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THE HYDROXYLATION OF ALKANES AND ALKYL CHAINS

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Abstract—A solution of 30% aqueous H_2O_2 in trifluoroacetic acid converts linear alkanes and cycloalkanes to an equilibrium mixture of secondary alcohols and their trifluoroacetates. There is no trace of further oxidation to ketones. Yields and conversions can be 70–90%, but are limited by elimination and epoxidation to form vicinal glycols. Linear alkyl chains are also hydroxylated in good yields with selectivity for introducing the alcohol group remote from electronegative substituents. The active reagent is trifluoroperoxyacetic acid, and it is effective in the presence of 4–10% water. When tertiary hydrogens are present, the oxidations are more complex.

Trifluoroperoxyacetic acid (per TFA) has been extensively studied for the hydroxylation of aromatic rings,[1,2] the epoxidation of alkenes,[1,3] the oxidation of unsaturated ketones,[4] the oxidation of amines and oximes to nitro compounds,[5] the conversion of ketones to esters (Baeyer–Villiger reaction),[6] and the conversion of alkenes to ketones.[1] It has been used by two groups of workers to oxidize alkanes.[7–9]

It was demonstrated with 1,2-dimethylcyclohexane that the oxygen was inserted into the tertiary CH with retention of configuration.[7,8] In the hydroxylation of pentane, 2-methylbutane, and methylcyclohexane, it was shown that there was a strong selectivity for oxidation of $t > s > p$.[9]

In both studies, very large excesses of alkane were used, a 660:1 ratio of alkane to CF_3CO_3H in one study[7,10] and a 100:1 ratio in the other.[9] Both studies anticipated further oxidation and used large excesses of alkane to avoid such complications.

Cycloalkanes. A solution of 30% aqueous H_2O_2 in trifluoroacetic acid (TFA) oxidizes cyclohexane to cyclohexanol, which subsequently equilibrates to a mixture of cyclohexanol and cyclohexyl trifluoroacetate. Using a 15% excess of H_2O_2 and a reaction time of 24 hr at 25°, analysis by gc (gas chromatography) showed 78% cyclohexyl trifluoroacetate, 17.7% cyclohexane, 0.3% cyclohexanol, 2.7% A and 1.2% B.[11] The percentages refer to band areas. These are close to mol percentages. There were no detectable bands of either cyclohexanone or ε-caprolactone. The gc results were confirmed by an NMR spectrum of the reaction mixture.[11] A similar distribution of products was obtained from 20 min runs at reflux (80–85°).

The reactions can be conducted with anhydrous trifluoroperoxyacetic acid (per TFA) in CH_2Cl_2. However, it is far more convenient to use 30% aqueous H_2O_2 in TFA. The presence of 4–10% H_2O does not affect yields and has only a minor effect on rates. The reaction mixtures remain completely colorless at all times.

The initial production of alcohol rather than trifluoroacetate was shown by sampling the reactions at intermediate stages and showing that the amount of alcohol exceeded that at equilibrium. To cite two examples, when 4% H_2O was present, 20% of the product is alcohol at 30% conversion and when 5% H_2O was present, 9% of the product was alcohol at 50% conversion. In both cases, the equilibrium amount of cyclohexanol would be below 1%.

It is remarkable that there is no further oxidation to cyclohexanone even in the presence of 15–100% excesses of H_2O_2. Also there is no ε-caprolactone, which forms by action of per TFA on cyclohexanone. In the gc, both ketone and lactone were well-resolved from each other and from cyclohexyl trifluoroacetate so that they would have been detected if present in 0.1% yield.

This failure to form ketone is not a matter of the alcohol being protected as the trifluoroacetate since there are significant amounts of free alcohol present throughout the reaction.

Side product A was separated by preparative gc. The retention time and NMR identified A as the trifluoroacetate of *trans* 1,2-cyclohexanediol. This suggests that the principal side reaction is equilibration of the products with alkene, epoxidation of the alkene, and solvolysis to the glycol and its trifluoroacetate.

Cyclododecane has a limited solubility in TFA so stirring was used. After 24 hr at 25° with a 2-fold excess of H_2O_2, nearly all the cyclododecane had dissolved. The solution contained cyclododecyl trifluoroacetate and cyclododecane in a 80:20 ratio. No other products were evident by gc or NMR. Side products became evident after 3 days.

