster than *endo*-2-norbornenol. Apparently adsorption through the double bond hinders the norbornenol molecule from attaining the necessary orientation (*cf.* Figure 1) for facile oxidation; thus a lower oxidation rate results. Similarly, the oxidation of isopulegol (22) is very slow and leads to a mixture of undefinable products.[44] Slow reactions and anomalous products were also observed in certain oxidation attempts of various 3β-hydroxy-Δ^5 steroids.[44]



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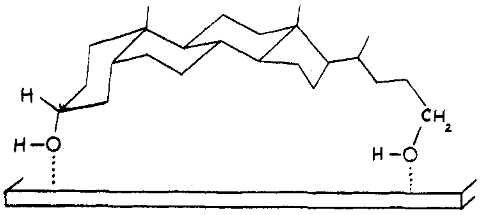
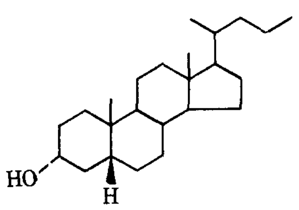


Figure 4. Model for cholane-3α,24-diol (23) adsorption.

In contrast, it was found[2] that certain diols oxidized more rapidly than the corresponding ketols. Furthermore, the selectivity of the oxidation was lost. Both of these *hitherto unexplained findings can* now be explained on the basis of our adsorption model. To illustrate, consider the oxidation of cholane-3,24-diol (23).

Adsorption of this compound obviously cannot take place through the face of the molecule because of the angular methyl groups, etc. According to our model, adsorption through the back side involving both hydroxyl groups would lead to an arrangement as depicted in Figure 4.

Close inspection of the group orientations around C-3 and C-24 shows that the hydrogen which is attached to the third carbon cannot approach the surface of the oxidant in the required manner (Figure 1). Consequently, the selective oxidation of C-3 does not take place despite the fact that the oxidation of cholane-3α-ol (24) is much faster than the oxidation of cholane-24-ol (25).



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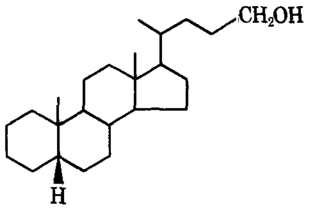

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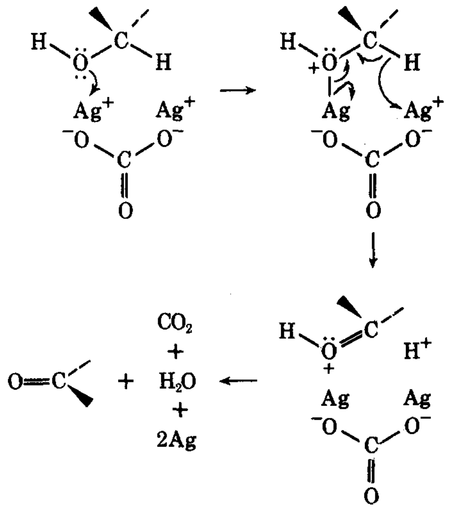
B. Mechanistic. In our preliminary communication[3] we have proposed a model for the mechanism of this oxidation. This is shown in Scheme I. It consists essentially of the following steps.

Scheme I
Postulated Mechanism for the Oxidation of Alcohols by Silver Carbonate Precipitated on Celite



(1) A reversible adsorption[39] of the alcohol on the surface of the oxidant with the oxygen electrons forming a coordinate covalent bond with the silver ions.

(2) Orientation of the carbon–hydrogen bond so that the

HCOH groups are coplanar and perpendicular to silver carbonate/Celite surface.

(3) A concerted irreversible homolytic shift of electrons to generate reduced silver atoms, hydrogen ions, and a protonated carbonyl compound.

(4) A collapse of these species to products with the carbonate ion acting as a hydrogen ion acceptor, thereby generating carbonic acid which is immediately decomposed to carbon dioxide and water.

All of the published data as well as the results described in this paper are consistent with and lend support to these models.

