

PERMANGANATE OXIDATIONS AND THE CARBOXYL GROUP

by

J. ANTHONY MacPHEE

B.Sc., St. Francis Xavier University, 1965

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in the Department

of Chemistry

We accept this thesis as conforming to the
required standard

THE UNIVERSITY OF BRITISH COLUMBIA

February, 1970

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study.

I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Chemistry

The University of British Columbia
Vancouver 8, Canada

Date March 2/1970

ABSTRACT

Supervisor: Professor Ross Stewart

In order to study the possible effects on permanganate oxidation reactions of a carboxyl substituent near the reacting centre, three systems were investigated.

The first of these systems consisted of the 2- and 4-benzhydrylcarboxylic acids. It was found that the 2-compound reacted more slowly than the 4-compound. The activation parameters at pH 5.45 show that the rate difference is accounted for entirely in terms of the difference in entropy of activation between the two compounds. Solubility difficulties prevented a study of the reaction below about pH 5. The kinetic results in more basic solution indicate that the pK corresponding to alcoholic OH ionization is greater for the 2-isomer than the 4-isomer. This behaviour is readily explained by examining the pK 's of several model compounds.

The second system consisted of phthalaldehydic acid and terephthalaldehydic acid. The behaviour expected for aldehydes is observed except for phthalaldehydic acid at pH 1.55. The kinetic results for phthalaldehydic acid suggest rather strongly that it exists as 3-hydroxy-phthalide in acid solution (pH 1.55) and as the free aldehyde above pH 6. This result is shown to be in accord with previous work dealing with the diverse chemical behaviour of phthalaldehydic acid.

The third system was the 2-carboxy cyclohexanol system. The pH-rate profiles of a number of isomeric 2-carboxy cyclohexanols were investigated as well as that of the parent compound, cyclohexanol. It was found that cis-2-hydroxy-cyclohexanecarboxylic acid (XIV) showed a bell-shape rate maximum in its pH-rate profile around pH 6, while trans-2-hydroxycyclohexanecarboxylic acid did not. The parent compound, cyclohexanol, does not show such an effect - the pH-rate profile is almost flat in the region pH 4 to 8. The pH-rate profiles of cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X), cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid (XI), and trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (XII) were also investigated. A mechanism is proposed which involves two opposed dissociation equilibria involving hydrogen ions. A comparison of the reactivity of XIV in protium oxide with that in deuterium oxide gives evidence consistent with the mechanism. The conformational aspects of the reaction (elucidated by means of the conformationally biased compounds -X, XI and XII) were found also to be consistent with the proposed mechanism. It was possible to make a decision between the two kinetically indistinguishable forms of the proposed mechanism on the basis of the assembled data.

Table of Contents

	<u>Page</u>
Introduction	2
Object of the Research	19
General Experimental	21
Kinetic Methods	21
Kinetic Equations	24
Temperature Control	27
Buffer System	28
Activation Parameters	28
Compounds and Reagents	30

Section A

Oxidation of 2- and 4-Benzhydrolcarboxylic Acids

Experimental	41
Product Analysis	45
Results	45
Activation Parameters	50
Discussion	52

Section B

The Oxidation of Phthalaldehydic Acid and Terephthalaldehydic Acid

Experimental	60
Products	63
Results	63
Discussion	66

Section C

The Cyclohexanol System

Experimental	79
Products	81
Results	83
Cyclohexanol	84
Cis- and trans-2-hydroxycyclohexanecarboxylic acids	87
The 5-t-butyl-2-hydroxycyclohexanecarboxylic acids	95
Conformations	98
Activation Parameters	106
Discussion	107
Suggestions for Further Work	144
Observations	146

List of Tables

<u>Table</u>		<u>Page</u>
I	Rate data for 2-benzhydrolcarboxylic acid	46
II	Rate data for 4-benzhydrolcarboxylic acid	46
III	Oxidation of 4-benzhydrolcarboxylic acid in base.....	50
IV	Temperature studies on 2- and 4-benzhydrolcarboxylic acids..	52
V	Rate data for terephthalaldehydic acid and phthalaldehydic acid	65
VI	Temperature studies on phthalaldehydic acid and terephthalaldehydic acid	66
VII	Rate data for cyclohexanol	87
VIII	Rate data for cis-2-hydroxycyclohexanecarboxylic acid.....	91
IX	Rate data for trans-2-hydroxycyclohexanecarboxylic acid.....	91
X	Rate data in deuterium oxide for cis-2-hydroxycyclohexanecarboxylic acid	92
XI	Rate data for trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid	95
XII	Rate data for cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid	96
XIII	Rate data for cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid and trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid	98
XIV	Temperature studies on cis-2-hydroxycyclohexanecarboxylic acid	106
XV	Analysis of rate data for cis-2-hydroxycyclohexanecarboxylic acid according to Reaction Schemes I and II	119
XVI	Analysis of rate data for compound XIV in deuterium oxide according to Reaction Schemes I and II	120
XVII	Analysis of rate data for compound X according to Reaction Schemes I and II	122
XVIII	Collection of data for compounds XIV(H ₂ O), XIV(D ₂ O) and X(H ₂ O) according to Reactions Schemes I and II	123
XIX	Activation parameters at pH 5.88 of cis-2-hydroxycyclohexanecarboxylic acid	139

List of Figures

Figure		Page
I	Rate plot for the oxidation of 2-benzhydrolcarboxylic acid..	43
II	Rate plot for the oxidation of 4-benzhydrolcarboxylic acid..	44
III	pH-rate profile for 2-benzhydrolcarboxylic acid oxidation...	47
IV	pH-rate profile for 4-benzhydrolcarboxylic acid oxidation...	48
V	Kinetic behaviour of 4-benzhydrolcarboxylic acid in base....	51
VIa	Temperature dependence of 2-benzhydrolcarboxylic acid oxidation	53
VIb	Temperature dependence of 4-benzhydrocarboxylic acid oxidation	54
VII	Rate plot for the oxidation of phthalaldehyde acid	61
VIII	Rate plot for the oxidation of terephthalaldehydic acid	62
IX	pH-rate profiles for oxidation of phthalaldehydic acid and terephthalaldehydic acid	64
X	Temperature dependence of phthalaldehydic acid oxidation ...	67
XI	Temperature dependence of terephthalaldehydic acid oxidation	68
XII	Phthalaldehydic acid oxidation at pH 3.68	74
XIII	Phthalaldehydic acid oxidation at pH 1.55	76
XIV	Rate plot for cyclohexanol oxidation	85
XV	pH-rate profile for cyclohexanol oxidation	86
XVI	Rate plot for oxidation of cis-2-hydroxycyclohexanecarboxylic acid	88
XVII	Rate plot for oxidation of trans-2-hydroxycyclohexane carboxylic acid	89
XVIII	pH-rate profiles for the oxidation of cis-2-hydroxycyclo- hexanecarboxylic acid and trans-2-hydroxycyclohexane- carboxylic acid	90

<u>Figure</u>		<u>Page</u>
XIX	pD-rate profile in deuterium oxide for cis-2-hydroxycyclohexanecarboxylic acid	93
XX	pH-rate profile for the oxidation of trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid	94
XXI	pH-rate profile for the oxidation of cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid	97
XXII	NMR of cis-2-hydroxycyclohexanecarboxylic acid	100
XXIII	NMR of trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid	101
XXIVa	NMR of trans-2-hydroxycyclohexanecarboxylic acid	103
XXIVb	NMR of cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid	105

Always

we draw that line between form and void
and step across it solemnly
as though each day were genesis
and it is.

Gwendolyn MacEwen

ACKNOWLEDGEMENT

I would like to thank Professor Ross Stewart for his guidance and encouragement during the course of this work.

I would also like to thank the National Research Council of Canada for its financial munificence.

INTRODUCTION

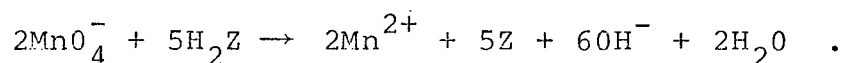
The oxidation of secondary alcohols by permanganate is a topic that has received a considerable amount of attention^{1,2,3,4,5}. Detailed mechanistic studies have been carried out by several researchers applying the theories and making use of the devices of modern chemical kinetics. As a result of these studies, certain mechanistic conclusions may be drawn about the permanganate oxidation of secondary alcohols, although some of the finer points are not free of ambiguity. The investigations of Stewart on benzhydrol¹, Stewart and Van der Linden on phenyltrifluoromethyl carbinols², Stewart and Mocek on fluoral hydrate⁵, and Littler on cyclohexanol^{3,4} all lend important information useful in framing a mechanistic picture of the reaction.

The mechanistic inferences are, in the main, drawn from the following experimental facts:

- a. The observed reactions are first order in permanganate and first order in alcohol, with the exception of the oxidation of benzhydrols in sulfuric acid solutions⁶.
- b. The product is a ketone. If the ketone is enolizable further degradation of the molecule may take place making kinetic studies more difficult and limiting the usefulness of the reaction synthetically.

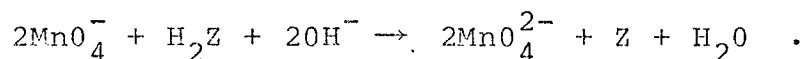
c. The stoichiometry⁷ of the reaction depends upon the acidity of the medium and to some extent on the character of the reductant. This of course has been known for some time.

In strong acid (designating the reductant as H_2Z and the product ketone as Z) we have:

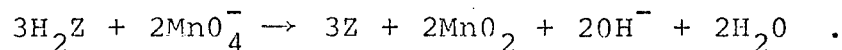


In general, the reduction of manganese from Mn(VII) to Mn(II) requires a strong reductant such as oxalic acid as well as strong acid. The oxidation of benzhydrol in acid solution⁶ yields Mn(IV) as product but Littler⁴ appears to observe Mn(II) as product in the oxidation of cyclohexanol in 1 molar sulfuric acid.

In strong base we have:



In neutral, weakly acid and weakly alkaline solutions the stoichiometry is:



d. The rate versus pH plots for secondary alcohols exhibit three regions of contrasting behaviour.

The reaction is catalysed by strong acids. Littler³ has found that the rate of oxidation of cyclohexanol in

sulfuric acid solutions obeys the following kind of equation:

$$k = a + b [H_3O^+],$$

where a and b are constants. Fluoral hydrate oxidation⁵ in sulfuric acid solutions shows a first order dependence on the acidity (H_+) of the medium.

The reaction is also catalysed by strong base¹. The rate of reaction of benzhydrol in basic solution is given by

$$\frac{-d[MnO_4^-]}{dt} = k[H_2Z][MnO_4^-][OH^-] .$$

Benzhydrol does not ionize completely in aqueous solutions of strong base so that it is not possible to decide whether the role of hydroxide is the ionization of benzhydrol or something else. Studies on fluoro alcohols (such as aryltrifluoromethyl carbinols², fluoral hydrate⁵ and 1,1,1,3,3,3-hexafluoro-2-propanol⁸), which ionize completely in aqueous solutions, reveal the function of the base in producing alkoxide ion. The alkoxide ion is more reactive than the neutral alcohol.

In the region between pH \approx 2 to 10 the rate (excluding the fluoro alcohols which ionize in this region) is almost, but not quite, independent of acidity^{1,3}. A small increase in the rate is observed as the acidity is increased from pH 10 to 2.

e. Experiments using MnO_4^{18-} indicate that the oxygen found in the product ketone does not originate in the oxidant¹.

f. Substantial deuterium isotope effects have been observed. For the oxidation of benzhydrol in neutral as well as in basic solution the value of k_H/k_D is about 7^{1,9}, while for cyclohexanol at pH 4.6 it is 4.4³. Still larger effects occur in the oxidation of aryltrifluoromethyl carbinols² (16 in the region of pH 7 up to 0.2N NaOH) and in the oxidation of fluoral hydrate⁵ (14 in the pH range 5-10). These results afford compelling evidence for the severing of the hydrogen attached to the alpha-carbon of the alcohol in the rate controlling step of the oxidation.

The disturbingly large isotope effect in the oxidation of aryltrifluoromethyl carbinols will merit some discussion later on in this thesis.

g. In two instances the effect of substitution in the aromatic ring on the oxidation of secondary alcohols has been studied^{2,9}.

Aryltrifluoromethyl carbinols², when oxidized under conditions such that the alcohol is predominately ionized, give the startling result of almost negligible substituent effect. The Hammett plot yields a dispiriting curvature which has not yet been adequately explained. The curvature is slight however and it is clear that any appropriate value of ρ must approach zero closely.

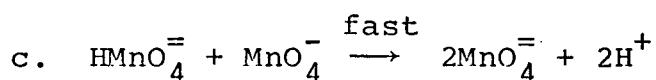
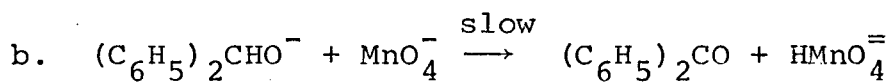
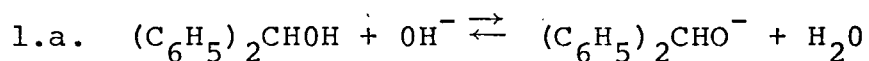
In the benzhydrol system at pH 7 the rates of p-Me and p-CO₂H, as well as the unsubstituted compound, have been measured⁹. Although the number of compounds is small, statistical analysis of the data does point out that the correlation is probably real and that the value of ρ is -0.72.

h. The acid catalysed part of the reaction bears some differences towards the reaction under other conditions. The isotope effect³ for cyclohexanol oxidation changes from $k_H/k_D = 4.4$ for the acid independent reaction to a value of 1.7 in 1.1 molar sulfuric acid. In addition to this the uncatalysed reaction appears to be unaffected when the solvent is changed from protium oxide to deuterium oxide, while there is a large solvent isotope effect in 0.45 molar sulfuric acid of $k_{D_2O}/k_{H_2O} = 2.37$ for the acid catalysed reaction³.

A change of reaction order from second to first as the medium becomes more acidic than H₀ -0.5 has been observed for the oxidation of benzhydrol⁶. When the total order is first there is a first order dependence on substrate concentration and zero order dependence on permanganate concentration. This behaviour of benzhydrol is quite different from that of cyclohexanol and is purported to be caused by rate determining formation of carbonium whose reaction with permanganate is extremely fast^{6,9}.

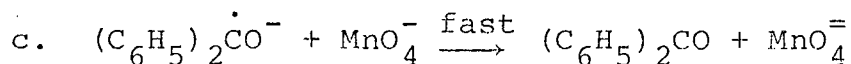
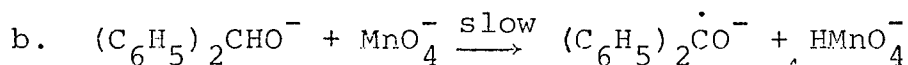
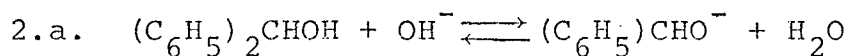
Having assembled at least a quorum of the facts the proposed mechanisms will now be delineated.