Cyclooctane emphasizes a limitation of the reaction. When the yield of cyclooctyl trifluoroacetate reached 46% (24 hr, 25°, 2-fold excess of H_2O_2), 10% of byproducts were already present. From 1–3 days, the yield of cyclooctyl trifluoroacetate remained approximately constant because formation was balanced by destruction. The destruction is presumed to involve formation of cyclooctene and conversion of cyclooctene to glycol since this was the principal side reaction with cyclohexane. No cyclooctanone could be detected by gc.

Linear alkanes. The solution of 30% H_2O_2 in TFA oxidizes linear alkanes to an equilibrium mixture of secondary alcohols and their trifluoroacetates. With hexane, yields of 2- and 3-hexanol can be >95% based on hexane consumed providing conditions are such that only 50% of the hexane reacts (15% excess H_2O_2 for 24 hr at 25° or 30 min at reflux, 83°). If longer reaction times are used in order to more completely use up the

H_2O_2, elimination and epoxidation cause increasing amounts of vicinal glycols.

With larger alkanes, bis hydroxylation is observed. For example a 15% excess of H_2O_2 on decane produced 29% unreacted decane, 61% decanols, and 10% decanediols. The retention times of the latter indicated that they were remote diols arising from bis hydroxylation rather than vicinal glycols from epoxidation of decenes.

The yield of primary alcohol (1-hexanol) from hexane was 0.2% of the hexanols produced. This agrees when an estimate of <0.6% of 1-pentanol from pentane.[9] This proportion of primary alcohol was presumed to hold for other substrates, although overlapping gc bands prevented a direct estimate except when 1-nonanol and 9,10-dihydroxyoctadecanoic acid were used as substrates.

The data in Table 1 show little selectivity between secondary positions. This contrasts somewhat with the report that hydroxylation of pentane gave a ratio of 1.5 for C-2:C-3 instead of the statistical value of 2.[9]

The inertness of secondary alcohols towards oxidation to ketones was not evident from the prior study of pentane.[9] The 100-fold excess of pentane, the rapid conversion of alcohol to ester due to excess anhydride, and the treatment of crude product with LAH all served to prevent the observation of this inertness.

Linear alcohols. 1-Octanol and 1-nonanol were hydroxylated with 30% H_2O_2 in TFA. The distribution of products (Table 2) shows that there is a strong tendency for remote substitution, although it is not as intense as that found in aminium radical hydroxylations[12] and chlorinations.[13-16] The similar pattern for 1-nonanol and 9,10-dihydroxyoctadecanoic acid (Table 2) emphasizes that remote selectivity depends largely on distance from electronegative substituents in the reactant. Four isomeric decanols show similar remote selectivities (Table 2).

The selectivity for ω-1 hydroxylation over ω-2 hydroxylation must be a result of both positions being deactivated with the ω-2 being more deactivated. Accordingly, 1-octanol was observed to react somewhat slower than alkanes.

The yields of products from direct hydroxylation decrease as the hydroxylation is forced to take place at positions closer to the initial OH group. This is evident from the decrease in yields in the series 2,3,4 and 5-decanol (Table 2). There was no evidence for ketones or triols. The side products were presumed to be vicinal diols since their gc bands (as trifluoroacetates) were between those of the reactant decanols and the remote decanediols.

A run was conducted on 1-octanol using 2.3 mols of H_2O_2 per mol of 1-octanol for 2 hrs at reflux. The % conversion increased to 78%, 71% of which were 1,x-octanediols of the non-vicinal type and 7% were other products.