Experimental Section

General. Melting points were taken on a Thomas-Hoover "Uni-Melt" or a Reichert apparatus and are uncorrected. The nmr spectra were recorded either on Varian T-60 and A-60 or a Jeol Model JNM-C-60 M spectrometers, with tetramethylsilane as an internal standard, and are reported in parts per million. Infrared spectra were recorded on a Perkin-Elmer 257 and 357 or on a Beckman IR-5 A spectrophotometer. Ultraviolet spectra were recorded on a Unicam SP 800 or on a Beckman DU-2 spectrophotometer. Mass spectra were taken on a Varian CH 5 III spectrometer. Optical rotations were measured with the aid of a Perkin-Elmer 141 polarimeter. Gas chromatographic analysis of the aliphatic compounds were performed on a Carlo-Erba Model GI apparatus equipped with a 5% Carbowax 20M on Chromosorb P, 3-m column. The analysis of steroids was performed on a Varian Aerograph Model 1400 gas chromatograph equipped with a flame ionization detector and a 5-ft column which was packed with Chromosorb Z (100-200 mesh) treated with DMCS and impregnated with 2% fluorosilicone QFI. Analyses were performed by the Laboratoire Central de Microanalysis du CNRS.

Unless otherwise stated, deuterated products were prepared by lithium deuteride reduction of the corresponding carbonyl compounds. The silver carbonate/Celite reagent of the oxidations was prepared in the standard way[1] and predried prior to use for 3 days under vacuum at 60°. This reagent contains approximately 1 mequiv of silver carbonate per 0.57 g.

When other supports were used an identical procedure for the preparation of the reagent was followed except that the weight of Celite was replaced by an equal weight of another support.

For the studies of the surface effects the standard procedure for preparing the oxidizing agent was modified to include two, three, and four times the normal amount of Celite. All other aspects of the preparation remained the same.

All oxidations were carried out by simple reflux of a solution of the alcohol containing the oxidizing agent. At the end of the reaction the products were isolated by simple filtration, washing of the solid phase, and evaporation of the solvent.

The isotopic composition of the deuterated samples was determined either by nmr, which involved integrating the spectra and taking the average of at least ten integrations, or by mass spectrometry, which involved a comparison of the molecular ion peak for the protium compounds with that of the dueterium compounds after making suitable corrections for the isotopic abundance of ^{13}C. The first method afforded a precision of ±5% and the second ±2%.

All of the steroid samples used in this investigation were either available from previous studies or prepared by standard methods. Thin layer chromatography was conducted on silica plates (Merck, 0.05-0.2 mm), impregnated with silver nitrate (7%) and eluted with pentane-ether.

Stoichiometry. Method A. A sample of benzhydrol (312.9 ± 0.2 mg, 1.7 mmol) was dissolved in reagent-grade heptane (300 ml) and introduced into a 500-ml flask equipped with a reflux condenser. The condenser was fitted with a preweighed absorption tube filled with "Mallcosrob"[20] (30-50 mesh) followed by two traps containing indicating silica gel and potassium hydroxide pellets, respectively.

The system was flushed with nitrogen gas prior to the installation of the absorption tube and traps. The mixture was then treated with an excess of silver carbonate/Celite reagent (5 g, *ca.* 9 mmol) and heated under reflux.

A continuous stream of pure nitrogen gas was maintained throughout the reaction to displace the carbon dioxide produced. When the evolution of carbon dioxide ceased (*ca.* 24 hr) the heating was discontinued, the system was purged with nitrogen gas, and the absorption tube was removed, capped, and weighed.

The experiments were performed in triplicate, the reported values being the average of the three runs. The results of these experiments are summarized in Table I.

An identical system, but containing no alcohol, was set up as a control. When the effluent of this control experiment was tested with barium hydroxide solution there was no precipitate formed. Thus it was established that silver carbonate did not decompose under these conditions. However, there was still a small increase in the weight of the absorption tube due to the mechanical entrainment of solvent and moisture droplets by the carrier gas. This weight (25.0 mg) was subtracted from the weight gained by the absorption tube (108.3 mg) used in the sample run, to obtain the net weight of the carbon dioxide produced during the reaction.

Method B. Several standard solutions of benzophenone in spectral grade heptane were prepared and their ultraviolet absorption was measured at 278 mμ. A plot of these absorbances *vs.* the concentrations gave a good straight line, obeying Beer's law. The resulting graph was used in all subsequent oxidations of benzhydrol to ascertain the quantity of benzophenone produced.