The reaction in basic solution between benzhydrol and permanganate clearly involves formation of alkoxide ion which then reacts with permanganate to lose hydrogen either as hydride ion or hydrogen atom. The observation that the deuterium isotope effect is large and that the oxygen of the oxidant does not appear in the oxidized product leads to this conclusion¹. The mechanism, if one considers a hydride transfer as the rate controlling step, can be written as:



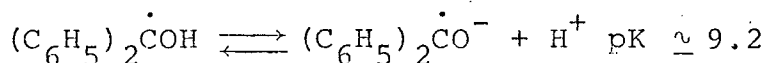
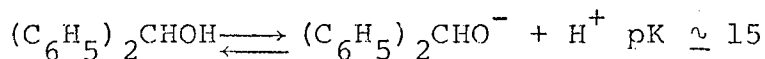
Reaction 1.c. has been indicated by Pode and Waters¹⁰ to be a very rapid reaction so that the Mn(V) species $HMnO_4^-$ would not be observed during the reaction if the reaction sequence represented by Equation 1 represents the true situation.

If one visualizes a rate controlling step involving hydrogen atom transfer from the anion to permanganate it is possible to describe it in the following way:



Mechanism 2 has gained considerable popularity over mechanism 1^{7,34} for reasons which we will now consider. The principal reason for the lack of faith in mechanism 1, which was initially favoured, rests chiefly upon the insensitivity of the oxidation of aryltrifluoromethyl carbinols to substitution in the aromatic ring. For rate-determining hydride transfer a negative value of ρ is anticipated while, as pointed out above, ρ is effectively zero^{2,8}.

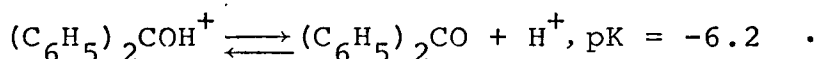
The enhanced rate of oxidation of benzhydrol in base can be rationalized easily in terms of a hydrogen atom transfer mechanism. The pK's of benzhydrol¹¹ and ketyl radical¹² corresponding to the following equations have been estimated.



The higher acidity of the ketyl radical tells us that ketyl radical anion is more stable relative to ketyl radical than benzhydrol anion is relative to benzhydrol itself. Consequently the reaction, if it proceeds with hydrogen atom transfer and the transition state resembles products, should be faster for

benzhydrol anion than for unionized benzhydrol.

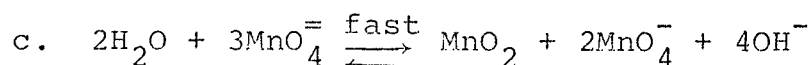
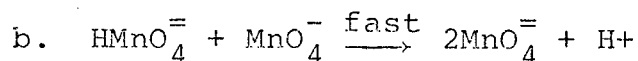
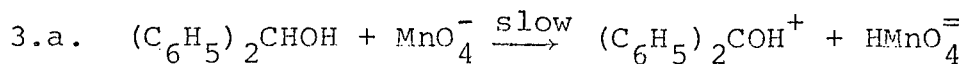
Unfortunately the foregoing constitutes an argument that is not unique. A discussion of the same kind can readily be made to include a hydride transfer mechanism as well. One would expect hydride loss to be easier from the anion than from the uncharged substrate because the former is more electron rich but the argument used to rationalize a hydrogen atom transfer mechanism may also be used here. The pK of benzophenone, corresponding to the following equilibrium, has been measured¹³ in sulfuric acid solution.



This pK says that benzophenone is more stable relative to protonated benzophenone (both initial products of hydride removal from benzhydrol and benzhydrol anion respectively) than benzhydrol anion is to benzhydrol. So the reaction of benzhydrol anion to form benzophenone should be faster than the reaction of benzhydrol to form protonated benzophenone, if the transition state resembles products sufficiently for these stability relationships to apply.

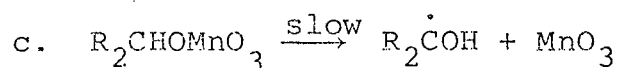
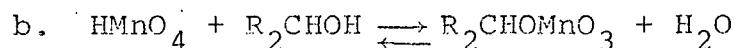
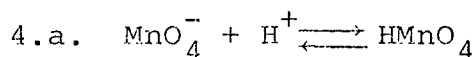
The reaction in neutral solution is much slower¹. Presumably the reacting species are neutral benzhydrol and permanganate ion. The isotope effect under these conditions is still large⁹ ($k_{\text{H}}/k_{\text{D}} = 7.3$ at pH 7) and as mentioned

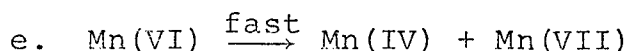
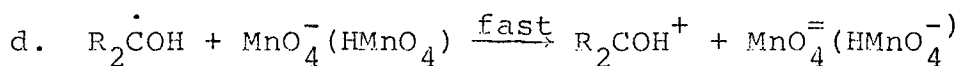
previously a rho value of -0.72 was observed⁹. These results argue more strongly in favour of a hydride abstraction mechanism (3) than one which involves hydrogen atom abstraction.



Reaction 3.b. involving Mn(VII) and Mn(V) was shown by Pode and Waters¹⁰ to be instantaneous. Reaction 3.c., the disproportionation of manganate to permanganate and manganese dioxide is known to occur in solutions which are less basic than about 1 molar in hydroxide ion. In solutions which are neutral or acidic the disproportionation is instantaneous¹⁴.

The permanganate oxidation of cyclohexanol in acid solution has been studied by Littler³. The dependence of rate constant on acidity has already been mentioned. On the basis of the reduced deuterium isotope effect (1.7 at 27°C) and the rate enhancement (2.4) in D₂SO₄/D₂O the following mechanism for the acid catalysed mechanism was proposed³:

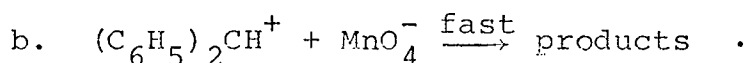
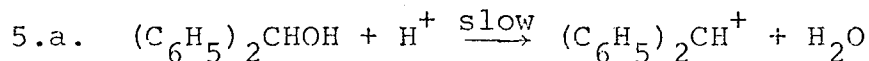




If one considers the large deuterium isotope effects commonly observed in permanganate oxidations,⁷ the small effect noted in this case seems indicative of some change involving the rate controlling step. The change proposed in 4.b. and c. is probably a reasonable alternative. The rate enhancement in deuterated acid solution is entirely in accord with the known weakening of acids¹⁵ in deuterium oxide. In deuterated acid solution the equilibrium 4.a. will be displaced to the right causing 4.b. to be displaced to the right as well, resulting in an acceleration of the slow step 4.c.

In sulfuric acid solutions the oxidation of benzhydrol has been investigated in some detail by Banoo and Stewart^{6,9}. The most unusual feature of this reaction is the change from second order kinetics to first order in solutions more acidic than $\text{H}_0 - 0.5$. The reaction was found to be first order in benzhydrol and zero order in permanganate over a five-fold variation in permanganate concentration. The isotope effect ($k_{\text{H}}/k_{\text{D}}$) in the region $\text{H}_0 = -0.5$ to -1.2 is 1.1, contrasting with the result at pH 7 where the isotope effect is 7.3. The rate constant is found to correlate with the acidity of the medium as reflected by the H_0 function. The mechanism under these conditions is thought to be the

following:

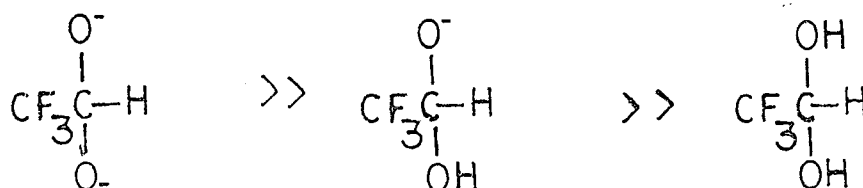


The rate determining ionization of benzhydrol was proved by measuring the rate of ionization at comparable acidities in the absence of permanganate. The agreement between the rate of ionization and the rate of oxidation is close. The fast step presumably consists of the formation of an ester $(C_6H_5)_2CH-O-MnO_3$ whose various modes of decomposition are discussed by Banoo and Stewart⁶.

A discussion of the alkaline oxidation of aryltrifluoromethyl carbinols would be similar to that for benzhydrol. In the case of the fluoroalcohols it is possible to demonstrate the function of hydroxide ion because of the enhanced acidity resulting from the attached fluorine. The alcohols studied by Stewart and Van der Linden² had pK values in the vicinity of 12. Under conditions such that the alcohol was only slightly ionized the rate is directly proportional to hydroxide ion concentration. However as the alcohol becomes completely ionized the influence of hydroxide ion levels off. This surely indicates that the kinetic dependence on hydroxide ion is the result of a pre-equilibrium of the kind in Equation 1.a. and not anything more complicated than that. The failure of substituents to have any measurable effect on the rate has

already been noted.

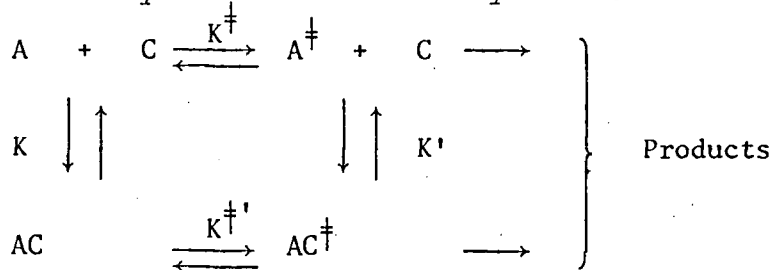
The permanganate oxidation of fluoral hydrate has received some attention⁵ and although it is not actually a secondary alcohol the resemblance is close enough for a profitable discussion of it here. One of the most striking features of the reaction is the different reactivity shown by the various species derived from fluoral hydrate. The order of reactivity towards MnO_4^- is as follows:



This is the order to be expected if the oxidation involves hydride ion removal from the fluoral hydrate species. However, because oxidation involves a loss of electrons, this is the behaviour that might be observed, no matter what the mechanism might be (hydride or atom loss). This same point has been brought forward elsewhere¹⁶.

A most interesting sidelight of this work is the theoretical discussion given by Kurz^{17,18} involving a treatment termed by that author as "Transition State Characterization". If it is possible to observe a reaction which is catalysed and the same reaction uncatalysed, one is able, using Kurz' treatment, to calculate the virtual equilibrium for the decomposition of the transition state with the catalyst present to a transition state in which the catalyst is absent. The scheme

presented by Kurz will clarify this.



Here A is the reactant and C is the catalyst. The virtual equilibrium of interest is represented by K' . The equilibrium is termed virtual because experimentally it does not take place since transition states have very short lifetimes. A knowledge of K , K^\ddagger and K'^\ddagger enables one to infer K' as in any thermodynamic cycle. That activation equilibria and a virtual equilibrium are involved in no way alters the validity of the treatment.

If k_1 refers to the unimolecular reaction (Rate = $k_1[A]$) and k_2 to the bimolecular reaction (Rate = $k_2[C][A]$), the equations of Kurz for the dissociation of the catalysed transition state into the uncatalysed transition state are:

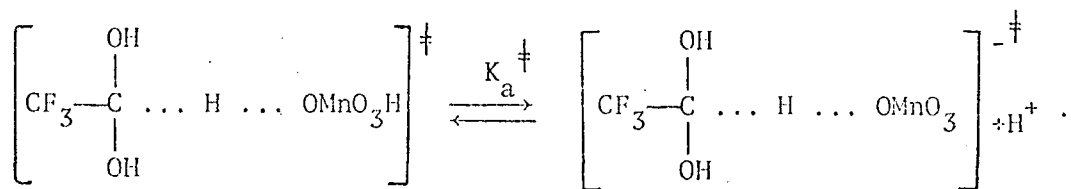
- 6.a. For H^+ catalysis $pK_a^\ddagger = \log(k_2/k_1)$
- b. For OH^- catalysis $pK_a^\ddagger = \log(k_1 k_2) + pK_w$.

Since hydroxide ion catalysis will be referred to it is best to clarify what is meant by this. It consists of a pre-equilibrium proton removal from the substrate and subsequent reaction not involving catalyst. Such a pre-equilibrium

distinguishes specific hydroxide ion catalysis from general base catalysis and here we are concerned with the former.

The application of 6.a. or 6.b. is simple. From the experimental results it is possible to calculate what the virtual equilibrium constant is. By assuming alternately that the transition state involves no reaction or complete reaction it is possible, in principle, to compute a value of the constant for these extreme cases. The experimental value should lie between the two extremes and by assuming a linear change in pK_a^\ddagger resulting from various degrees of bond formation one can calculate the degree of bond formation corresponding to the real situation.

To be more concrete one might calculate the equilibrium constant for the following, using the data of Stewart and Mocek^{5,17}:

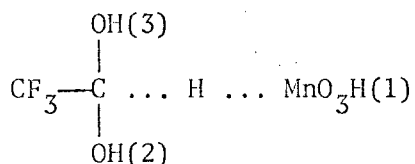


The appropriate equation to use in this case is 6.a. To make an estimate of K_a^\ddagger one first considers what the mechanism might be. This discussion follows closely that given by Kurz¹⁸ and we will use his estimates of the pK 's of the various species of interest.

If the mechanism for both catalysed and uncatalysed reactions involves transfer of hydride ion from substrate to permanganate, one can say that in the case of 0% bond formation at the transition state the ionization resembles that of HMnO_4 ($\text{pK} = -5.1$)⁵ while for 100% reaction at the transition state the ionization resembles that of H_2MnO_4^- (pK estimated at 9). The value of pK_a^\ddagger calculated from the experimental data is 0.4. These three numbers give a value of 39% for the extent of bond making at the transition state.

The alternative mechanism, hydrogen atom transfer, may be treated in the same way. For 0% bond formation the pK estimate is still the same. For 100% reaction at the transition state the dissociation resembles that of H_2MnO_4 (estimated $\text{pK} = -1.0$). The experimental value of 0.4 falls outside the range allowed and consequently the mechanism involving hydrogen atom transfer is not considered valid. Of course, if the catalysed and uncatalysed reactions differ in mechanism this formalism breaks down.

Kurz has examined the fluoral hydrate oxidation for the situations in which each of the protons number below can be considered as ionizing from the transition state



and the result is invariably similar to that quoted - the experimental pK_a^\ddagger is compatible with hydride ion transfer but not hydrogen atom transfer. Kurz has suggested that this result could be invalidated if the successive reactions between fluoral hydrate and permanganate alternated with respect to mechanistic type but this logical alternative has not been considered seriously.

Barter and Littler⁴ have observed that a variety of one-electron oxidants (V(V), Ce(IV), Mn(III), Co(III)) attack ethers very much more slowly than alcohols under neutral or mildly acidic conditions, while permanganate does not. These one-electron oxidants presumably have no mode of reaction other than hydrogen atom transfer or electron transfer. Permanganate has a choice between hydride and hydrogen atom transfer and its failure to behave like these other oxidants may indicate a different mechanism - namely hydride transfer. An ether is formally similar to a secondary alcohol, R_1R_2CHOX , where X represents an alkyl group instead of hydrogen. Indeed an ether, were it oxidized by hydride loss, might react more readily than the corresponding secondary alcohol because of the inductive effect of the alkyl group⁴.

SUMMARY

The main point of argument with respect to the permanganate oxidation of alcohols concerns whether hydrogen atom or hydride ion is being assumed by permanganate in the transition state⁷. The principal argument used in favour of the former viewpoint is the failure of aryltrifluoromethyl carbinols to exhibit a substituent effect². Arguments based on the effect of substituents on the oxidation of benzhydrol in neutral solution⁹ and theoretical considerations evolved by Kurz¹⁸ indicate that the hydride mechanism is more probable. However the situation might be regarded as open and calling for further investigations which might solve the mechanistic dilemma in a more conclusive way.