Linear carboxylic acids. Linear acids containing 7, 8, 10, 12, 14, 16 and 18 carbons were hydroxylated with 30% H_2O_2 in TFA. The C_8 product has a strong coconut odor and the C_{10} product had an odor of peaches which is evidence for the γ-lactones of the respective 4-hydroxy acids.[17]

The NMR spectra of the products in CCl_4 show bands at 4.4 and 5.22 δ. The 5.22 bands are due to trifluoroacetate substituents on the chain. Their area relative to the area of the COOH or α-CH_2 (2.4 δ) were used to calculate the yield of hydroxy present as the trifluoroacetate (Table 3). The 4.4 bands are identified as due to the lactones of the 4- and 5-hydroxy acids. Their yields were calculated in an analogous manner. The sum of the yields calculated from the 4.4 and 5.22 bands is the total yield of hydroxylated acid. These total yields were in agreement with estimates calculated from the gain in weight of products compared to reactants. The amount of lactone was in accord with the amount of 4 and 5-hydroxylation expected from data on hydroxylation of alcohols (Table 2).

With hexadecanoic (palmitic) acid, the hydroxy acids were oxidized with 70% HNO_3 to diacids, and the diacids analyzed by gc of their methyl esters.[18] The relative molar amounts of the diacids from C_5 to C_{14} were 8, 8, 7, 8, 9, 10, 6, 6, 6 and 4.[11] This shows that the OH group has been introduced nearly random except for the usual avoidance of positions close to the electronegative OH group.

Table 1. Distribution of alcohols from hydroxylation of linear alkanes with H_2O_2 (15% excess) in TFA

Alkane	Time (hrs)	T (°C)	% Conv.	Relative yields of alcohols 1-	2-	3-	4-	5-
hexane	24	24°	45[a]	0.2	52	48	--	--
heptane	1	83°	75[b]	c	41	40	19	--
decane	0.5	83°	71[d]	c	30	26	21[e]	21[e]

[a] Of the 45% products, 43% were 2 and 3-hexanol. The remaining 2% was composed of a gc band close to 1-hexanol (1.6%) and three bands of retention time longer than 1-hexanol (0.4%).

[b] The longer reaction time led to more side products presumably due to elimination and epoxidation. Of the 75% yield of products, 62% were heptanols and the remaining 13% were present as 8 gc bands. One band overlapped that of 1-heptanol and the other 7 had longer retention times.

[c] The yield cannot be determined because the band is a small shoulder on a larger unidentified band.

[d] Of the 71%, 61% were decanols and 10% were diols, largely of the remote (non-vicinal) type.

[e] Incompletely resolved.

Table 2. Products from hydroxylations with H_2O_2 (15% excess) in TFA (80–85°, 1 hr)

Reactant	% Conv.	Relative yields (product designated by position of the introduced HO)[a,b]						
		ω-1	ω-2	ω-3	ω-4	ω-5	ω-6	(c)
1-octanol[d]	55	36	32	18	9	0	0	5
1-chlorooctane	56	37	30	20	10	0	0	3
1-nonanol	56	29	26	20	14	7	0	4
9,10-dihydroxy-octadecanoic acid	--	36	29	21	10	0	0	4
2-decanol	52	30	29	23	10	e	(0)[f]	8
3-decanol	50	39	29	15	e	(0)[f]	e,g	17
4-decanol	30	49	37	e	(0)[f]	e,g	--	14
5-decanol	29	31[h]	6(2)[i]	(0)[f]	e,g	--	--	57

[a] The yield of ω product was 0.1% in the case of 1-nonanol and the dihydroxy acid. Overlap of gc bands prevented a direct estimate with the other substrates.

[b] Most of the diols could be identified by the following principles. Retention times of gc bands increase as the distance between HO groups increases. Yields increase as the hydroxylation is more remote. In certain cases the same diol must arise from different sources. For example, 2,8-decanediol is the ω-1 product from 3-decanol and the ω-2 product from 2-decanol. Identity of retention times was demonstrated in such cases.

[c] Area of unidentified bands (largely vicinal diols).

[d] Revised from values in ref. 11.

[e] One of the unidentified bands could be this product.

[f] Presumed to be zero based on results with 1-octanol and 1-nonanol.

[g] A vicinal diol that presumably arises entirely by elimination and epoxidation.

[h] 2,6-Decanediol.

[i] Two equal bands are present which must be 3,6-decanediol (ω-2 from the longer chain) and 2,5-decanediol (ω-1 from the shorter chain). Both are δ-hydroxylation products at a secondary position and would be expected to appear in comparable amounts.