An aliquot (250 ml) of a standard solution of benzhydrol (150.2 mg/l., 0.816 mmol/l.) in spectral grade heptane was introduced in each of four identical flasks (500 ml) equipped with reflux condensers and drying tubes filled with indicating silica gel. Thus each aliquot contained 0.2 mmol of benzhydrol. Samples of silver carbonate/Celite reagent corresponding to 1, 0.75, 0.5, and 0.25 equiv were introduced into each of the flasks, respectively. The mixtures were simultaneously heated under reflux for approximately 5 days to ensure completeness of reaction. The heating was then discontinued, and, after the solids had settled, aliquots were withdrawn and their absorption at 278 mμ was measured. The respective concentrations of benzophenone were then determined with the aid of the standard Beer's law curve. The determinations were performed in quadruplicate, the reported values being the average of the four runs. These results are summarized in Table II.

Oxidation of Cyclopropylcarbinol. Commercial sample[45] of cyclopropylcarbinol (1 ml, *ca.* 10.7 mmol) was dissolved in hexane (60 ml) and treated with silver carbonate/Celite reagent (18 g, 3 equiv). The mixture was oxidized under reflux for a period of 40 hr. After filtration of the solids and removal of most of the solvent, the mixture was fractionally distilled. This gave a quantitative yield of pure product: ir (CCl_4) 3080, 3000, 1450, 1230, 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1 (4 H, m), 3.4 (1 H, m), 9.9 (1 H, s, aldehyde proton); 2,4-dinitrophenylhydrazone, mp 185-186° (lit. mp 186-187.5°).

The above data confirmed that the only product of the oxidation was cyclopropylaldehyde.

Oxidation of Methylcyclopropylcarbinol. A commercial sample[45] of methylcyclopropylcarbinol (1 ml, *ca.* 10.2 mmol) was dissolved in hexane (60 ml) and treated with silver carbonate/Celite reagent (18 g, 3 equiv). The mixture was oxidized under reflux for a period of 2 days. The product was isolated by filtration of the solids and removal of the solvent: ir (CCl_4) 3080, 3000, 1420, 1380, 1020, 900, 1690 cm^{-1} (C=O); nmr ($CDCl_3$) 0.8 (4 H, m), 1.7 (1 H, m), 2.1 ppm (3 H, s); semicarbazone mp 117-120° (lit. mp 118-120°).

The above data confirmed that the only product of the oxidation was methyl cyclopropyl ketone.

Oxidation of Dicyclopropylcarbinol. A commercial sample[45] of dicyclopropylcarbinol (1 ml, *ca.* 8 mmol) was dissolved in hexane (60 ml) and treated with silver carbonate/Celite reagent (18 g, 4 equiv). The mixture was oxidized under reflux for a period of 2 days. The product was isolated by filtration of the solids and fractional distillation: ir (CCl_4) 3010, 3080, 1400, 1020, 1685 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1 (8 H, m), 2 (2 H, m).

The above data confirmed that the only product of the oxidation was dicyclopropyl ketone.

Effect of Free-Radical Initiator. A solution of benzhydrol in hexane (50 ml, 152 mg/l.) was added to each of two cylindrical reaction vessels (100 ml) equipped with reflux condensers. A sample of azobisisobutyronitrile (25 mg) was added to one of the tubes. Subsequently each tube was treated with 5 equiv of silver carbonate. The mixture was then refluxed under nitrogen in a constant-temperature bath (115°) for a period of 50 min. The tubes were then removed. After the solid had settled the supernatant liquids were assayed for benzophenone by ultraviolet spectroscopy with the aid of a standard Beer's law curve. It was found that the tube with the free-radical initiator contained only traces of benzophenone while the other tube showed approximately 35% oxidation. Duplicate runs under identical conditions, either with or without an inert atmosphere, gave similar results.

Oxidation of (−)-1,2,2-Triphenylethanol. A sample of (−)-1,2,2,-triphenylethanol[46] ([α]D −117°, 285 mg, *ca.* 1 mmol) was dissolved in anhydrous benzene (100 ml) and treated with silver carbonate/Celite reagent (3 g, *ca.* 5 equiv). The mixture was refluxed and the reaction progress was monitored by thin layer chromatography. At approximately 50% oxidation the heating was discontinued. After removal of the solids and evaporation of the solvent a mixture of the unreacted alcohol and oxidized product (phenylbenzhydryl ketone) was isolated. The two components were separated by thin layer chromatography on silica plates eluted with benzene. The unchanged alcohol was then recrystallized from hexane and dried under vacuum over phosphorus pentoxide. Thus a pure (mp 81–82°) sample of unreacted 1,2,2-triphenylethanol was recovered. The optical rotation of this sample was found to be unchanged.