OBJECT OF THE RESEARCH

The motivation behind investigating the permanganate oxidation of carboxyl substituted secondary alcohols lies in the ability of this substituent to influence the course and rate of a reaction by bonding directly with the reacting centre in the transition state. "Neighbouring group participation" of this kind is well documented^{19,20,21}.

A variety of roles can be assumed by the carboxyl function depending on the energetics of the reaction in question. Substitution reactions occurring at a saturated carbon centre can be greatly accelerated by suitably placed carboxylate but this effect is not observed for the unionized carboxyl group. The nature of the participation is clearly indicated for the case of the solvolysis of sodium 4-bromobutyrate in neutral solution²². The observed product is not 4-hydroxy butyrate but rather the corresponding lactone.

Ester hydrolyses involving esters of various kinds have received a great deal of attention²⁰. Intramolecular effects involving both carboxyl and carboxylate catalysis have been discovered by many workers^{21,23}.

In view of this and certain speculative features of permanganate oxidations outlined in the introduction and to be considered later, it seemed worthwhile to undertake an examination of permanganate oxidations in relation to carboxyl effects.

GENERAL EXPERIMENTAL

Kinetic Methods

Two analytical methods were used to determine reactant concentration as a function of time in this work - a. titration and b. spectrophotometric.

a. The most commonly used technique is the standard iodometric determination of manganese species with oxidation level greater than two. This mode of analysis has been used in permanganate oxidation work very frequently^{7,24}. The method consists of mixing the manganese solution to be analysed with a dilute solution of sulfuric acid (0.2M) containing excess iodide. The manganese is reduced to manganese of oxidation state two and at the same time an equivalent amount of iodine is formed. The iodine is titrated with standard thiosulfate solution using a starch indicator. It is customary to carry out the analysis under a blanket of carbon dioxide. The iodide solution is prepared by addition of carbonate to water, then an excess amount of sulfuric acid and finally solid potassium iodide. The carbon dioxide liberated when the sulfuric acid is added purges the solution of dissolved oxygen and provides a protective layer during the analysis. Oxygen oxidizes iodide to iodine and the precaution is necessary when the total number of equivalents of iodine produced in the analysis is small.

b. Some of the kinetic experiments, in particular those conducted in basic solution, in deuterium oxide and in the presence of low concentrations of substrate, were followed using a spectrophotometric technique.

The oxidation in basic solution produces a different manganese product than in neutral and acid solution. In solutions more basic than about pH 12 the manganese product is manganate, $\text{MnO}_4^{=}$. The visible spectra of permanganate and manganate are quite distinct with maximum absorbances at different wavelengths. However, there appears to be no suitable wavelength at which only one of these species is found to absorb. Consequently it is necessary to measure the absorbance at two different wavelengths and calculate the concentration of each species from the known extinction coefficients at these wavelengths. The wavelength chosen were those noted by Stewart⁷ after Zimmerman, namely 426 $\text{m}\mu$ and 522 $\text{m}\mu$. Absorbance measurements were made using a Bausch and Lomb 502 recording spectrophotometer.

This is true for an arbitrary mixture of manganate and permanganate. In the present case initially there is only permanganate and with time manganate gradually replaces it keeping the total amount of manganese constant. At 522 $\text{m}\mu$ the extinction coefficient of permanganate is 2370 and of manganate 387⁷. Thus for a 1 cm. path length the absorbance A is

$$A_{522} = 2370[\text{MnO}_4^-] + 387[\text{MnO}_4^{=}] \quad .$$

However we know that the manganate is generated as the permanganate is used up giving us

$$\text{MnO}_4^- = (A_{522} - 387[\text{MnO}_4^{=}]_0)/1983 \quad .$$

Thus with the additional constraint of having the sum of MnO_4^- and $\text{MnO}_4^{=}$ a constant it is possible to determine the concentration of both species from the absorbance at a single wavelength.

The reaction in neutral and acidic solution produces MnO_2 as the manganese product. The pH of the solutions was maintained with phosphate buffers and it was noted that the product MnO_2 shows no tendency towards precipitation, under the conditions used, until a day or more had elapsed. This is contrasted with the less versatile carbonate buffers which tend to deposit MnO_2 solid early in a kinetic run and make them unsuitable. This reluctance of phosphate buffers to deposit MnO_2 has been noted before²⁴ and makes them useful for studies in which permanganate is reduced to Mn(IV).

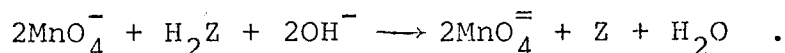
In the present work the spectrophotometric method was employed for runs carried out in deuterium oxide solvent and those in which the concentration of substrate had to be small because of low solubility. In these cases the

absorbance was measured at 525 $m\mu$ and the rate constant determined in a manner discussed below. For absorbance measurements at 525 $m\mu$ a Cary 16 spectrophotometer was used.

Kinetic Equations.

The reactions were invariably first order in substrate concentration and first order in permanganate concentration. Because manganese species were the only ones observed analytically and because two different stoichiometries prevail at different acidities the exact form of the kinetic equations is dependent on several factors.

a. When the pH of the medium is greater than about 12 the following stoichiometry holds:



A special form of the kinetic equation obtains when the reactants are mixed in precisely their stoichiometric quantities. In this case starting with

$$7. \quad - \frac{d[\text{MnO}_4^-]}{dt} = k[\text{MnO}_4^-][\text{H}_2\text{Z}]$$

we have, after expressing the substrate concentration in terms of permanganate concentration

$$8. \quad \frac{kt}{2} = \frac{1}{[\text{MnO}_4^-]} - \frac{1}{[\text{MnO}_4^-]_0} .$$

Here $[\text{MnO}_4^-]$ represents the concentration of permanganate at time t and $[\text{MnO}_4^-]_0$ is the initial concentration. Equation 8. can be expressed in terms of the volume (V_t) of thiosulfate needed to titrate aliquots of the reaction mixture, giving:

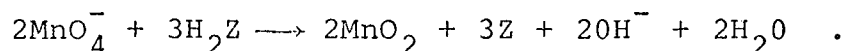
$$9. \quad kt = \frac{1}{[\text{H}_2\text{Z}]_0} \frac{V_0 - V_t}{V_t - \frac{4V_0}{5}} .$$

If, however, the reactants are initially combined in a non-stoichiometric ratio $a = [\text{H}_2\text{Z}]_0 / [\text{MnO}_4^-]_0$,

the kinetic expression takes the following form:

$$10. \quad kt = \frac{4.606 a}{[\text{H}_2\text{Z}]_0 (2a-1)} \log \left[\frac{V_t + V_0 (2a-5)/5}{2a (V_t - \frac{4V_0}{5})} \right] .$$

b. If the medium is more acidic than about pH 12 the following stoichiometry operates:



Mixing the reactants initially in stoichiometric proportions leads to

$$11. \quad \frac{3kt}{2} = \frac{1}{[\text{MnO}_4^-]} - \frac{1}{[\text{MnO}_4^-]_0}$$

and also

$$12. \quad kt = \frac{1}{[\text{H}_2\text{Z}]_0} \frac{V_0 - V_t}{V_t - \frac{2V_0}{5}} \quad .$$

When the ratio $a = [\text{H}_2\text{Z}]_0 / [\text{MnO}_4^-]_0$ is

non-stoichiometric we have:

$$13. \quad kt = \frac{4.606a}{[\text{H}_2\text{Z}]_0 (2a-3)} \log \left[\frac{3(V_t + V_0(2a-5)/5)}{2a(V_t - \frac{2V_0}{5})} \right] \quad .$$

Because of their simplicity Equations 12. and 9. were most frequently used. Equations 13 and 10. apply to a few kinetic runs and their use is noted where applicable. The more general Equations 13. and 10. have not been previously derived and their derivations are consequently given in Appendix A. The remaining equations have been in use for some time and their derivations are to be found elsewhere⁷.

The rate constants were determined using the various expressions by plotting the appropriate function against time. The slope of this straight line is directly related if not actually equal to the rate constant. The slope can be determined either graphically or by the method of least squares. It was found that if the points do not have much scatter the values of the rate constant determined graphically and by least squares were closer to each other than the reproducibility of the rate determination.

Temperature Control

Most kinetic experiments were carried out in a flask immersed in a water bath which is furnished with a 100 Watt heater, a movable-contact thermoregulator, and an electronic relay. Cooling was afforded by a copper coil immersed in the bath through which tap water flowed. The flow-rate could be adjusted so that the heater went through an on-off cycle every minute or so. The bath was stirred by a motor-driven propellor stirrer. The precision of the temperature control is believed to be about $\pm 0.05^{\circ}\text{C}$.

For runs involving lower temperatures than could be produced by the water-bath system a thermoelectric immersion cooler was used. The cooler was immersed in a bath of ethylene glycol in a large wide-mouth Dewar flask. Stirring was accomplished by bubbling air briskly through the bath by means of a copper tube leading to the bottom of the Dewar. The precision of the temperature control is about the same or better than that using the conventional water bath.

The runs followed spectrophotometrically were invariably performed at 25°C . Temperature control was maintained by circulating water from a thermostated water bath through a thermostating block cell-holder within the spectrophotometer.

Buffer System

Since the reaction either generates or consumes hydroxide ion depending upon the conditions and is, in any case, pH dependent, the use of buffers is necessary. In this work phosphate buffers were used almost exclusively. The desired pH was attained by starting with about 0.15 molar K_2HPO_4 and adding either droplets of concentrated sulfuric acid or particles of potassium hydroxide solid. A calculation of the ionic strength taking into account the ionic species resulting from the buffer as well as sulfate ion indicates that this quantity is remarkably constant in the pH- range 3 to 9. If the buffer concentration is 0.143 molar the ionic strength at pH 9 is 0.43 and it falls to 0.37 at pH 3. So, considering the usefulness of this buffer system with respect to dissolved Mn(IV) and the near constancy of the ionic strength over such a wide range of acidity, phosphate buffers seemed a suitable choice.

Activation Parameters

Enthalpies (ΔH^\ddagger) and entropies (ΔS^\ddagger) of activation were calculated from rate versus temperature data using the well-known Eyring equation²⁵

$$k = \kappa \frac{k_B T}{h} e^{\frac{-\Delta H^\ddagger}{RT}} e^{\frac{\Delta S^\ddagger}{R}}$$

where k is the second order rate constant in units of liters per mole per second, k_B is Boltzmann's constant, h is Planck's constant, R is the gas constant and T the absolute temperature. The transmission coefficient κ is assumed to be unity as is customary²⁶.

The actual computation was done using the logarithmic form of the Eyring equation.

$$\log \left(\frac{k}{T} \right) = \log \left(\frac{k_B}{h} \right) + \frac{\Delta S^\ddagger}{2.303R} - \frac{\Delta H^\ddagger}{2.303RT}$$

A plot of $\log \left(\frac{k}{T} \right)$ against $1/T$ results in a straight line of slope $-\Delta H^\ddagger/2.303R$ and an intercept of $\log \left(\frac{k_B}{h} \right) + \Delta S^\ddagger/2.303R$. The slope and intercept were determined using a least squares computer program. The program also calculated the standard error in the slope and intercept as well as the coefficient of correlation. Wherever activation parameters are cited herein these data are also supplied.

COMPOUNDS AND REAGENTS

3-Phenylphthalide

First 2-benzoylbenzoic acid was prepared from benzene and phthalic anhydride using the procedure given by Vogel²⁷.

This compound was reduced using sodium borohydride. To 5 grams of 2-benzoylbenzoic acid in 50 ml. of water, an excess of sodium borohydride was added slowly with stirring. The 2-benzoylbenzoic acid was not completely dissolved at the beginning of the reaction but became so as the aqueous solution became basic on addition of sodium borohydride. After stirring for a few minutes the solution was carefully acidified by addition of droplets of concentrated sulfuric acid while stirring vigorously. The white precipitate, obtained in almost quantitative yield, was filtered with suction and washed several times with water. After two recrystallizations from carbon tetrachloride and drying under reduced pressure the compound melted at 113-114 (Lit. m.p. 113-114²⁸).

Benzhydrol-4-carboxylic acid

From 4-benzoylbenzoic acid (Aldrich # B1240) benzhydrol-4-carboxylic acid was prepared by sodium borohydride reduction. To 5 grams of 4-benzoylbenzoic

acid in 50 ml. of water, excess sodium borohydride was added slowly with stirring. Five minutes after the compound went completely into solution the solution was acidified with concentrated sulfuric acid, added dropwise with vigorous stirring. A white precipitate formed which was filtered with suction, washed with water several times and dried. The amount was almost quantitative. After two recrystallizations from CHCl_3 :EtOH-4:1 and drying under reduced pressure a compound was obtained whose melting point was 165-66(Lit. m.p. 164-65²⁹).

Phthalaldehydic acid

This compound was purchased from the Aldrich Chemical Co. (# 11,601-7). After a treatment with decolorizing carbon in ether solution it was recrystallized from water to constant melting point. The final compound consisted of white plates melting at 96.5-97.5(Lit. m.p. 97²⁹).

Terephthalaldehydic acid

Obtained from Fluka Chemische Fabrik (# 21870), this compound was purified by recrystallization to constant melting point from water containing a trace of ethanol. The final melting point was 255-56(Lit. m.p. 256³⁰).

Cis-2-hydroxycyclohexanecarboxylic acid

Both isomers of 2-hydroxycyclohexanecarboxylic acid were prepared by the catalytic hydrogenation of ethyl 2-oxocyclohexanecarboxylate. This latter compound was prepared by the method of Organic Syntheses, Coll.Vol.II,p.531.

The procedure used for the reduction and work-up was similar to that given by Pascual, Sistare and Ragas³¹. A solution of 17 grams of ethyl 2-oxocyclohexanecarboxylate in about an equal volume of methanol was reduced in a Paar hydrogenation apparatus at an initial pressure of 50 lbs./in.² above atmospheric pressure. As catalyst 200 mg. of Adams' Catalyst was used. The duration of the reduction was about 20 hours after which time the catalyst was removed by filtration and the methanol taken off using the rotary evaporator. The remaining liquid was distilled at 18 mm/Hg pressure. The first fraction consisted of unreduced starting material and the reduction product was collected at 115-120°C. The distillate was poured into 45 ml of hot 8N NaOH with stirring. Some frothing occurred. When the liquid became homogeneous (after a few minutes), the stirring was interrupted and the solution allowed to cool. A copious white precipitate formed which was filtered with suction. The filtrate was washed with 2 ml of ethanol and dried. The white salt

was dissolved in the smallest possible amount of water, acidified with 6N HCl, saturated with ammonium sulfate and extracted continuously with ether overnight. The ether extract was dried and the ether removed to yield 7 grams of an oil which solidified slowly on standing. Several recrystallizations of this solid from ether yielded pure cis-2-hydroxycyclohexanecarboxylic acid, m.p. 81-82(Lit. m.p. 82).

Trans-2-hydroxycyclohexanecarboxylic acid

This compound was obtained by combining the alcohol wash solution and the mother liquor remaining from the hydrolysis of the reduced ethyl ester and refluxing for about a day. The mother liquor contained a substantial amount of base and any cis-isomer present was transformed into trans-isomer during the refluxing. This transformation to a more stable isomer is practically a proof of structure for both compounds. The basic refluxed solution was acidified to Congo-red with 6N HCl and worked up just as was the cis-isomer. The product, pure trans-2-hydroxycyclohexanecarboxylic acid, melted at 110-111(Lit. m.p. 111³¹).

Trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid

The synthesis of this compound involves the

reduction of ethyl 2-oxocyclohexanecarboxylate with sodium borodeuteride.

About 20 ml. of absolute ethyl alcohol were added to 0.985 gm of sodium borodeuteride (0.024 mole) and the mixture was chilled in an ice-water bath. The ester (11.7 gm, 0.069 mole) was added to 20 ml of absolute ethyl alcohol and this solution was also chilled. The solution containing the borodeuteride was added dropwise with stirring to the ethanolic solution of the ester. Addition was complete in about a half-hour. The solution was stirred at room temperature for another half-hour and then made acidic to Congo-red with 6N HCl. Water (30 ml) was added and ethanol and water were removed together at reduced pressure until only water and the reduced ester remained. Basic hydrolysis was accomplished by addition of 8 gm. of solid sodium hydroxide dissolved in 20 ml. of water. This basic solution was extracted with ether to remove any cyclohexanone derived from unreduced ester and the ether extract was discarded. The basic solution was chilled and acidified with 6N HCl to Congo-red. After saturation with ammonium sulfate the solution was extracted continuously with ether, the extract dried and the ether removed to yield an oil which slowly solidified. This crude material (6.6 gm) was dissolved in 5% sodium bicarbonate and after further purification by

extraction with ether was regenerated in the usual way. To this material was added hot 8N sodium hydroxide solution (50 ml) and the clear solution which resulted was allowed to return to room temperature with stirring. Chilling in an ice-water bath caused the solution to cloud slightly and after standing overnight a copious white precipitate was deposited. This precipitate was collected by filtration with suction and the neutral acid was obtained in the manner described for cis-2-hydroxycyclohexanecarboxylic acid. Several recrystallizations from ethyl acetate gave a compound (m.p. 80-81), whose structural proof will be considered later as deduced from N.M.R. evidence.

Ethyl 5-t-butyl-2-oxocyclohexanecarboxylate

The procedure used in this synthesis is similar to that of Organic Syntheses, Coll.Vol.II,531 for ethyl 2-oxocyclohexanecarboxylate.

A quantity of sodium (0.33 mole) was added to 150 ml of anhydrous ethanol in a 2 litre three-neck round-bottomed flask fitted with a condenser topped by a drying tube. The liquid was stirred using a magnetic stirrer and when the sodium had completely reacted the flask was surrounded by an ice-water bath to bring the temperature of the ethoxide solution below 10°C. A solution of ethyl oxalate (0.33 mole)

and 4-t-butylcyclohexanone (0.33 mole) together, combined with 50 ml of anhydrous ethyl alcohol, was added over a period of an hour to the sodium ethoxide solution. Stirring was continued overnight and the reacting mixture gradually came to room temperature as the ice in the ice-water bath was depleted.

Then concentrated sulfuric acid (10 ml) in 75 gm of ice was added, followed by 1 litre of water. After stirring for a few minutes a heavy oil settled to the bottom of the flask. This oil was separated from the rest of the liquid which was extracted with four 200 ml portions of benzene. The benzene extracts and the oil were combined and washed twice with 200 ml portions of water. After standing for some time to allow the water to separate from the benzene layer, the benzene was removed using the rotary evaporator. The remaining liquid was distilled at a pressure of 0.5 mm/Hg and was collected between 120 and 130°C. The distillate was heated for two hours at 165°C and 40 mm/Hg pressure in the presence of about a gram of crushed glass and a trace of iron powder (0.2 mg). At the end of the two hour period the expulsion of carbon monoxide appeared to have ceased. The temperature was reduced to about 130°C and the pressure reduced to 0.5 mm/Hg. Distillation occurred and the product was collected between 90 and 92°C. The

weight of product (37.8 gm) corresponded to a yield of 51.5%.

Analysis for $C_{13}H_{22}O_3$ (226.3)

Found (calculated): 69.12(68.99)%C, 10.00(9.80)%H. $n_D^{20} = 1.4805$

Cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid

This compound was prepared by catalytic reduction of ethyl 5-t-butyl-2-oxocyclohexanecarboxylate. The ester (10.1 gm) was added to 50 ml of glacial acetic acid along with 800 mg of Adams' catalyst. Reduction was carried out in a Paar type hydrogenator using an initial pressure of 50 lb./in.² above atmospheric pressure. The duration of reduction was 48 hours.

The solution was filtered to remove the catalyst and combined with 100 ml of water. This was extracted with two 100 ml portions of low-boiling petroleum ether. The extracts were combined and shaken with 5% sodium carbonate solution and dried. The solvent was removed using the rotary evaporator and the liquid residue was distilled at 0.6 mm/Hg pressure and collected at 92-95°C. The distillate was hydrolysed with 30 ml of hot 6N sodium hydroxide solution from which the sodium salt precipitated on cooling. The salt was dissolved in water and the acid precipitated by acidifying to Congo-red with 6N HCl. This slurry of compound and water was extracted with ether. The ether was dried

and removed to yield a crude solid. This solid was recrystallized to constant melting point from a mixture of low-boiling petroleum ether and benzene. After five recrystallizations the melting point rose to a constant 149-50 (Lit. m.p. 149-149.5³²).

Cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid

This compound was synthesized by reduction of ethyl 5-t-butyl-2-oxocyclohexanecarboxylate with sodium borohydride, hydrolysis with strong base and separation of the appropriate isomer from the mixture by fractional crystallization of the sodium salt from a solution of sodium hydroxide.

Sodium borohydride (0.945 gm) and ethyl 5-t-butyl-2-oxocyclohexanecarboxylate (10.0 gm) were separately dissolved in two 20 ml portions of absolute ethanol. The sodium borohydride solution was added to the solution of the ester over a period of fifteen minutes. After complete addition the mixture was stirred at room temperature for another thirty minutes. Then water (15 ml) was added and stirring continued for another hour. The solution was made acid to Congo-red by addition of 6N HCl and more water (100 ml) was added. Removal of the ethanol using the rotary evaporator caused the reduced ester to

separate from the remaining aqueous layer. The ester was taken up with ether and the aqueous layer extracted twice more with 50 ml volumes of ether. The combined extracts were dried and the solvent removed. The resulting liquid was subjected to reduced pressure distillation as mentioned in the immediately preceeding synthesis. The distillate was hydrolysed in 3N sodium hydroxide solution and refluxed for an hour. Upon cooling a precipitate formed which was collected. The precipitate and the mother liquor were worked up separately in the usual way. The precipitate was found to contain two isomers which accounted for nearly all of the available material. The mixture of acids was dissolved in 50 ml of 1N sodium hydroxide and on cooling gave a precipitate. This precipitate, after work-up, gave a pure compound which melted at 144-45 (Lit. m.p. 145-46³²) after recrystallization from benzene. The mother liquor yielded a mixture of two components in nearly equal amounts. The melting points of this compound and the immediately preceeding isomer are very close but differences in IR and NMR spectra show that they are distinct compounds.

Trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid

This compound was isolated from a mixture of isomeric acids obtained from ethyl 5-t-butyl-2-oxocyclohexanecarboxylate by reduction with sodium

borohydride. The mixture of acids (10 gm) was dissolved in the minimum amount of hot saturated sodium bicarbonate solution. Upon cooling in an ice-water bath a precipitate was formed. The mother liquor and the precipitate were separated and the liquid worked up as usual to yield a solid which when recrystallized three times from petroleum ether-benzene gave a compound of melting point 133-34 (Lit. m.p. 133-35³²).

5-t-Butyl-2-oxocyclohexanecarboxylic acid

This compound was prepared according to the procedure of Sicher et al³².

Sodium deuterioxide and deuterio sulfuric acid

Both of these compounds (NaOD and D_2SO_4) were prepared using methods given in Inorganic Isotopic Syntheses³³ (Procedures 7A and 31A).

Dipotassium deuterium phosphate

Several exchanges of K_2HPO_4 with D_2O afforded K_2DPO_4 with no detectable hydrogen content.

SECTION A

THE OXIDATION OF 2- AND 4-BENZHYDROLCARBOXYLIC ACIDS

Experimental

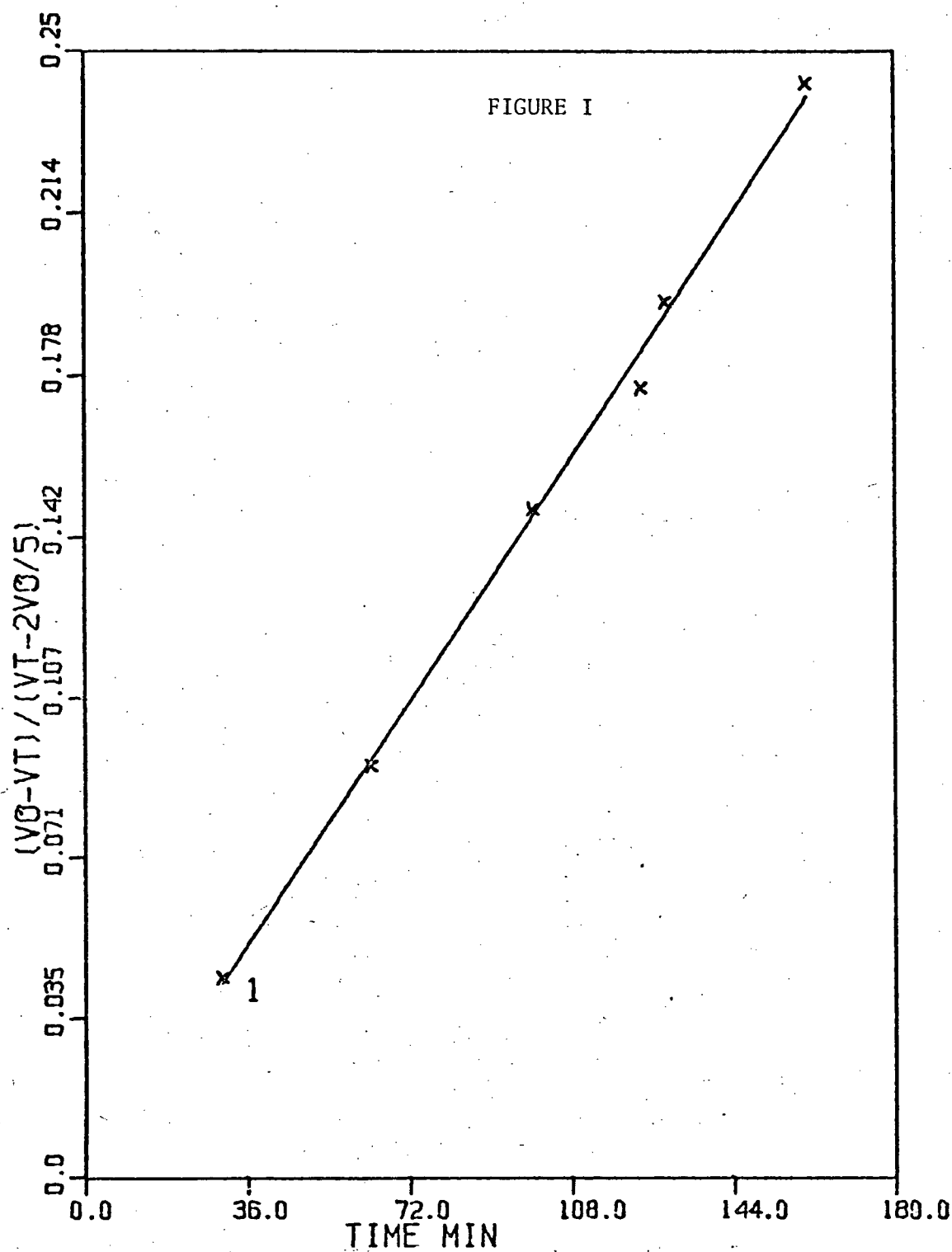
The syntheses of 3-phenylphthalide and 4-benzhydrolcarboxylic acid have been indicated previously. A solution of the anion of 2-benzhydrolcarboxylic acid was prepared for use in the kinetic experiments by the hydrolysis of 3-phenylphthalide using 0.1N potassium hydroxide. For the kinetic runs on 4-benzhydrolcarboxylic acid a stock solution containing that compound and an equivalent amount of 0.1N potassium hydroxide was used.

Kinetic experiments at pH values less than 12 had an initial substrate to permanganate ratio of 1.5, while those above pH 12 had a ratio of 0.5. These ratios correspond to the known stoichiometries operative in these regions and necessitate the use of kinetic equations 9. and 12. The runs at the 3:2 stoichiometry were followed by titration and those at the 1:2 stoichiometry were followed spectrophotometrically. Several runs were carried out using non-stoichiometric proportions of reactants and were analysed by the appropriate equations (10. and 13.). These results demonstrate the validity of equations 10. and 13. but due to their awkwardness they were not used further.

Figures I and II display two fairly representative rate plots. The run described by Figure I was carried out as follows:

To a 100 ml erlenmeyer flask, fitted with a B-24 stopper and two side arms sufficient to admit a glass-electrode and a calomel-electrode, were added 15 ml of 0.02370M 2-benzhydrylcarboxylate, 10 ml of 1M K_2HPO_4 and 25 ml of water. The pH of the solution was adjusted by careful addition of solid KOH. Mixing was effected using a magnetic stirrer. After adjusting the pH, the flask was placed in a water bath at 25°C and allowed to approach thermal equilibrium for about 30 minutes. Then 10 ml of 0.02370M potassium permanganate solution, also at 25°C, was added. The solution was stirred quickly and 5 ml aliquots were then withdrawn at intervals. These aliquots were quenched with acidic iodide solution and the liberated iodine titrated with 0.01945M sodium thiosulfate.

The procedure for the run of Figure II is identical to that of the run in Figure I, except of course for the change of substrate. For the more rapid runs a wide-mouth 5 ml pipette was used. This is the case for the run of Figure II. For slower runs, such as that of Figure I, a conventional volumetric pipette was found to be more precise.