Table 3. Yields of hydroxylated linear carboxylic acids

Number of carbons	% Yield of hydroxy acids 25°, 24 hrs		83-86°, 1 hr	
	trifluoro-acetate	lactone	trifluoro acetate	lactone
7	--	--	17	15
8	--	--	40	17
10	--	--	53	19
12	53	10	--	--
14	58	10	70	12
16	64	7	68	14
18	--	--	76	12

The validity of the analytical method was demonstrated by HNO_3 oxidation of 12-hydroxyoctadecanoic acid to give 52% of the C_{12} diacid (dodecanedioic), 46% of the C_{11} diacid (undecanedioic), and 2% of the C_{10} diacid (decanedioic). Catalytic amounts of NH_4VO_3 were used. When this was omitted, the yield of the C_{10} diacid increased to 8–10% and two other products appeared in the gc, each in about 10% yields. The NH_4VO_3 is clearly advantageous as it is in the HNO_3 oxidation of cyclohexanol and cyclohexanone where it serves to reduce the yield of C_4 and C_5 diacids and increase the yield of C_6 adipic acid.

Octylamine. The NMR spectrum of the product indicated that a 15% excess of H_2O_2 gave a 35% conversion of octylamine to aminooctanols. No oxidation of the amino group was evident. In accord with this, trimethylamine was inert to H_2O_2 in TFA at 25°.

Branched alkanes. The action of 30% H_2O_2 in TFA and anhydrous per TFA on branched alkanes is more complex than the simple hydroxylations observed with linear alkanes. The studies concentrated on 2-methylbutane (isopentane). Reactions were conducted at 25° with a 1.15:1 ratio of H_2O_2 to 2-methylbutane. The nature of the products were sensitive to reaction variables.

With excess TFA anhydride in TFA, the reaction was complete after 4 days. At that time 2-methylbutane, 2-methyl-2-butyl trifluoroacetate, and 3-methyl-2-butanone were present in the ratios 25:25:50 (NMR). An intermediate (the trifluoroacetate of 2-methyl-2,3-butanediol) can be directly observed by NMR. Its yield maximizes at 25% at 24 hr reaction time. The reaction path is evidently hydroxylation, elimination to 2-methyl-2-butene, epoxidation, solvolysis to the glycol, and acid-catalyzed rearrangement. This was the only set of conditions in which 2-methyl-2-butyl trifluoroacetate was a significant product.

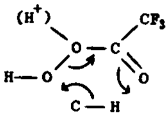
With anhydrous per TFA in CH_2Cl_2, 3-methyl-2-butanone was the only product. This result has a bearing on the distribution of alcohols reported for the hydroxylation of 2-methylbutane by per TFA in CH_2Cl_2.[9] The crude product was treated with LAH and the alcohol analyzed by gc. It is evident from the above results that some of the 3-methyl-2-butanol arose from hydroxylation at the tertiary position, elimination to alkene, epoxidation and glycol formation, pinacol rearrangements to 3-methyl-2-butanone and LAH reduction. This would lead to the value for hydroxylation at C-3 being too high and the value for C-2 being too low. A similar situation probably exists for methylcyclohexane. The conclusion is that the ratio of t:s is higher than the values reported.[9]

When 4–10% H_2O is present, the hydroxylation takes yet another course. 2-Methyl-2-butyl trifluoroacetate can be detected, but it is never more than 5–10% of the NMR band area. Acetone and ethyl trifluoroacetate appear early following by methanol (as its acetate and trifluoroacetate) and acetic acid. After one day these four species were present in the ratios 1:6:2:7. It is evident that the initial tertiary alcohol equilibrates with the hydroperoxide. This rearranges in acid via "RO^+" as reported.[19] The migration of ethyl predominates over Me migration[19] so that ethanol and acetone predominate over methanol and 2-butanone as products of the rearrangement. The stoichiometry requires that the methanol arises from a further Baeyer–Villiger reaction on acetone to form methanol and acetic acid.

