Oxidation of Secondary Alcohols with t-Butyl Hypochlorite in the Presence of Pyridine

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When treated with t-butyl hypochlorite and pyridine in methylene dichloride, secondary alcohols give the corresponding ketones in very high yield. The relative reactivities of a number of *p*-substituted 1-phenylethanols containing electron-donating and -withdrawing substituents were investigated. Oxidation of *cis*- and *trans*-4-t-butylcyclohexanol, as well as some other cycloalkanols, proceeds with the same relative rate. On the basis of this and other data a cyclic transition state and loss of α-hydrogen of the starting alcohol as hydride ion are proposed as characteristics of the reaction mechanism.

The ready oxidation of *cis*- and *trans*-2-butylcyclohexanol with t-butyl hypochlorite in the presence of pyridine (TBHC–Py) was noted by Grob,[1] but later received little attention. The reaction of secondary alcohols with TBHC, without pyridine, in different solvents is well known and early work has been reviewed by Anbar and Ginsburg.[2]

In this report we present our results on the oxidation of secondary alcohols with TBHC–Py. The practical advantages of this novel procedure and our broader interest in 'positive' halogen chemistry prompted this mechanistic study.

The role of pyridine is crucial; without pyridine the reaction usually proceeds to give a mixture of ketone and α-chloroketone[2,3] and only a few cases are reported, for steroid alcohols, where the reaction takes place without chlorination.[4]

We used secondary aliphatic (cyclic and acyclic) and benzylic alcohols, containing no other functional groups. Results are presented in Table 1. For oxidation in methylene dichloride the proportion of reactants was one mole of TBHC and one mole of pyridine per mole of alcohol used; after mixing the components at room temperature oxidation is complete in *ca*. 1 h.

The yield of ketones is very high (Table 1) and the only other products found were t-butyl alcohol, pyridine hydrochloride, and some unchanged starting alcohol. The structure of the alcohol (open chain, or cyclic of various ring size, or with electron-donating or -withdrawing groups in the benzylic alcohols) had no effect on the yield of products. The yields and rates of oxidation are independent of light (incandescent lamp, 300 W) or oxygen. The ratios, however, are solvent dependent. Thus the relative times required for complete loss of oxidizing power of a solution containing TBHC–Py and propan-2-ol in different solvents are: in methylene dichloride 1, benzene 2, and carbon tetrachloride 5.

The oxidizable hydrogen of the alcohol (α-hydrogen), in an ionic oxidation, can be removed from the reaction site as a hydride or proton. In each case a full or partial (in the case of concerted breaking of α-C–H and O–H bonds) positive or negative charge on the α-carbon of the alcohol is developed. The sign and magnitude of the charge on the α-carbon in the transition state can be estimated using relative rates of oxidation of suitably substituted benzylic alcohols. This was done for a number of *p*-substituted 1-phenylethanols and the results are presented in Table 2. The deuterium isotope effects were determined for *cis*- and *trans*-4-t-butylcyclohexanol, on the basis of relative rates of oxidation of undeuteriated and α-deuteriated epimer, using 1-(*p*-methylphenyl)ethanol as reference alcohol. The values calculated this way were k_H/k_D 1.60 for the *cis*- and 1.35 for the *trans*-isomer.