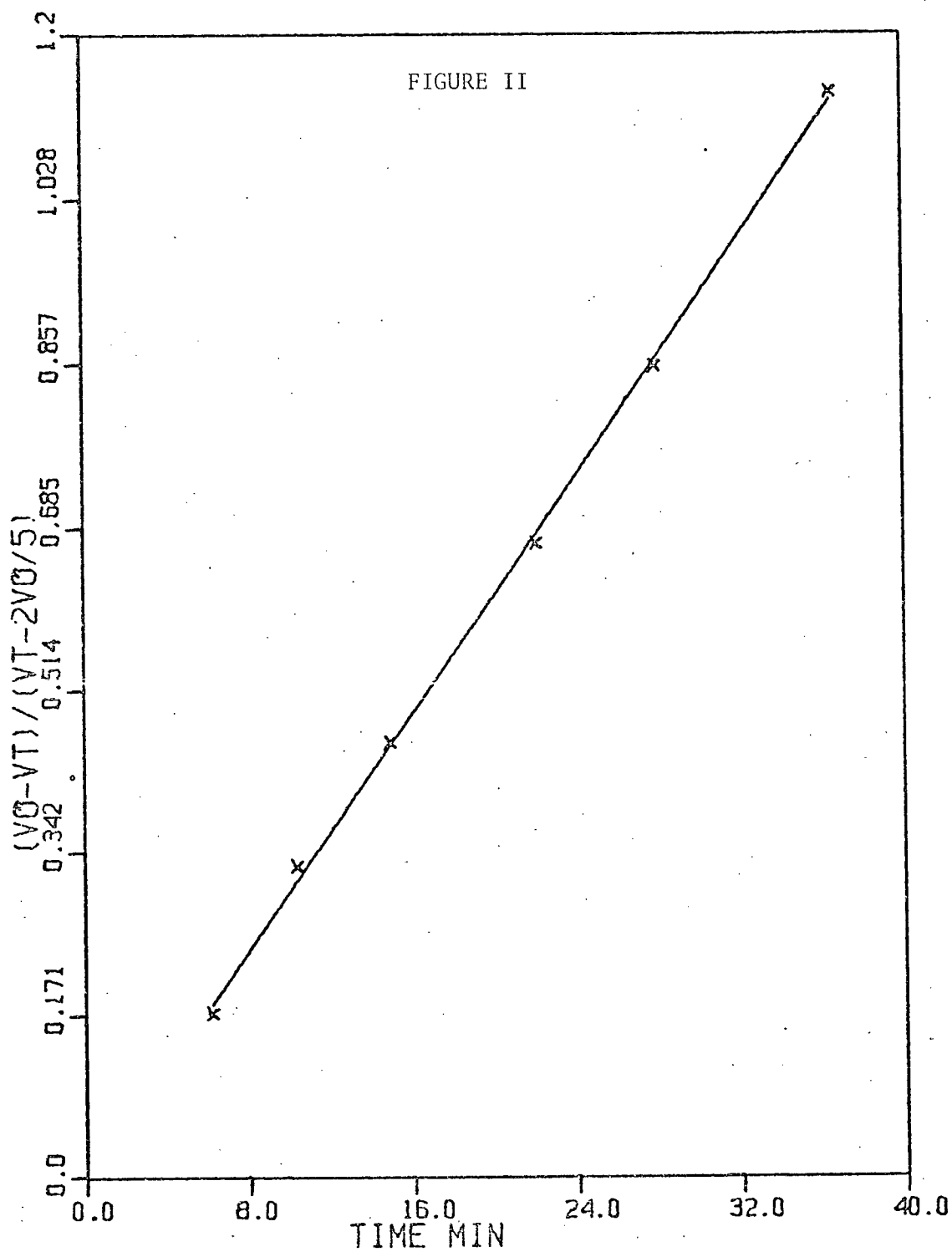
Rate plot for 2-benzhydrylcarboxylic acid oxidation

$[\text{MnO}_4^-] = 0.00395\text{M}$ $\text{pH} = 10.75$ $T = 25^\circ \text{C}$

$[\text{3-phenylphthalide}] = 0.00593\text{M}$

Ionic Strength = 0.5 $k = 0.251 (\text{L/M/Min})^*$

*L/M/Min abbreviated for litre mole⁻¹ minute⁻¹ throughout.



Rate plot for 4-benzhydrylcarboxylic acid oxidation

[4-benzhydrylcarboxylic acid] = 0.00593M

$[\text{MnO}_4^-] = 0.00395\text{M}$

$T = 25^\circ \text{C}$

$\text{pH} = 10.45$

Ionic Strength = 0.5

$k = 5.12 \text{ (L/M/Min)}$

Product Analysis

Using conditions similar to those of kinetic experiments several solutions were quenched at about 60% reaction by the addition of acidic sodium bisulfite. In the case of the 2-compound the quenched mixture was found to contain only 3-phenylphthalide and 2-benzhydrolcarboxylic acid in amounts quantitatively corresponding to the extent of reaction. The acid and lactone were taken up in ether and separated using aqueous bicarbonate solution. The acid was titrated against standard NaOH and the lactone was hydrolysed with NaOH and back titrated. The physical properties of the acid and lactone were measured (I.R., m.p.) and found identical with those of authentic samples.

For the 4-compound separation of product and reactant mixtures was not attempted. The reaction was allowed to go to about 100% completion as indicated by the rate constant appropriate to the conditions used. The physical properties of the product obtained from the quenching were identical to those of 4-benzhydrolcarboxylic acid and the quantity was 98% of that expected.

Results

Two fairly typical rate plots were given in Figures I and II, one for the 2- and the other for the 4-compound. The function plotted as ordinate in each case implies that the

reactants were present initially in stoichiometric amounts.

The variation of rate with the pH of the medium is given in Tables I and II. These results are also exhibited graphically in Figures III and IV.

TABLE I

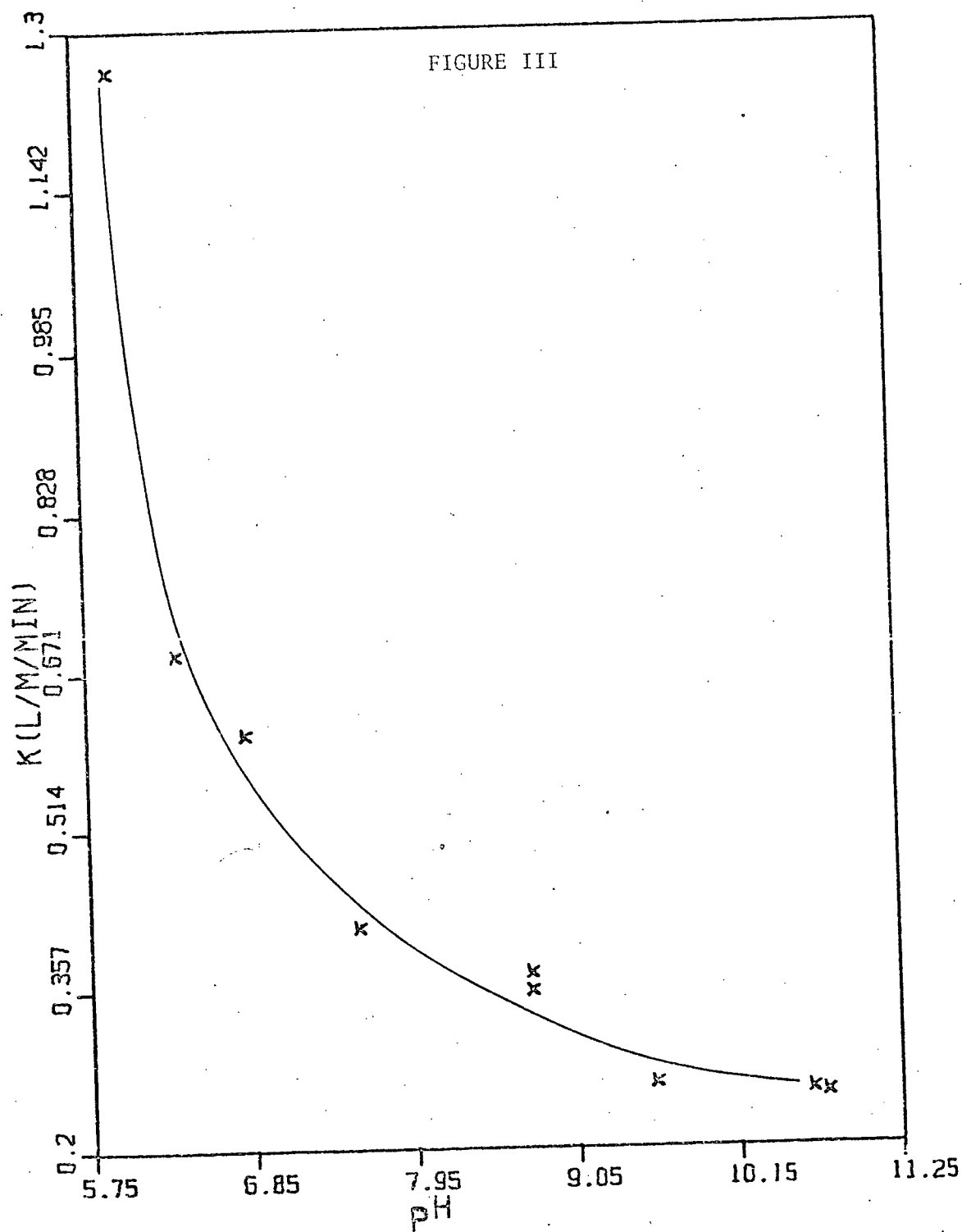
2-benzhydrylcarboxylic acid oxidation

pH	k (L/M/MIN)	T=25°C $[H_2Z]_0/[MnO_4^-]_0=3/2$
6.37	0.690	Ionic Strength = 0.5 $[MnO_4^-] = 0.00395M$
6.83	0.609	
7.58	0.417	
8.75	0.372	
8.75	0.355	
9.58	0.262	
10.45	0.254	
10.75	0.251	
12.73	1.13	

TABLE II

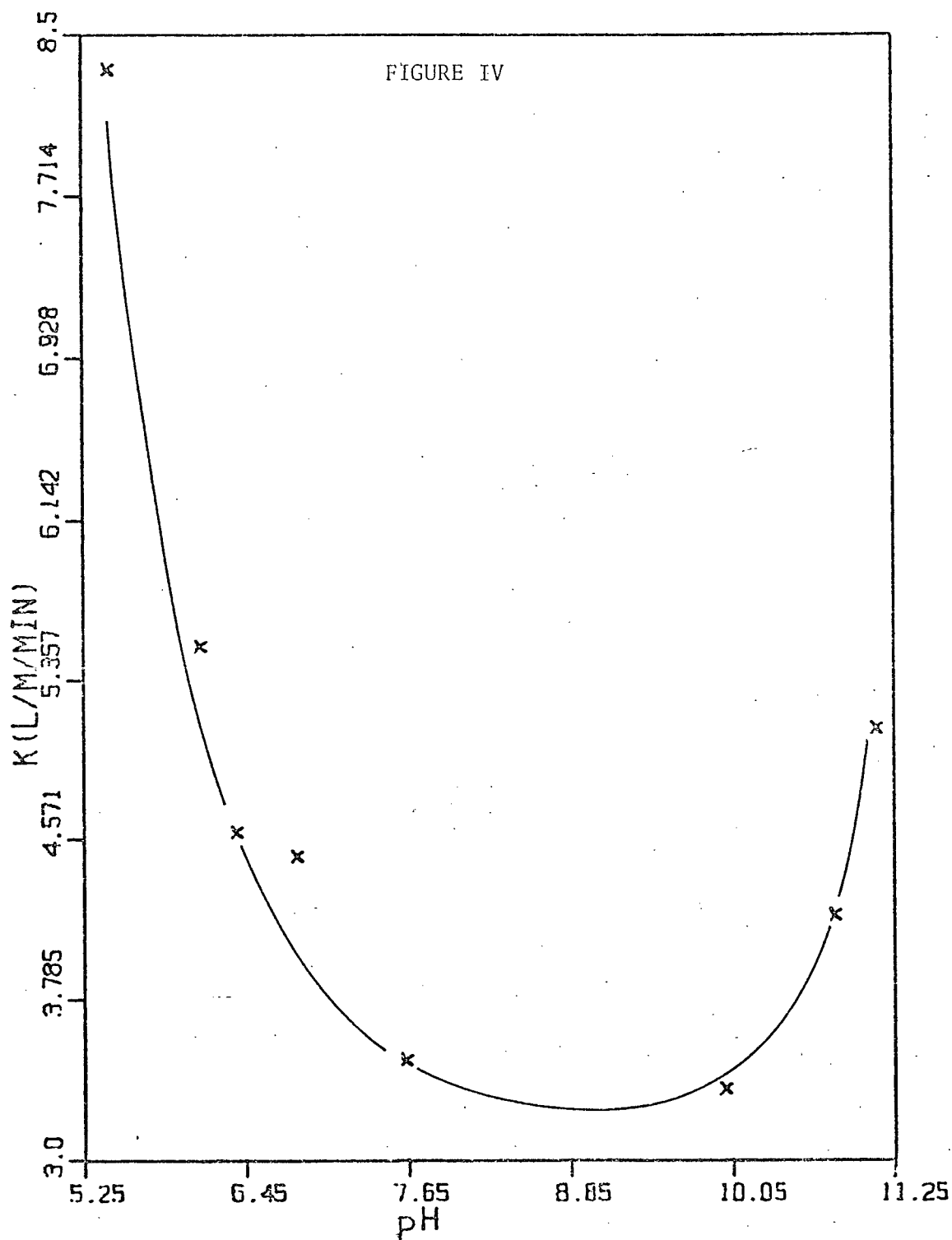
4-benzhydrylcarboxylic acid oxidation

pH	k (L/M/MIN)	T=25°C $[H_2Z]_0/[MnO_4^-]_0=3/2$
5.45	8.33	Ionic Strength = 0.5 $[MnO_4^-] = 0.00395M$
6.12	5.53	
6.38	4.61	
6.83	4.49	
7.63	3.49	
10.00	3.35	
10.81	4.20	
11.13	5.12	



2-benzhydrylcarboxylic acid

$T = 25^\circ\text{C}$ Ionic Strength = 0.5



4-benzhydrylcarboxylic acid pH - rate profile

$T = 25^{\circ} \text{C}$. Ionic Strength = 0.50

The most obvious feature of these two Figures is the greater reactivity of the 4-compound. At pH 8, for example, the rate ratio of the 4-compound to the 2- is about 9.

In the region below pH 8 both compounds react faster as the pH is lowered. The oxidation of benzhydrol exhibits a similar effect but this occurs at much higher acidity (at pH 1) so that the two phenomena cannot be related. The simplest explanation is that the neutral acid molecule reacts faster than its anion. If this were the case the observed rates should reflect the ionization of the acid. Unfortunately this is difficult to establish. For the 2-compound formation of 3-phenylphthalide, the corresponding lactone, takes place during the oxidation reaction below about pH 5. The lactone is very insoluble in water and precipitates leaving the concentration of substrate in solution uncertain. In addition, the solubility of the 4-compound, when unionized, appears to be very low as well.

In the vicinity of pH 10 to 11 Figure III shows behaviour distinct from that of Figure IV. For the 2-compound the rate does not seem to vary much between pH 9.5 and 11. The 4-compound shows a rate increase in this region of almost two-fold and in this respect it resembles benzhydrol. The data of Table I show that the oxidation rate of the 2-compound does increase as the basicity increases to pH 12.75. This

increase is about five-fold relative to the rate at pH 11. The 4-compound shows a much more dramatic rate increase. The rate at pH 12.75 relative to that at pH 10 is greater by a factor of 125. The data of Table III (and Figure V) show that there is a first order dependence on hydroxide ion concentration for the oxidation of the 4-compound. Benzhydrol also behaves in this way.