Influence of Solvent Polarity. To ascertain the influence of the polarity of the solvent a number of concurrent independent oxidations of 1-heptanol (0.1 ml) were carried out in the usual way[1] but each time utilizing a different solvent. In each case the same volume of solvent (50 ml) and the same amount of silver carbonate (10 equiv) were used. The course of the reaction was followed by gas chromatography.

In another set of experiments two samples of benzhydrol (5.8 mg) were independently and concurrently oxidized with silver carbonate/Celite (187.0 mg). The first oxidation was carried out in benzene and the second in a mixture (50 ml) of hexane (35%) and heptane (65%). After 45 min the reactions were stopped and the solids were filtered, washed, and discarded. The solvents were then carefully evaporated through a fractionating column. The crystalline residues which remained in each flask were then dissolved in spectral-grade heptane (50 ml) and ultraviolet absorption of the resulting solutions was measured at 278 mμ. The amount of oxidized product (benzophenone) was determined with the aid of a standard Beer's law calibration curve.

Finally, two samples (0.2 mmol) of 5α-androstan-3β-ol were oxidized with silver carbonate/Celite reagent (6 equiv). One oxidation was performed in benzene and the other in *tert*-butyl alcohol. Analyses of the mixtures were performed by gas chromatography. The results from all the above oxidations are summarized in Table III.

Surface Effects. To establish the role of Celite in these oxidations, four different samples of the oxidant were prepared in the standard way[1] except that, during the preparation of each successive sample, an amount of Celite was added corresponding to two, three, and four times the normal amount. The samples were then dried in an identical fashion and analyzed for their silver carbonate content. Subsequently six samples of benzhydrol (7.5 mg) were dissolved in spectral grade heptane and introduced in six identical reaction vessels equipped with reflux condensers. Each mixture was then treated with a different sample of the oxidizing reagent, making sure in each case that the weight used supplied each system with the appropriate number of equivalents of silver carbonate. The last flask contained the standard silver carbonate/Celite reagent to which a quantity of free Celite was added. Thus the last flask contained the usual silver carbonate reagent plus an additional amount of free Celite, making the total Celite content equal to that contained in the reagent which was prepared with twice the usual amount of Celite. The samples were then simultaneously immersed in a constant-temperature bath (114°) and partially oxidized.

After removal from the bath the reaction solution was quenched by refrigeration. When the solids had settled the supernatant liquids were examined by ultraviolet spectroscopy at 278 mμ and the quantity of benzophenone produced in each case was determined with the aid of a standard Beer's law curve. This experiment was repeated several times in both hexane and heptane. Although the individual results were not entirely reproducible, the trend was. The data and calculated results are shown in Table IV.

Monodeuterated Alcohols RCHDOH. These compounds were prepared essentially by the previously described methods[47,48] except that the esters $RCOOCH_3$ were replaced by the aldehydes RCHO. The isolation and purification of the products was achieved either by gas chromatography [R = Ph, OMeOPh, *m*-NO_2Ph, $CH_2{=}CH$, $CH_3(CH_2)_5$] or by thin layer chromatography (Citral). The deutrium analysis showed 97–98% monodeuterated products and no dideuterated products; 1.5–2.5% of OD products were also obtained.

Primary Alcohols RCD_2OH. These compounds were also prepared by the previously published methods.[47,48]

o,o′-**Bis(hydroxymethyl)biphenyl (8).** A sample of the methyl ester of biphenic acid[49] (5 g) dissolved in anhydrous tetrahydrofuran (30 ml) was added under nitrogen to a suspension of lithium aluminum hydride (1.5 g) in anhydrous tetrahydrofuran (100 ml). After 2-hr reflux, decomposition of the mixture in the usual way, and work-up, an 80% yield of crude diol was obtained.

The crude product was purified by recrystallization from ethyl acetate/heptane (1:1). The pure product melted at 112°.

o,o′-**Bis(hydroxymethyl)biphenyl-d_4 (9).** This product was prepared by a procedure identical with the above except that lithium aluminum deuteride was used in place of lithium aluminum hydride.

o,o′-**Bis(hydroxymethyl)biphenyl-d_2 (7).** A sample of *o,o′*-bis(hydroxymethyl)biphenyl (4 g) was dissolved in benzene and was oxidized in the usual way by silver carbonate on Celite (100 g). After 10 hr the heating was discontinued. Removal of the solids followed by evaporation of the solvents afforded an oil which crystallized spontaneously (75% crude yield). Upon two recrystallizations from benzene–heptane (1:1) a pure product (mp 156°) was obtained.