It was suggested by Grob[1] that the first step in the reaction of secondary alcohols and TBHC–Py is the formation of an intermediate secondary hypochlorite, which in the next step reacts with pyridine producing ketone and pyridine hydrochloride. This mechanism should have the following characteristics: exchange between TBHC and the secondary alcohol would be a reversible process producing secondary hypochlorite and t-butyl alcohol; the breaking of the α-C–H bond of the secondary hypochlorite is such that hydrogen is transferred to the base (pyridine) as a proton, while chlorine is separated as the anion. This process can be one step (concerted breaking of C–H and O–Cl bonds) or two steps (the loss of α-hydrogen in the first and breaking of the O–Cl bond in the second step), but in any case followed by development of a partial or full negative charge on the α-carbon of the secondary hypochlorite. The second characteristic of this mechanism is related to the oxidation of *cis*- and *trans*-4-t-butylcyclohexanol, where if the hypochlorite is an intermediate, the epimer with an axial hypochlorite group (equatorial α-hydrogen) must react faster with pyridine than the epimer with an equatorial hypochlorite group. From our results, however, it appears that the intermediate formation of a secondary hypochlorite does not take place as the first step in the reaction. Addition of a large amount of t-butyl alcohol fails to decelerate the rate, as would be expected for the reversible formation of a secondary hypochlorite. Also, the stability of the separately prepared hypochlorite in the presence of pyridine is lower than the stability of our reaction system. Cyclohexyl hypochlorite (0.01 mol) in methylene dichloride (100 ml), for example, requires, after mixing with an equimolar amount of pyridine, a 20-fold shorter time to decompose (at 20 °C) than the corresponding mixture of TBHC–Py and cyclohexanol.

The results of the oxidation of *cis*- and *trans*-4-t-butyl-cyclohexanol are also not in agreement with postulated characteristics of a hypochlorite intermediate, because, as can be seen from Table 3, both epimers are oxidized by TBHC–Py at the same rate.

Another possible pathway for this reaction is direct reaction of secondary alcohol and TBHC. As can be seen from Table 3, electron-donating substituents of *para*-substituted 1-phenyl-ethanol increase and electron-withdrawing substituents decrease the rate of oxidation, which is what would be predicted by removal of α-hydrogen as a hydride. Accordingly, a mechanism where α-hydrogen is lost as hydride ion to the positive chlorine of TBHC is proposed, but small effects of substituents and solvent favour concerted breaking of both the α-C–H and O–H bonds, with development of a small positive charge on the α-carbon of the alcohol.

The hydride mechanism makes it possible for ethers with an α-hydrogen to react with TBHC–Py, where the carbenium ion

Table 1. Oxidation of secondary alcohols with TBHC–Py

Alcohol	ROH–TBHC–Py–CH_2Cl_2 (mmol–mmol–mmol–ml)	Yield of ketone (%)[a]
Butan-2-ol	34—40—40—300	96
Pentan-2-ol[b]	56—60—60—500	90
Octan-2-ol[b]	76—80—80—750	93
Decan-2-ol	6—6—6—60	97
Decan-3-ol	6—6—6—60	99
1-Cyclopropylethanol	11—12—12—100	95
5-Methylhexan-2-ol[b]	50—54—54—500	93
$(CH_2)_nCHOH$		
$n = 4$[b]	69—70—70—700	90
$n = 5$[b]	60—65—65—600	91
$n = 6$—11	5—5—5—60	>95
$XC_6H_4C(CH_3)HOH$		
X = H[b]	49—50—50—500	92
X = Cl, Br, Me	10—11—11—100	>92
$RC_6H_{10}OH$		
R = trans-2-Bu^n	7—7—7—65	99
R = cis-2-Bu^n [b]	44—46—46—480	91
R = trans-4-Bu^t	10—10—10—80	99
R = cis-4-Bu^t	10—10—10—90	95
R = cis- + trans-2-Me[b]	54—56—56—540	91

[a] Calculated from g.c. using chlorobenzene as internal standard unless otherwise stated. [b] Ketone isolated by distillation. All yields based on starting alcohol.