TABLE III

4-benzhydrolcarboxylic acid oxidation

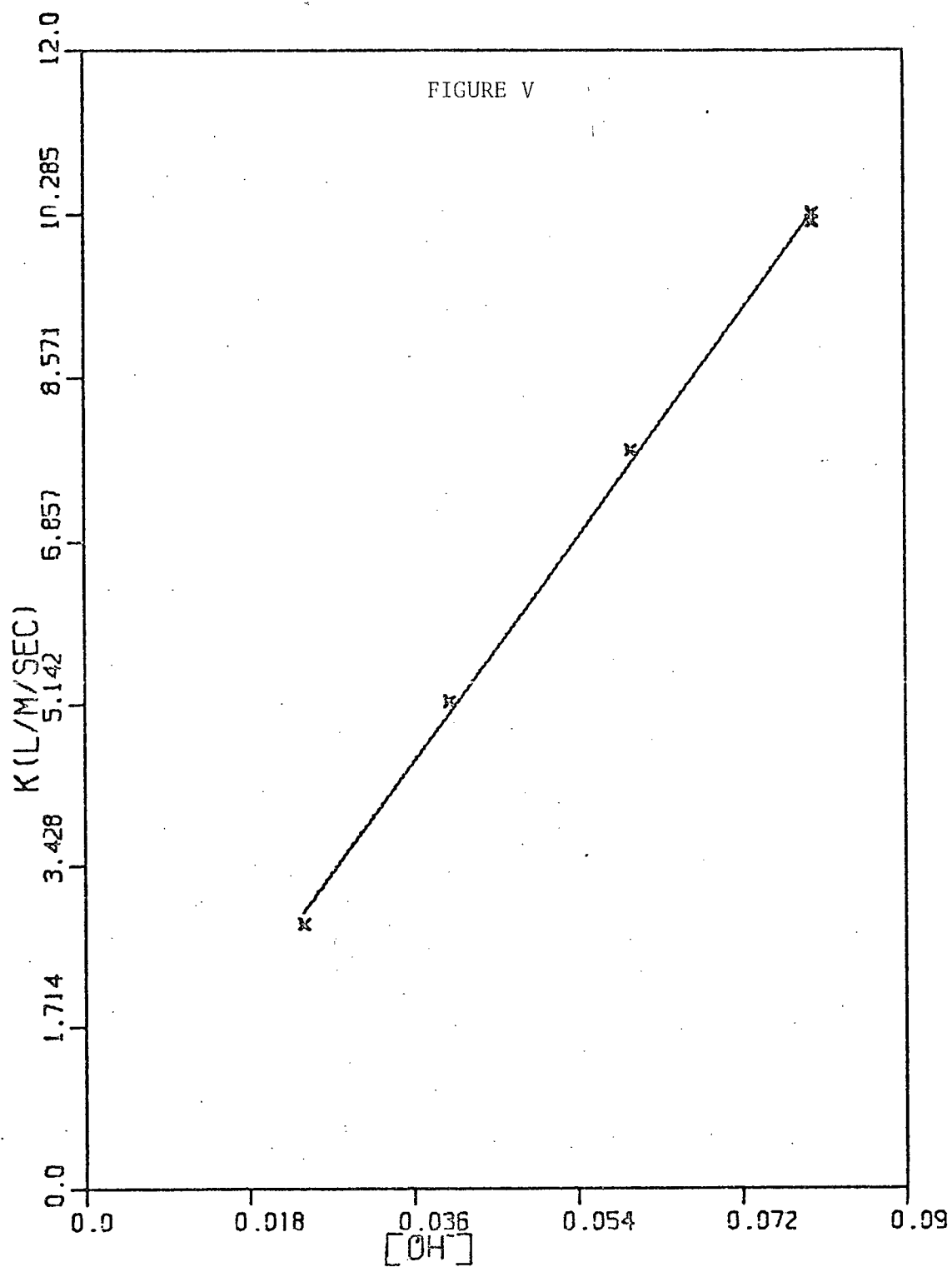
basic solution

T = 25°C

k (L/M/SEC)	[OH ⁻]	$[H_2Z]_0 / [MnO_4^-]_0 = 1/2$
2.80	0.024	$[MnO_4^-]_0 = 0.000290M$
5.17	0.04	
7.80	0.06	
10.30	0.08	
10.20	0.08	

Activation Parameters

Temperature studies on both compounds at pH 5.45 were performed. The results are given in Table IV and Figures VIa and VIb. As can be seen from the data, the rate difference between the two compounds at pH 5.45 is, within experimental error, determined entirely by the difference in entropy of activation.



4-benzhydrylcarboxylic acid oxidation

Basic Conditions $T = 25^\circ C$

TABLE IV

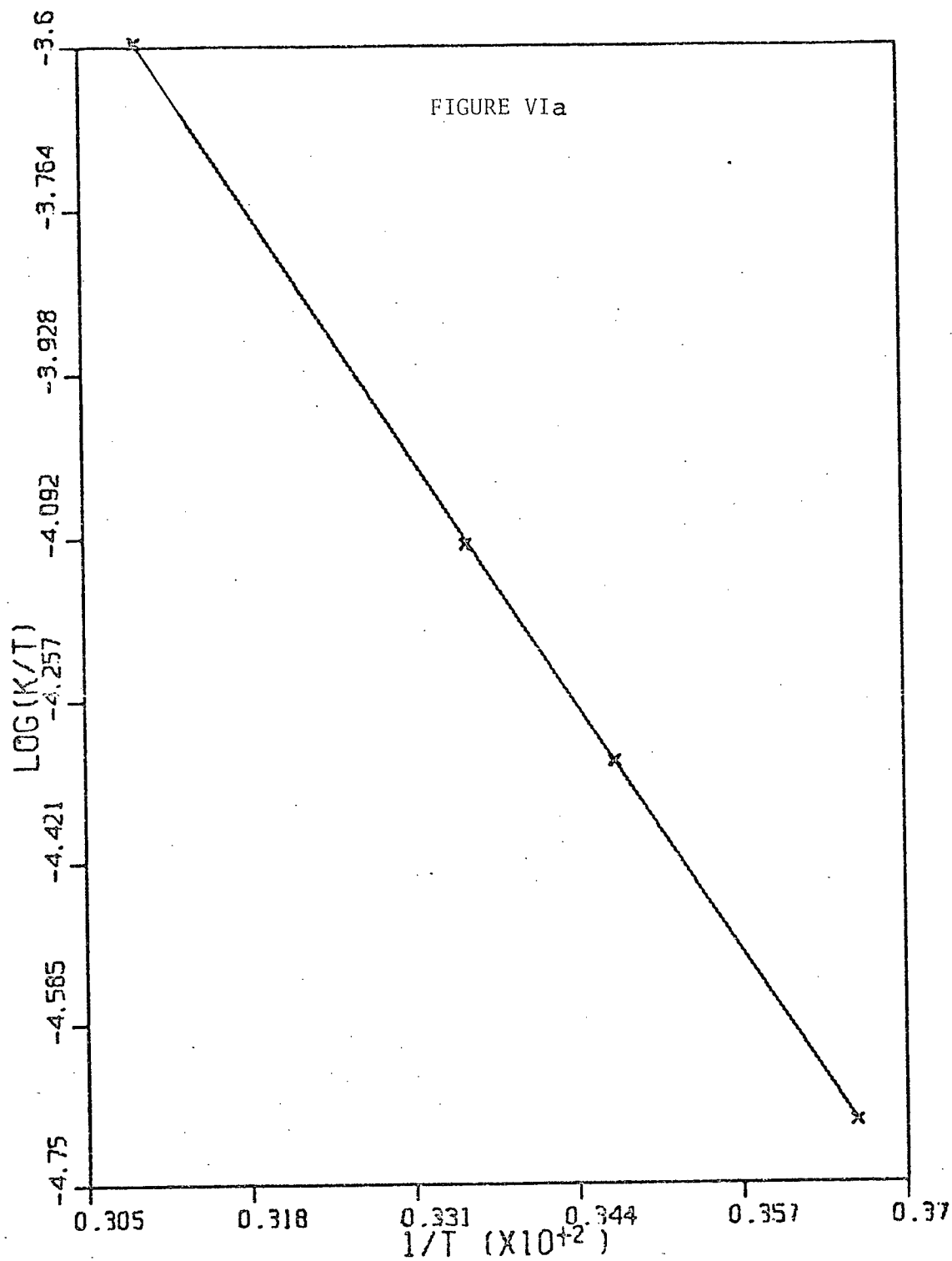
Temperature Studies

4-benzhydrolcarboxylic acid		2-benzhydrolcarboxylic acid
T °C	k (L/M/SEC)	k (L/M/SEC)
0	0.0328	0.00562
15	0.0808	0.0138
25	0.139	0.0237
40	0.310	
50		0.0819
ΔH^\ddagger (Kcal/°Mole)	8.94 \pm 0.1	8.80 \pm 0.1
ΔS^\ddagger (eu)	-32.4 \pm 0.3	-36.4 \pm 0.5
Corr. Coeff.	0.999	0.999
pH = 5.45		

Discussion

One reason for investigating the oxidation of 2-benzhydrolcarboxylic acid was to look for rate enhancement effects which might be produced by this group in proximity to the reacting centre. Consequently the 4-compound in which the carboxyl group is remote from this centre was to serve as a control. The fact that the 4-compound reacts faster than the 2- frustrates this approach. The 2-compound has diminished reactivity for reasons which will now be considered.

Earlier the mechanistic possibilities of this reaction were outlined. The reaction in neutral solution probably involves a one-step reaction in which either hydrogen atom or hydride ion is transferred to permanganate. The transition state for such a reaction might be written as I.

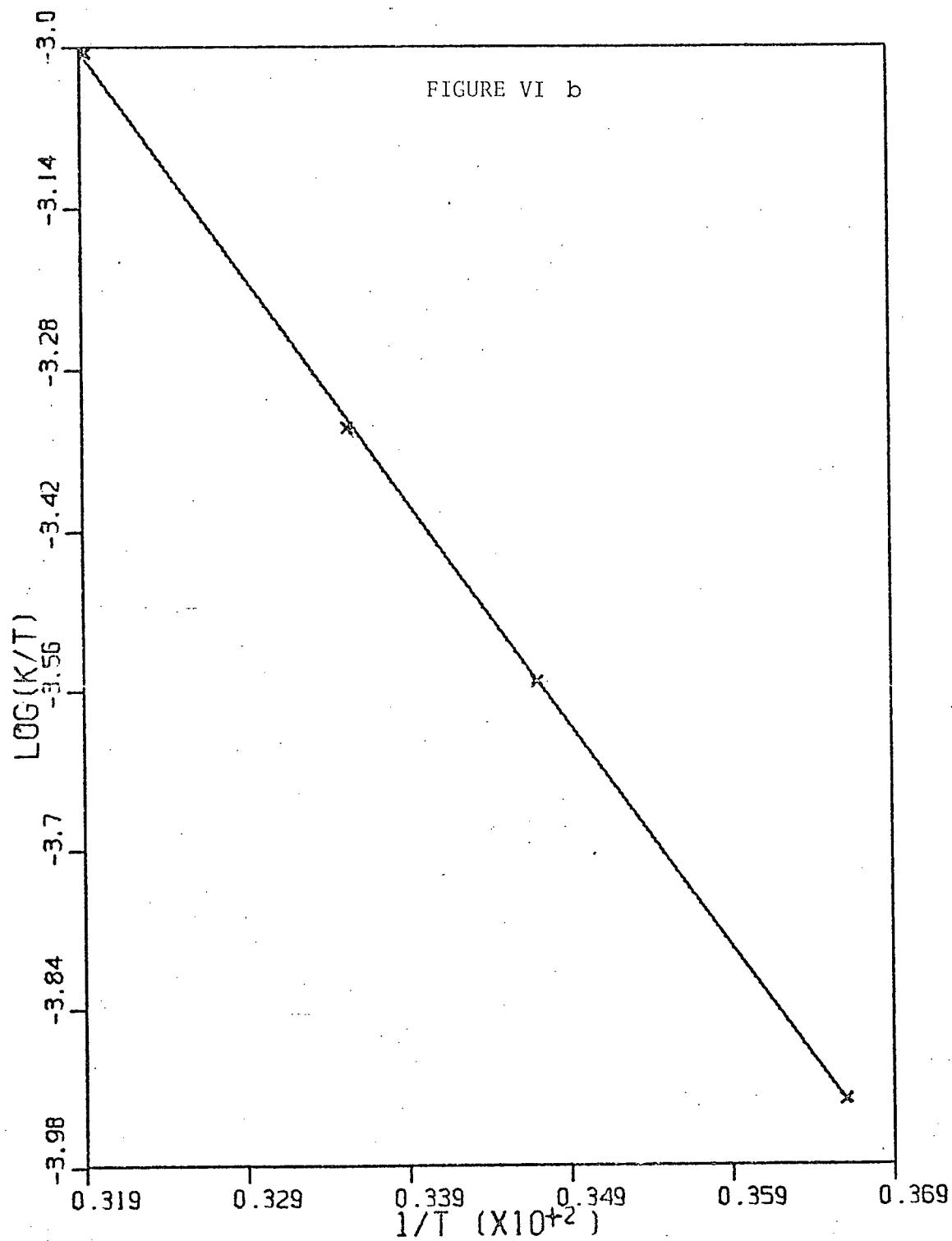


2-benzhydrylcarboxylic acid oxidation

pH = 5.88

$\Delta H^\ddagger = 8.8 \pm 1$ $\Delta S^\ddagger = -36.4 \pm 0.5$

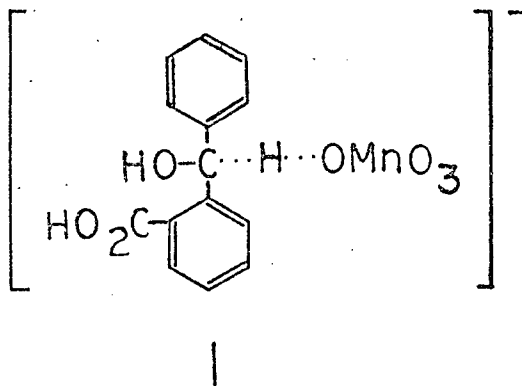
Correlation Coefficient = 0.999



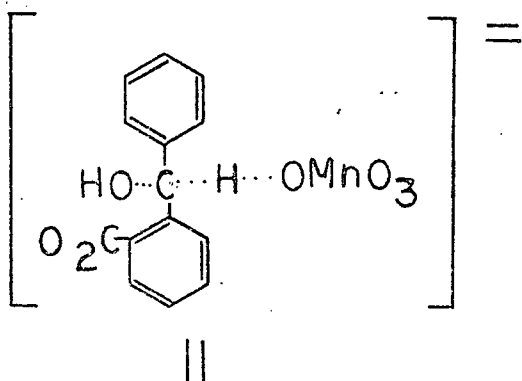
4-benzhydrylcarboxylic acid oxidation

$$\Delta H^\ddagger = 8.9 \pm 0.1 \text{ (Kcal/}^\circ\text{Mole)} \quad \Delta S^\ddagger = -32.4 \pm 0.3 \text{ (eu)}$$

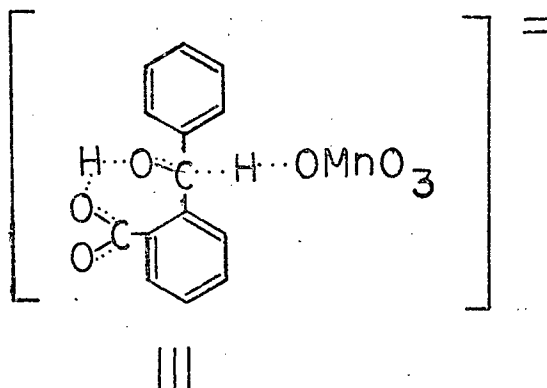
Correlation Coefficient = 0.999



At pH 7 the carboxyl group must be ionized and we might consider the transition state to look more like II.



In the event of hydride transfer to permanganate the organic product is a protonated benzophenone ($\text{pK}_{\text{BH}} \approx -6$) and for hydrogen atom transfer it is the ketyl radical ($\text{pK}=9.2$). Because of the instability of protonated benzophenone in neutral solution it is possible that the transition state could be stabilized by a simultaneous loss of hydride ion and a proton to form a transition state resembling III.



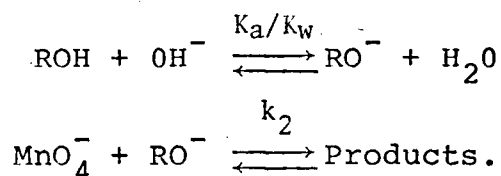
No substantial stability would be achieved by such a transition state for a hydrogen atom transfer mechanism since, in neutral solution, the ketyl radical and its anion are of comparable stability.