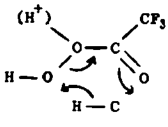
Mechanism. It has been generally assumed that per TFA is the active reagent in H_2O_2-TFA systems. A cyclic concerted mechanism was proposed for the oxidation of alkanes.[9] The foundation for such a proposal would seem to rest with a later study which demonstrated that *cis* and *trans* 1,2-dimethylcyclohexane gave different stereoisomeric 1,2-dimethylcyclohexanols and that the hydroxylation occurred with retention.[7,8,10] This stereospecificity eliminates mechanisms involving alkyl radical, alkyl cation, and alkyl anion intermediates since these would equilibrate stereochemically. The formation of significant, though small, amounts of primary alcohols is additional evidence against alkyl cation intermediates. The conduct of the reaction in media of moderate acidity is evidence against alkyl anion intermediates.

Structure 1 is regarded as the most likely transition state. The isomeric structure 2 can be ruled out because it would lead to initial formation of trifluoroacetate. The transition state proposed earlier[9] was the 4-membered ring version of 2. This is not in accord with alcohol being the initial product and the 4-membered ring is regarded as less probably than 6-membered rings.

The curves arrows are drawn in the direction to show the development of HO^+ character in the per TFA. Hart has emphasized this HO^+ nature[1] and the selectivity for remote hydroxylation supports the electrophilic nature of the reagent.



1



2

An added H^+ is shown in 1 and 2, although the evidence is tenuous. Hart found that BF_3 catalyzed oxidations with per TFA showing that per TFA is susceptible to acid catalysis.[1] The data in Table 4 show that the rate is relatively invariant from 10–5% H_2O, but begins to increase going to 4% H_2O.

TFA is a stronger acid (pK 0.3)[20] than per TFA (pK 3.7).[21] Since 13.6% H_2O is equimolar TFA and H_2O, 4–10% H_2O will react with TFA and leave the concentration of unionized per TFA relatively unchanged. The variation from 5–10% H_2O occurs in the TFA buffering region. Based on these facts, the data is interpreted to mean that the small decrease in acidity from 5–10% H_2O is balanced by the small increase in activity coefficient for cyclohexane. The result is a nearly constant rate. The change from 5 to 4% H_2O begins to move out of the buffer region and the 2-fold increase in rate suggests acid catalysis and the inclusion of H^+ to give a positively charged transition state.

Further evidence for the acid catalysis are the observations that hydroxylation did not occur in media containing >50% of methanol, dioxan, or $CH_3OCH_2CH_2OCH_3$.

Inverse organic chemistry. Certain oxidizing agents have the singular character of attacking alkanes far faster than functional groups such as alcohols, carboxylic acids, amides, esters and halides. If such groups are present, oxidation occurs at sites remote from the functional group. The inhibitory effect is complete up to 3–4 carbons away and is still evident 8–10 carbons distant.[22] These oxidizing

Table 4. Rates of hydroxylation of cyclohexane by 30% H_2O_2 in TFA at 30°

% H_2O[a]	4	5	6	7	10
% Conversion at one hr	27	13	12	12	(11)[b]

[a] The initial concentrations (in mols ℓ^{-1}) were 0.46 cyclohexane and 1.06 H_2O_2.

[b] This run was stirred because it was heterogeneous for the first 90 mins. The analysis was conducted after the sample became homogeneous, and the % completion for one hr was estimated by interpolation.

agents are R_2NHCl^+ with light[13,15,22] or Fe II,[13] amine oxides and dialkylhydroxylamines with Fe II,[12] the per TFA hydroxylations described herein, and a multitude of microbiological hydroxylations.[23–25] With these reagents, the usual role of functional group and paraffin has been reversed to a considerable degree. The inversion is not complete. For example electron rich C=C and C≡C are reactive.[1]

Since alcohols and acids were inert, it was of interest to determine the behavior of ketones, which possess an intermediate state of oxidation. It was already apparent from the studies of per TFA on 2-methylbutane that this alkane competed to some degree because ketones were final products. A direct competition experiment between equimolar 3-pentanone and isopentane showed an initial rate ratio of 6. In a competition between equimolar cyclohexanone and cyclohexane, only the ketone reacted. These competitions used 30% H_2O_2 in TFA.

In the microbiological systems, hydroxylation can occur remote from the keto group and without effect on the keto group.[23] The same result takes place in hydroxylations by Fe II plus amine oxides.[26] However, R_2NCl α-chlorinates ketones in 10–70% H_2SO_4[27] by an ionic mechanism. It is not known whether the photochlorination could compete.