Table 2. 1-Phenylethanols: relative rates of oxidation

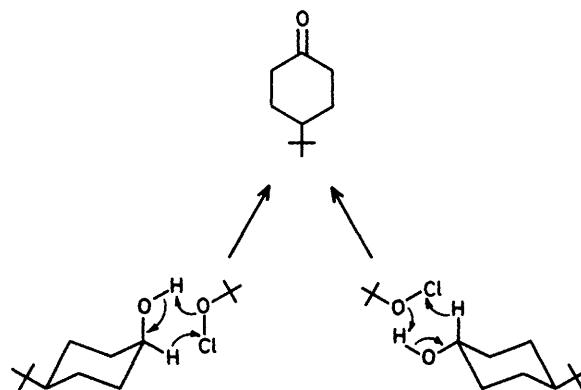| 1-Phenylethanol	Relative rate[a]
p-Bu^t	1.60
p-Me	1.28
p-H	1.00
p-Cl	0.90
p-Br	0.65

[a] In methylene dichloride at 19.2 °C. Calculated from g.c. using chlorobenzene as internal standard. Starting concentrations: $[ROH]_0^1 = [ROH]_0^2 = 0.01$, $[TBHC]_0$ 0.005, $[Py]_0$ 0.005M.

Table 3. Cycloalkanols: relative rates of oxidation

Cycloalkanol	Relative rate[a]
trans-4-t-Butylcyclohexanol	0.90
cis-4-t-Butylcyclohexanol	0.90
Cyclohexanol	0.90
Cyclopentanol	0.90
1-Phenylethanol	1.00

[a] In methylene dichloride at 19.2 °C. Calculated from g.c. using chlorobenzene as internal standard. Starting concentrations: $[ROH]_0^1 = [ROH]_0^2 = 0.01$, $[TBHC]_0$ 0.005, $[Py]_0$ 0.005M.

formed by hydride breaking of the α-C–H bond would be stabilized by resonance with oxygen. We found this to be the case, whereby aliphatic and benzylic ethers undergo reaction with TBHC–Py at the same rate as the corresponding alcohols.[5]

We also propose a cyclic transition state for this reaction, on the basis of the relative rates of oxidation of cis- and trans-4-t-butylcyclohexanol, where both epimers are oxidized at the same rate (Table 3). With a linear transition state, the cis-isomer with its more exposed α-hydrogen would react faster with TBHC than the trans-isomer with its axial α-hydrogen, approach of TBHC to the latter being more difficult. The similar reactivity of

this epimeric pair of alcohols (and, in fact, all alcohols investigated here) support a transition state in which accessibility of both hydroxy group and the hydrogen at the reaction centre are about equally important (Scheme). It is significant that oxidation of the same pair of alcohols with NBS or molecular bromine proceeds with a similar conformational insensitivity attributed to the cyclic nature of the transition state.[6]

Scheme.

The magnitude of the isotope effect also indicates a cyclic transition state. It is known for many reactions, especially those involving a cyclic mechanism where the transition state is constrained to a non-linear configuration, that small isotope effects are normally observed. The calculations reported[7] show that the primary isotope effect depends on the transition state geometry and has consistently low values, k_H/k_D 1—2, for sufficiently non-linear configuration. The bromine oxidation of cyclohexanol, which proceeds with k_H/k_D 2.9, is a possible example of a six-membered transition state.[8] It is quite likely that in the case of TBHC–Py oxidation the arrangement in the

transition state is even more constrained, so that the divergence from linearity is greater than in the transition state controlling the bromine oxidation.

Finally, the role of pyridine is briefly discussed. It seems that pyridine serves as a trap for hydrochloric acid. Without pyridine, oxidation is followed by chorination of the ketone by molecular chlorine liberated from TBHC and hydrochloric acid produced during reaction. However, it may be that the role of pyridine in this reaction is not so trivial. There are indications that pyridine complexes with TBHC and we have isolated from a cold and relatively concentrated solution (see Experimental section) a semicrystalline substance, which decomposed at room temperature, producing, among other products, hydrochloric acid and chlorine. The nature of such a complex could be of the electron donor–acceptor type (EDA),[9] analogous to the halogen–pyridine complex, which, as shown for chlorine–pyridine complex, possess oxidative properties.[10] Generally, this type of complex exhibits an electronic spectrum which is not the same as the sum of the spectra of the two individual molecules. We have prepared and examined the spectra (200—600 nm) of TBHC, Py, and TBHC–Py in methylene dichloride and carbon tetrachloride, but no difference in position or intensity of the characteristic maxima were observed. The absence of an absorption for the TBHC–Py complex could be explained if formation of the complex is reversible with the equilibrium far to the left, but addition of a three-fold excess of Py did not cause any change in the spectrum of TBHC–Py. Nevertheless, this is not proof that TBHC–Py complex does not exist and further work on this problem is in progress.