So for a hydride transfer mechanism one might expect the carboxylate group to interact favourably with the reacting centre to produce a lowering of energy and a faster rate. For the case of hydrogen atom transfer such interaction would not necessarily stabilize the transition state to a great extent. An observation of rate enhancement due to carboxylate participation in the transition state would probably mean a great deal. However the failure to observe such an effect is inconclusive. It does not argue in favour of either mechanism. The transition state may be too reactant-like to benefit from the stabilizing influence of the substituent (for hydride transfer) or the geometry may not be quite what is required. The negative observation can easily accomodate either mechanism.

The reaction in basic solution is of interest. There is a large rate enhancement for the 4-compound in basic solution and a dependence of the rate on hydroxide ion concentration. The 2-compound shows only a slight rate increase in this region.

It is now well established^{2,5} that the reason for this hydroxide ion dependence, also observed for benzhydrol, is the greater reactivity of the alkoxide ion relative to the neutral alcohol. The pK of benzhydrol has been estimated at about 15. At pH 13 benzhydrol is then about 1% ionized so that the alkoxide ion must be very reactive. A sufficient increase in the pK (about 1 unit) produced by a substituent would make the degree of ionization too small to observe a dependence on hydroxide ion in aqueous solution. This would be the case when the quantity of alcohol ionized is so slight as to make its contribution to the rate less than or of the same order as the contribution from the unionized alcohol. It appears then that for OH ionization 2-2-benzhydrolcarboxylate is a weaker acid than 4-benzhydrolcarboxylate. This is not an unusual observation since for example the second pK of phthalic acid is about 1 pK unit higher than the corresponding pK of terephthalic acid³⁵.

The slope of the line in Figure V should be given by $k_2 K_a / K_w$ if the reaction sequence is the following:



K_a is the acid dissociation constant of the alcohol, K_w the ion-product of water and k_2 the rate constant of the rate controlling step. For 4-benzhydrolcarboxylate the slope is 132 ± 3 and for benzhydrol it is 89 ± 4 . One might be able to infer something about the electronic requirements of the reaction were p-carboxylate not such an unfortunate choice of substituent. The Hammett σ value is, within experimental error, zero making this clearly impossible³⁶.

The activation parameters are worthy of comment. It appears that within experimental error the activation enthalpies of the two compounds are identical. The difference in rate is accounted for entirely by the difference in entropy of activation - the activation entropy of the 2-compound is more negative than that of the 4-compound by 4.0 ± 0.6 eu. It is perhaps unusual that the entire rate difference involves the entropy of activation only but it can be plausibly explained. The approach of the permanganate ion to form the transition state probably restricts the freedom of the aromatic rings. The presence of the ortho carboxyl group presumably causes restriction of internal motion to be more severe and the effect of this restriction is reflected in the entropy of activation.

The activation parameters for benzhydrol oxidation⁹ are $\Delta H^\ddagger = 5.7$ Kcal/^oMole and $\Delta S^\ddagger = -44.0$ eu at pH 7.

These values are significantly different from those determined for p-benzhydrolcarboxylate oxidation ($\Delta H^\ddagger = 8.9 \text{ Kcal/}^\circ\text{Mole}$ and $\Delta S^\ddagger = 32.4 \text{ eu}$) and the ability to correlate both rates in the same Hammett plot is another example of the arcane interplay between enthalpy and entropy which gives rise to linear free energy relationships.

SECTION B

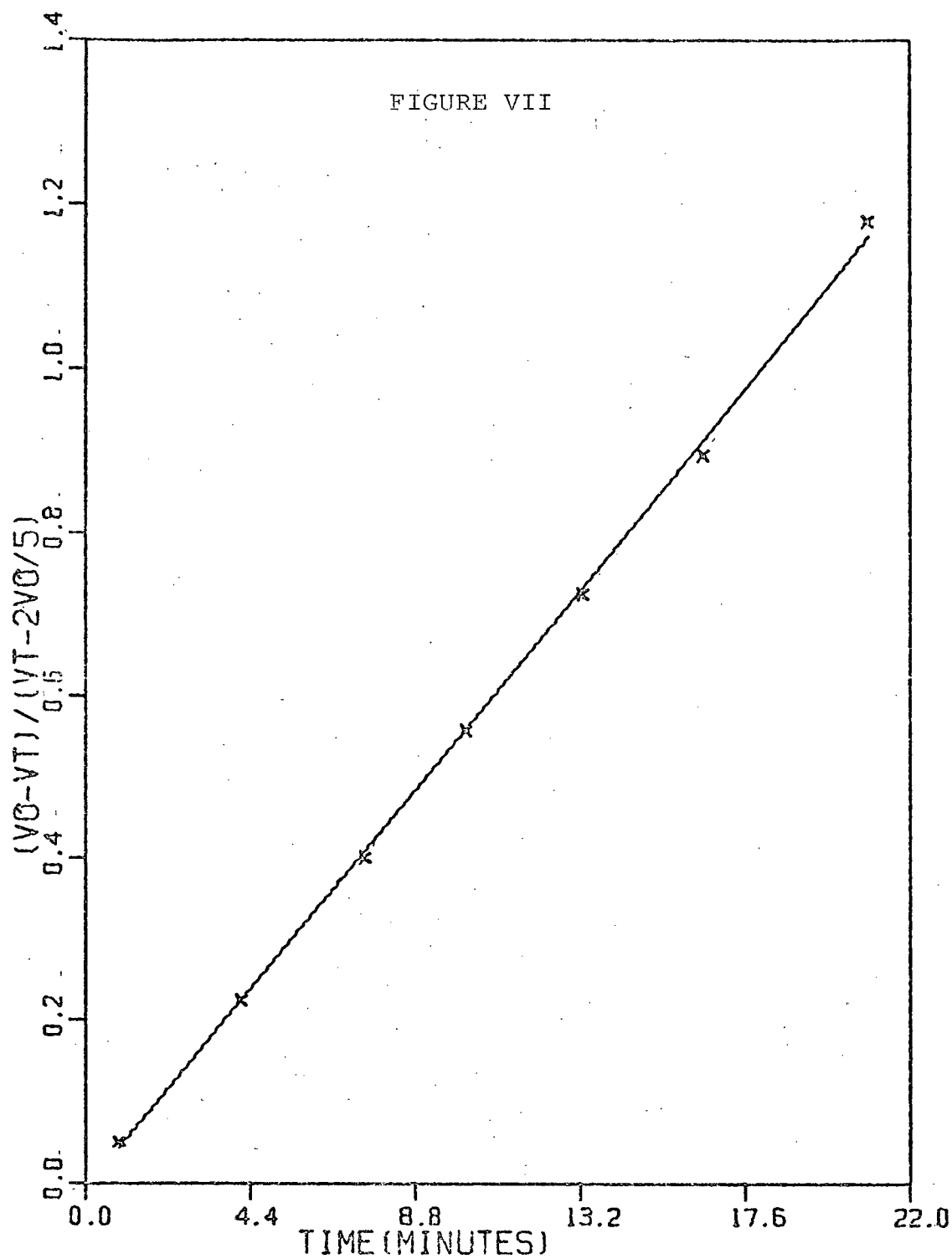
THE OXIDATION OF PHTHALALDEHYDIC ACID
AND TEREPHTHALALDEHYDIC ACID

Experimental

Aqueous stock solutions of both compounds were prepared of concentration 0.03473M. The initial concentration of substrate for kinetic runs was usually 0.00248M and the permanganate concentration two-thirds of this. The buffer system and other conditions pertinent to the kinetic experiments were essentially the same as for the kinetic studies on benzhydrols.

Two fairly representative rate plots are given in Figures VII and VIII.

The run in Figure VII refers to the oxidation of phthalaldehydic at pH 7.12 and 25°C. The run was carried out by adding to the reaction flask 40 ml of water, 10 ml of 0.03473M phthalaldehydic acid and 10 ml of 1M K_2HPO_4 . After adjusting the pH to a value of 7.12 by adding drops of concentrated sulfuric acid, the flask was placed in the water bath and allowed to come to thermal equilibrium for a half-hour. Then 10 ml of 0.02316M potassium permanganate, also at 25°C, was pipetted into the flask. After mixing, aliquots were withdrawn from time to time as the reaction proceeded. The



Rate plot for phthalaldehydic acid oxidation

$[\text{MnO}_4^-] = 0.00332\text{M}$

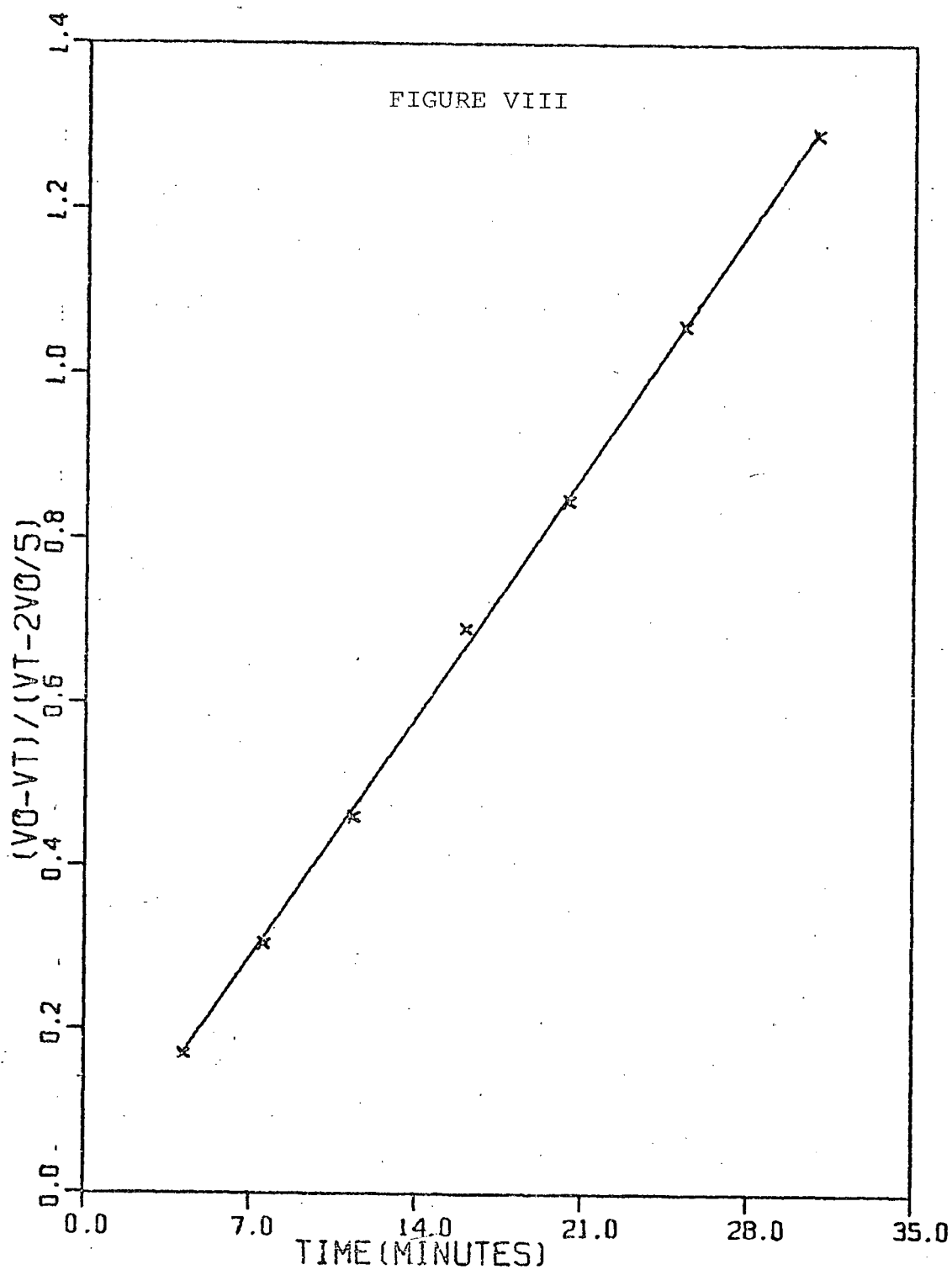
pH = 7.12

T = 25°C

$[\text{phthalaldehydic acid}] = 0.00496\text{M}$

Ionic Strength = 0.43

k = 11.2 L/M/MIN



Rate plot for terephthalaldehydic acid oxidation

$[\text{terephthalaldehydic acid}] = 0.00496\text{M}$ $\text{pH} = 8.90$

$[\text{MnO}_4^-] = 0.00332\text{M}$ $T = 25^\circ\text{C}$

Ionic Strength = 0.43

$k = 16.8 \text{ L/M/MIN}$

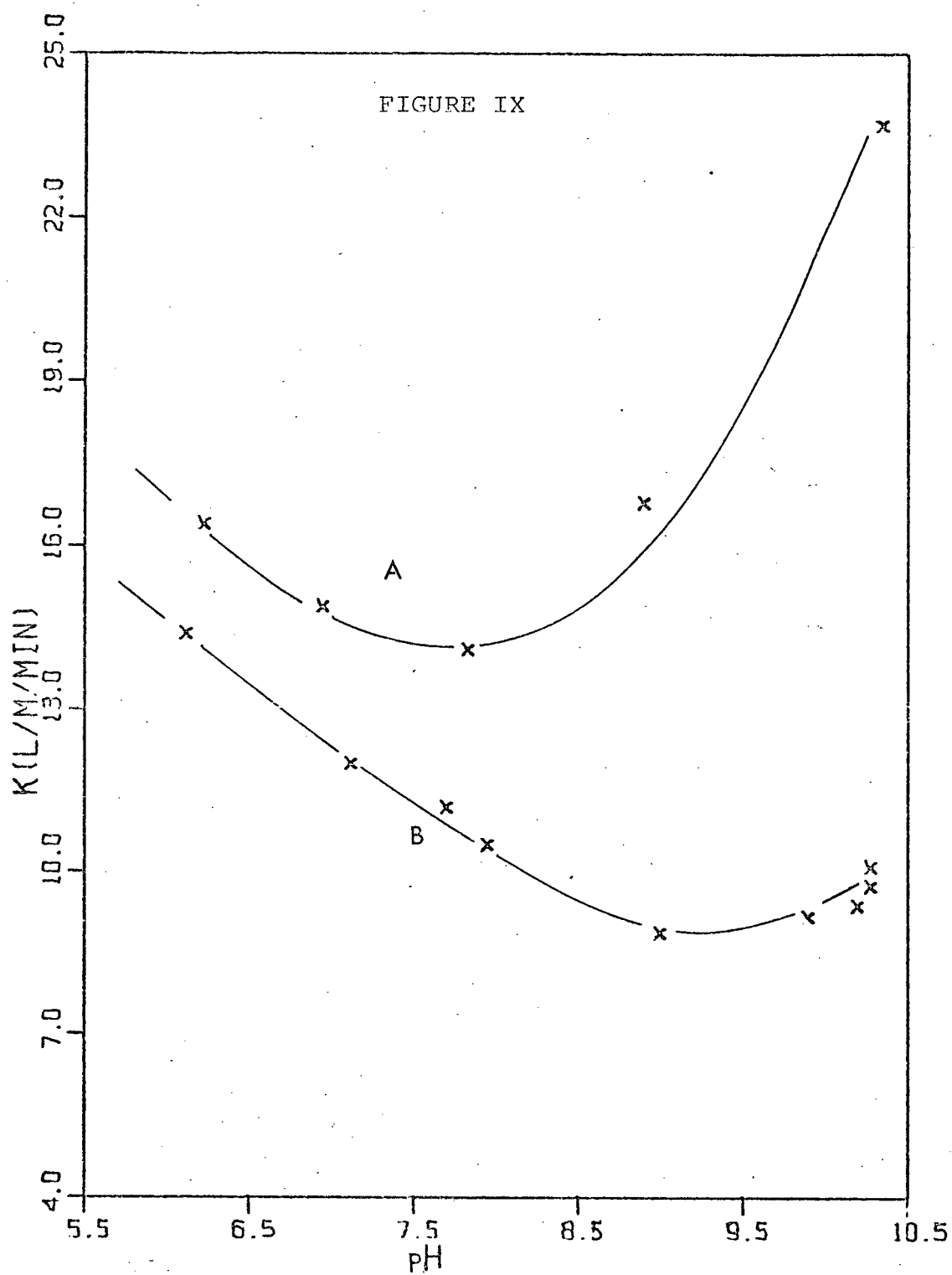
initial concentration ratio of phthalaldehydic acid to permanganate was 3:2 and the appropriate kinetic expression was used. The run referred to in Figure VIII concerns terephthalaldehydic acid at pH 8.90 and was carried out in virtually the same way as the run of Figure VII.