This product was identified by infrared and nmr spectroscopy as the lactone of biphenic acid: nmr ($CDCl_3$) δ 4.95 (2 H, s), 7.5 and 7.95 (3 H, 2 H, A_2B_2C aromatic system).

A sample of the lactone (2 g) was reduced in the usual way by lithium aluminum deuteride. Upon work-up an 87% yield of the diol 7 was obtained and found by nmr to have an isotopic purity of 99%.

Intramolecular Kinetic Isotope Effects. The details of the oxidations of alcohols of the type RCHDOH as well as the calculated results are summarized in Table V. The isotope effects were calculated from the ratios of the per cent deuterated aldehydes over the per cent nondeuterated aldehydes found in the product. The reported values include a correction for the protium aldehyde (*ca.* 1.5%) which derives from the undeuterated alcohols RCH_2OH.

Intermolecular Isotope Effects. Several 1:1 mixtures of deuterated and undeuterated alcohols were prepared and subjected to partial oxidation under the standard conditions previously described. After separation and purification of the products, deuterium assays were performed either by nmr or mass spectrometry. The kinetic isotope effect was calculated by means of the relation

$$\frac{K_H}{K_D} = \frac{\log (1/AX)}{\log 1/A(1 - X)}$$

where A is the per cent of unreacted alcohol in the mixture determined by gas or thin layer chromatography and X is the per cent of deuterium contained in the alcohol. The data and the calculated results for these oxidations are shown in Tables VI and VII.

Kinetic Isotope Effects from the Oxidations of Deuterated and Undeuterated *o,o′*-Bis(hydroxymethyl)biphenyl. The pertinent data and calculated results for these oxidations are summarized in Table VIII.

Kinetics. All the kinetic data and the calculated results are incorporated in Table IX. The oxidations were performed in heptane (900 ml) in a specially constructed reaction vessel which was equipped with an efficient reflux condenser and sampling ports capped with rubber septa. The reaction progress was followed by heating the mixture in a constant-temperature bath (115 ± 0.1°), removing aliquots (0.1 ml, 0.02% of the total volume), quenching them by refrigeration, allowing the solids to settle, and analyzing the supernatant liquid by gas chromatography. The chromatographs were integrated and the concentration of the alcohol was in each case calculated by means of the relation $C_t = C_0a/(a + b)$, where C_t is the concentration of unchanged alcohol at time t, C_0 is the initial concentration of the alcohol, a is the area under the alcohol peak, and b is the area under the aldehyde or ketone peak. The results obtained were then plotted and the specific rate constants were calculated from the slopes of the corresponding curves. After an initial induction period the results best fitted a pseudo-first-order reaction.

In a related experiment a mixture of 1-butanol (1 ml, 0.01 mol), 1-hexanol (1.25 ml, 0.01 mol), 1-octanol (1.67 ml, 0.01 mol), and 1-decanol (2.0 ml, 0.01 mol) in hexane (150 ml) was oxidized with silver carbonate/Celite (24 g, *ca.* 0.04 mol).

The reaction mixture was sampled after 7.5 and 18.5 days and the samples were analyzed by gas chromatography. The per cent oxidation of each alcohol was then determined by integrating the gas chromatographic peaks and dividing the area for each aldehyde peak by the corresponding total area (aldehyde plus unreacted alcohol). The results are shown in Table X.

Oxidation of Steroids. A. Competitive. All competitive oxidations were performed on equimolar (0.1–0.2 mmol of each alcohol), binary mixtures of steroidal stereoisomers with 1-3 equiv of silver carbonate in anhydrous benzene (10 ml). The reactions were monitored by removing aliquots (0.05 ml) at regular intervals and analyzing them by gas chromatography. The first sample was withdrawn when the reaction mixture began to darken. The combined value of all the aliquots was approximately 5% of the total volume.

The best separations were obtained at a column temperature of 180° and a nitrogen gas flow rate of 16 ml/min. Under these conditions the retention times of the steroids studied ranged from 5 to 18 min, the ketones being retained approximately twice as long as the alcohols. The following pairs of alcohols were oxidized: 5α-androstan-2β-ol (**10**) and 5α-androstan-2α-ol (**11**); 5α-androstan-3α-ol (**18**) and 5α-androstan-3β-ol (**19**); and 13α,5α-androstan-17β-ol (**16**) and 13α,5α-androstan-17α-ol (**17**).