Experimental

Gas Chromatography.—A Perkin-Elmer 3920 B instrument (flame ionization detector) was used for analytical purposes and a Varian Aerograph 920 instrument (thermistor detector) for preparative separations. The columns (2 m × 2 mm analytical; 2 m × 4 mm preparative) consisted of Carbowax 20M, Silicone GE XE-60 (Nitrile Gum), or Methyl Silicone OV-101, as stationary phases adsorbed on Chromosorb W or Chromosorb P (3% analytical; 10% preparative); the carrier gas was H_2 or Ar.

I.r. spectra were taken with a Perkin-Elmer model 197 spectrophotometer, u.v. spectra with a Varian Superscan 3 instrument, and n.m.r. spectra with a Varian A-60 spectrometer (60 MHz).

Reagents.—Solvents and reactants were either commercially available, received from Professor M. Lj. Mihailović, or synthesized by well established methods. Their physical constants were checked and in general their purity confirmed by g.c., i.r., and n.m.r. spectra.

Oxidations.—All experiments on a larger scale were carried out in a flask equipped with a magnetic stirrer, dropping funnel, and condenser. The alcohol and pyridine were placed into the flask together with the calculated amount of methylene dichloride, so that the concentration of both pyridine and alcohol was 0.1—0.2M. In equimolar amount of t-butyl hypochlorite was then added over 1 min and the mixture stirred for 1 h in an ice-bath. It was then washed with aqueous potassium iodide and sodium thiosulphate (if necessary), dilute hydrochloric acid, and aqueous sodium hydrogencarbonate. After drying (Drierite), the mixture was distilled over an efficient column, the ketone was collected, and identified by i.r. and

n.m.r. spectra. When working with small amounts of alcohols the yields of ketones were determined by analytical g.c., using an internal standard (chlorobenzene) added before reaction. The samples were taken by preparative g.c. and products identified by i.r. and n.m.r. spectra.

Relative Rate Determinations.—These were carried out in a small flask equipped with a magnetic stirrer, dropping funnel, and condenser, immersed in a constant-temperature bath (19.2 °C). The solution of the two alcohols (0.1M each) and pyridine (0.005M) in methylene dichloride was placed in a flask, together with the internal standard (chlorobenzene). t-Butyl hypochlorite (one half of the equimolar amount) was added in one portion and the mixture stirred for 1 h. After washing with dilute hydrochloric acid and sodium hydrogen carbonate and drying (Drierite), the mixture was analysed on g.c. and the relative reactivities were determined using the relation (log A/A_0)/(log B/B_0) = r, where A_0 and B_0 are the peak areas of the two alcohols relative to that of the internal standard prior to reaction, and A and B the quantities after reaction. The same procedure was applied to the determination of the deuterium isotope effect, where 1-(p-methylphenyl)ethanol was used as the reference alcohol. The relative reactivities of deuteriated and undeuteriated alcohols (cis- and trans-4-t-butylcyclohexanol) were calculated as for the relative rate determination.

t-Butyl Hypochlorite and Pyridine Adduct.—To a cold solution of pyridine (4.0 g, 0.05 mol) in methylene dichloride (50 ml) at −20 °C was added a precooled solution of TBHC (5.4 g, 0.05 mol) in methylene dichloride (50 ml) and the mixture was stirred for 1 min. The cold suspension was centrifuged and the sediment washed with cold methylene dichloride. After a second centrifugation and the separation of the supernatant methylene dichloride, the product was dried *in vacuo* in an ice–water bath. When exposed at room temperature, the product decomposed. The gaseous products of decomposition were analysed and identified as hydrochloric acid and chlorine.

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