EXPERIMENTAL

Hydroxylations. A typical experiment consisted of adding 1.1 ml of 30% aqueous H_2O_2 and 1 ml of cyclohexane to 20 ml of TFA. Products were isolated by adding the mixture to ice-water and extracting with CH_2Cl_2, CCl_4, ether, or pentane. A few experiments used anhydrous per TFA in CH_2Cl_2 and this was prepared from TFA anhydride and 98% H_2O_2 as described.[9]

Analyses. The alcohols and diols were converted to their trifluoroacetates with TFA or TFA anhydride at 25°. These were taken up in CH_2Cl_2 and washed with water before analysis by gc. Silicone OV-17 (Applied Science Labs., State College, PA) was the stationary phase for the cyclohexyl derivatives and SE-30 was used for all others. The detector was of the flame ionization type except for the cyclooctane and cyclododecane experiments where a thermal conductivity detector was used. The carrier gas was N_2. Commercial samples were available for the three pentanols, the three hexanols, 1-heptanol, the five decanols, the three cycloalkanols, the six cyclohexanediols and ϵ-caprolactone. Samples of the corresponding ketones were available in most cases. The 2,3 and 4-heptanols were available by reduction of the corresponding heptanones.

In alkyl trifluoroacetates, gc retention times increase as the trifluoroacetate group moves to the end of the chain. The 1-alkyl trifluoroacetates had the longest retention times and were well separated from the other isomers. The 2- and 3-pentyl trifluoroacetates were not resolved and the 2- and 3-hexyl trifluoroacetates were poorly resolved.

Earlier work[12] had established the relative retention times of the bis trifluoroacetates of the 1,x-octanediols. The bis trifluoroacetates of the 1,x-nonanediols were assumed to have an analogous pattern. Authentic samples of the 1,ω-alkanediols were available.

The hydroxylated 9,10-dihydroxyoctadecanoic acid was cleaved with H_5IO_6 to the 9-carbon hydroxy aldehyde. This was reduced with $NaBH_4$ in aqueous ethanol to form 1,x-nonanediols. These were analyzed by gc as their bis trifluoroacetates and diacetates.

Hydroxylated hexadecanoic acids (1.0 g) were cleaved by heating with 5 ml AcOH, 1.0 ml of 70% HNO_3, and 0.01 g of NH_4VO_3 for 1 hr at 90–100°. This treatment was shown to convert 12-hydroxyoctadecanoic acid to equal amounts of C_{11} and C_{12} diacid. Unreacted hexadecanoic acid would slowly react under these conditions by itself.[18] However, the short reaction time, the limited amount of HNO_3, and the reduction of HNO_3 concentration by preferential attack on the hydroxy acids all combine to leave hexadecanoic acid relatively untouched. The pattern of hydroxylation can be deduced from the relative amounts of diacids produced by the HNO_3 oxidation. The diacids were analyzed by gc of their dimethyl esters as described.[18]

In the hydroxylation of 1-chlorooctane, the products were initially analyzed by gc of the chlorotrifluoroacetates assuming that retention times increase with increasing distance between the two functional groups. This was checked by converting the chloro to acetate by refluxing with NaOAc in acetic acid and analyzing the diacetates by gc. The retention times of the diacetates were known.[12]

The various products from 2-methylbutane were analyzed by NMR of the reaction mixtures. Authentic samples were available for comparison.

Product stability. The trifluoroacetates isomerize on refluxing in TFA, but the reaction is slow and does not affect the data in Tables 1–3. Heating a soln of 2-decyl trifluoroacetate at reflux in TFA for 24 hr caused 25% of the 2-decyl ester to isomerize to the 3, 4 and 5 isomers. The bis trifluoroacetate of 1,7-octanediol also slowly isomerized to a more random distribution of substituents. The NMR spectra (continuously monitored on all runs) showed that hydroxylation was the only significant reaction.

Other peroxyacids. Cyclohexane was hydroxylated by a solution of 30% H_2O_2 in heptafluorobutyric acid and presumably other fluoro aliphatic acids could replace TFA. However, a variety of fluorine free peroxyacids and H_2O_2–acid mixtures failed to hydroxylate cyclohexane.

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