B. Noncompetitive. These oxidations were carried out under the same conditions as described in part A. However, the enormous difference in reactivity toward silver carbonate between the pairs of epimers 5α-androstan-6α-ol (**12**) and 5α-androstan-6β-ol (**14**) and 5α-androstan-7α-ol (**13**) and 5α-androstan-7β-ol (**15**) made it unnecessary to perform competitive oxidations. In fact, the oxidation of compound **14** with 6 equiv of silver carbonate was quantitative after 2 hr. In contrast, the epimeric alcohol **12** remained virtually unchanged even after 24 hr under the same conditions. Similarly, compound **15** was easily oxidized whereas its epimer **13** was not.

11-Methyl-11,12-dihydroxymethyl-9,10-dihydro-9,10-ethanoanthracene (20). This compound was prepared by the lithium aluminum hydride reduction (20% excess) of the adduct of anthracene and citraconic anhydride[50] in anhydrous tetrahydrofuran. The mixture was stirred under reflux for 1 hr and at room temperature for an additional 12 hr. Decomposition of the complex in the usual way followed by evaporation of the solvents afforded a 82% yield of crude product. After two recrystallizations from benzene a pure (mp 129°) sample of the diol **20** was obtained: ir ($CHCl_3$) 3180 cm^{-1} (OH); nmr (CCl_4) δ 7.25 (8 H, multiplet, aromatic protons), 4.15 (1 H, doublet, flagpole proton), 3.8 (1 H, singlet, flagpole proton), 3.22, 3.45, 4.23 (4 H, multiplets, nonequivalent hydroxymethyl protons), 1.8 (1 H, multiplet), 0.97 (3 H, singlet, methyl protons).

Oxidation of Diol 20. Two separate samples of the diol **20** were oxidized with silver carbonate (15 equiv), one sample in heptane and the other in benzene. After 12 hr of reflux the heating was discontinued and the products were isolated by filtration of the solids and evaporation of the solvents. Thus a white, crystalline material (mp 150-162°) was isolated. The infrared spectrum showed no hydroxyl bond, indicating that the oxidation was complete. A carbonyl band at 1765 cm^{-1} indicated the presence of five-membered-ring lactones. The ratio of the two lactones formed (**21a** and **21b**) was determined by simple integration of the nmr singlets produced by the respective 11-methyl groups (for **21a** methyl protons at 1.21 ppm; for **21b** at 1.14 ppm). Thus the nmr data showed that the yield of **21a** was 18% and of **21b** 82% regardless of the solvent used.

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Registry No. **8**, 3594-90-9; **10**, 1225-47-4; **11**, 20707-85-1; **12**, 20311-10-8; **13**, 19037-31-1; **14**, 32215-75-1; **15**, 19037-33-3; **16**, 14935-58-1; **17**, 14935-57-0; **18**, 7657-50-3; **19**, 1224-92-6; **20**, 43187-20-8; **21a**, 43187-21-9; **21b**, 43187-22-0; Ag_2CO_3, 534-16-7; benzhydrol, 91-01-0; Celite, 12279-49-1; 1-heptanol, 111-70-6; *p*-$MeOPhCH_2OH$, 105-13-5; *m*-NO_2PhCH_2OH, 619-25-0; $CH_2{=}CHCH_2OH$, 107-18-6; geraniol, 106-24-1; $PhCH_2OH$, 100-51-6; *o*-$MeOPhCH_2OH$, 612-16-8; $CH_3(CH_2)_8CH_2OH$, 112-30-1; $CH_3CH(OH)(CH_2)_7CH_3$, 1120-06-5; $PhCHOHCH_3$, 98-85-1; *o*-$MeOPhCHOHCH_3$, 13513-82-1; lactone of biphenic acid, 4445-34-5; 1-octanol, 111-87-5; 1-hexanol, 111-27-3; 2-hexanol, 626-93-7; 2-octanol, 123-96-6; 1-butanol, 71-36-3; cyclopropylcarbinol, 2516-33-8; cyclopropylaldehyde, 1489-69-6; methylcyclopropylcarbinol, 765-42-4; methyl cyclopropyl ketone, 765-43-5; dicyclopropylcarbinol, 14300-33-5; dicyclopropyl ketone, 1121-37-5; (−)-1,2,2-triphenylethanol, 26549-28-0.

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