Products

Several experiments were carried out in which the oxidation was permitted to proceed to nearly 100% completion. The quenched solutions appeared to contain only phthalic acid or terephthalic acid in nearly quantitative amounts.

Results

Second order rate constants were determined from about pH 6 to 10.5. The kinetic behaviour of the compounds in this region is displayed in Figure IX and the data are given in Table V.



pH-rate profiles

A-terephthalaldehydic acid

 $T = 25^{\circ}\text{C}$

B-phthalaldehydic acid

Ionic Strength = 0.43

TABLE V

Oxidation of Phthaldehydic Acid

pH	k (L/M/MIN)	
6.12	14.4	
7.12	12.0	
7.70	11.2	$[H_2Z]_O/[MnO_4^-]_O = 3/2$
7.95	10.5	
9.00	8.88	$[H_2Z]_O = 0.00496M$
9.90	9.19	
10.20	9.40	$T = 25^\circ C$ Ionic Strength = 0.43
10.28	9.76	
10.28	10.10	

Oxidation of Terephthalaldehydic Acid

pH	k (L/M/MIN)	
6.23	16.40	$[H_2Z]_O/[MnO_4^-]_O = 3/2$
6.95	14.90	
7.83	14.10	$[H_2Z]_O = 0.00496M$
8.90	16.80	
10.35	23.70	$T = 25^\circ C$ Ionic Strength = 0.43

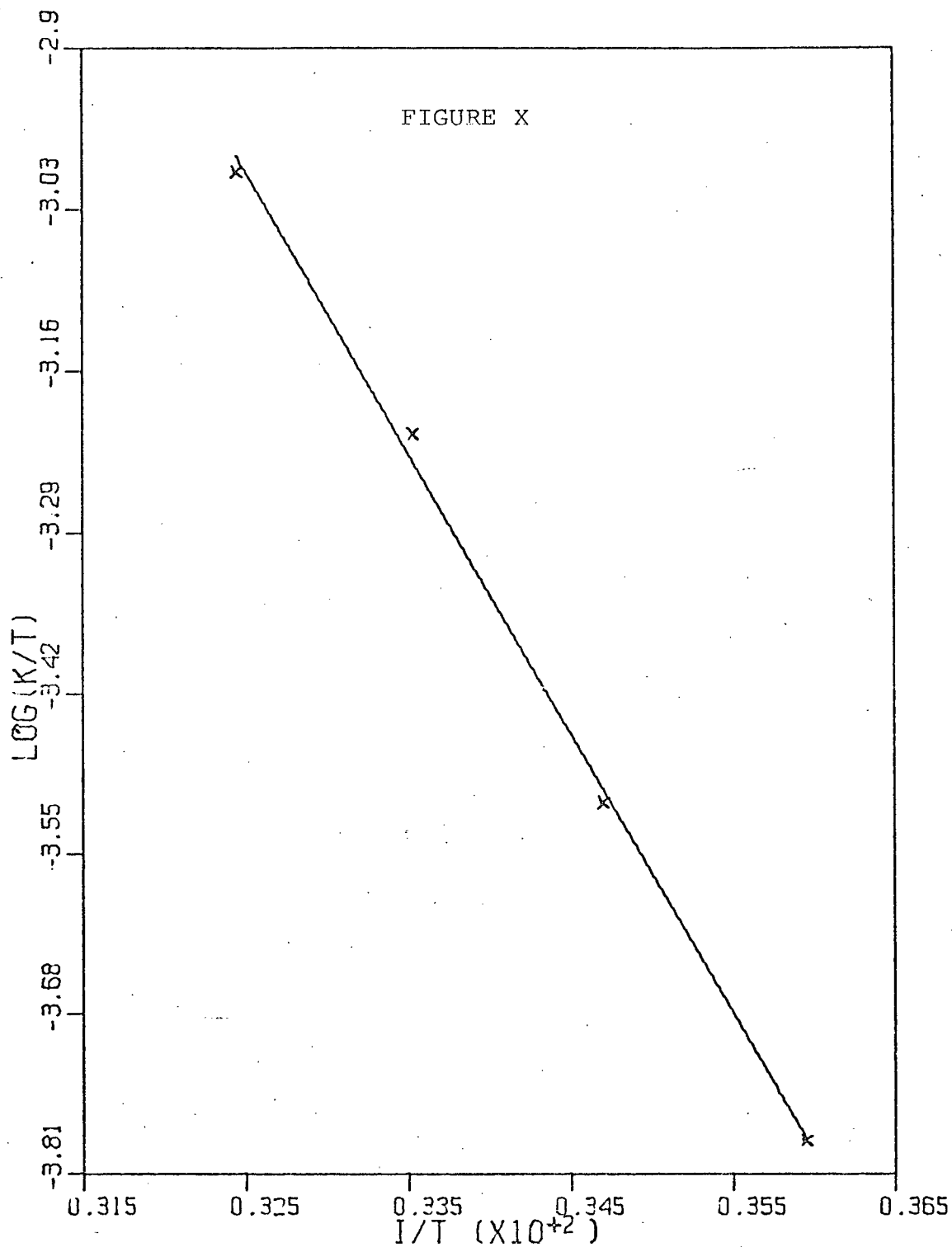
A temperature study was carried out on each compound at pH 8.1. Figures X and XI give the $\log (k/T)$ against $1/T$ plots for each compound and the results are tabulated in Table VI.

TABLE VI

T°C	k (L/M/SEC)	k (L/M/SEC)
	Phthalaldehydic acid	Terephthalaldehydic acid
5	0.0458	0.0663
15	0.0895	0.147
25	0.184	0.278
35	0.308	0.534
ΔH^\ddagger (Kcal/° mole)	10.4 ± 0.4	11.2 ± 0.3
ΔS^\ddagger (eu)	-27.1 ± 1.2	-23.4 ± 1.0
Corr. Coeff	0.999	0.999

Discussion

The curves given in Figure IX are very similar to those given by Wiberg and Stewart³⁷ for the permanganate oxidation of benzaldehyde and substituted benzaldehydes. The kinetic behaviour is everywhere second order with the observation that the reaction tends to become autocatalytic as the medium becomes more acidic than about pH 5. This behaviour is well-known¹⁶ and is thought to be caused by the action of lower oxidation states of manganese which would be present after the reaction had proceeded to some extent.

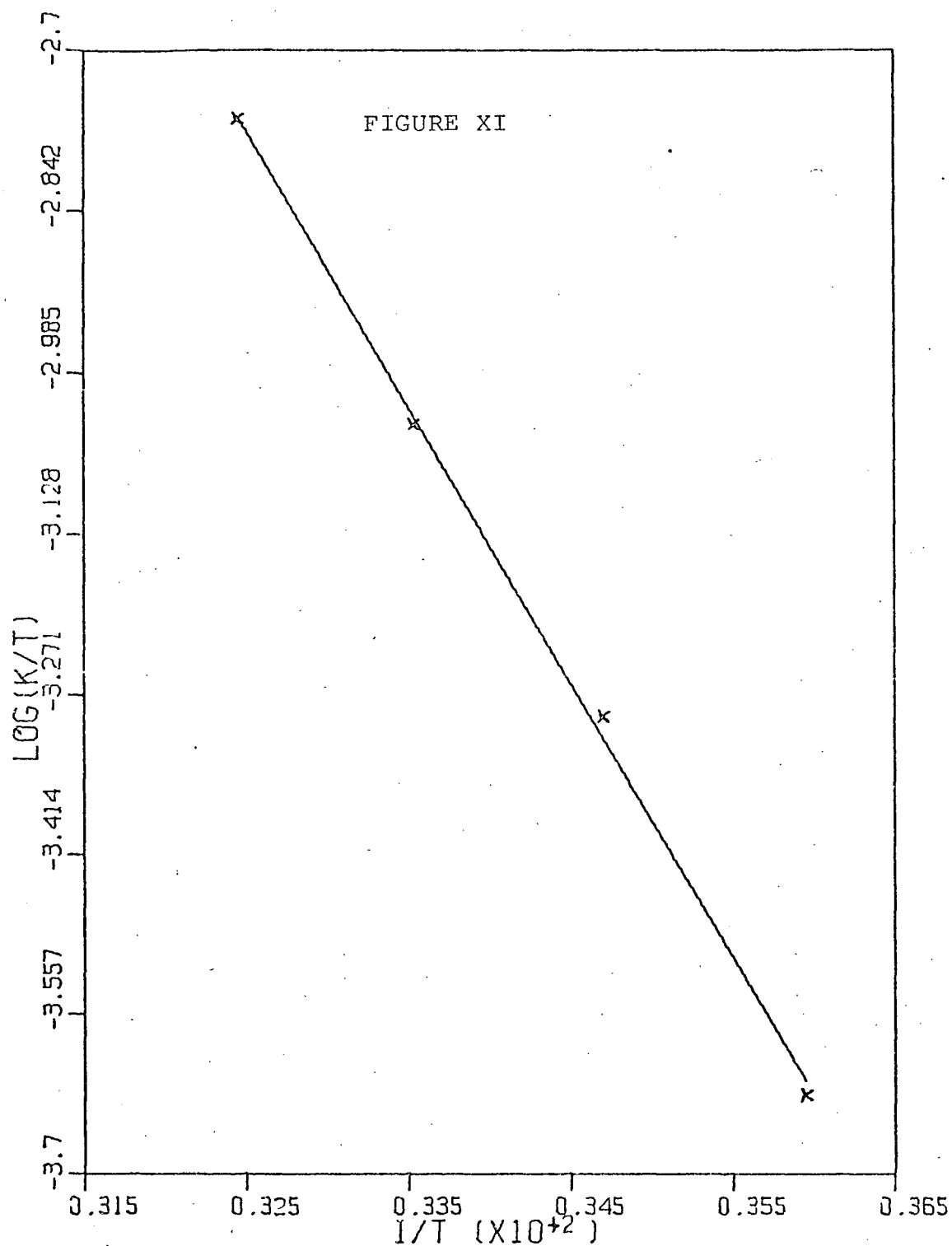


Phthalaldehydic acid oxidation

pH = 8.1

$\Delta H^\ddagger = 10.4 \pm 0.4$ (Kcal/ $^\circ$ mole) $\Delta S^\ddagger = -27.1 \pm 1.2$ (eu)

Correlation Coefficient = 0.999



Terephthalaldehydic acid oxidation

pH = 8.1

$\Delta H^\ddagger = 11.2 \pm 0.3$ (Kcal/ $^\circ$ mole) $\Delta S^\ddagger = -23.4 \pm 1.0$ (eu)

Correlation Coefficient = 0.999

The rate behaviour of the two compounds in this study is slightly different. In the pH region 5.5 - 7.5 the rate of the ortho compound is about 10% lower than the para compound and both decrease in reactivity in this region. At about pH 7.5 the para compound begins to undergo a rate increase which results in a two-fold exaltation by pH 10.5. The rate of the ortho compound continues to decrease after pH 7.5 but the decrease halts at about pH 9.5 and becomes a very slight increase by pH 10.5.

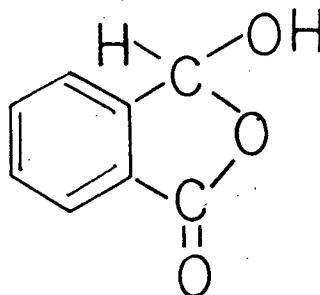
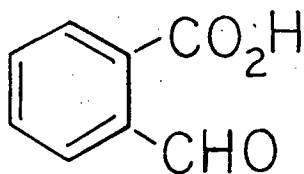
The studies of Wiberg and Stewart³⁷ indicate that the reaction corresponding to that part of the curve at lower pH depends upon the buffer concentration while the reaction at higher pH is base catalysed and is independent of the buffer.

The effect of substituents on the reaction has been determined by Wiberg and Stewart at pH 6.5 and 12.6 who find a ρ value of -0.25 at the former pH and a ρ of -1.8 for the latter. Some doubt has been raised concerning the exact mechanistic implications of these values³⁸. Consequently the mechanism must be viewed as requiring more elucidating experimental work and a discussion at this point not fruitful. The rate constants measured for terephthalaldehydic acid in this work appear to be of the correct magnitude although a direct comparison is not possible since the buffer

concentrations and ionic strengths are not the same in both cases.

The activation parameters determined in this work for phthalaldehydic acid ($\Delta H^\ddagger = 10.4 \pm 0.4$ (Kcal/°Mole), $\Delta S^\ddagger = -27.1 \pm 1.2$ (eu) are, within experimental error, the same as those determined by Wiberg and Stewart for benzaldehyde ($\Delta H^\ddagger = 10.0 \pm 0.3$ Kcal/°Mole, $\Delta S^\ddagger = -26.2 \pm 1$ eu). The activation parameters referring to the oxidation of terephthalaldehydic acid are not significantly different from this ($\Delta H^\ddagger = 11.2 \pm 0.3$ Kcal/°Mole, $\Delta S^\ddagger = -23.4 \pm 1.0$ eu). It does not appear that any meaningful conclusion can be drawn from the magnitude of these parameters. It suffices to say that they are "normal".

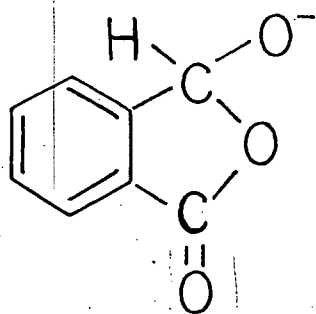
o-Benzaldehydecарboxylic acid or, as it is more commonly known, phthalaldehydic acid has been represented as either one of the following structures:³⁹



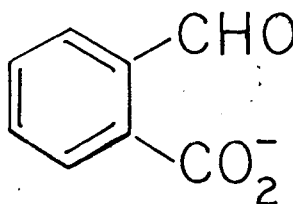
Evidence based on the infrared spectrum of the compound as a solid and as a solute in water has been obtained which indicates that the compound exists in the ring-closed form rather than the ring-open form⁴³. The chemical properties of this compound are not exclusively those that one would consider appropriate for a ring-closed compound (the lactol). It has, for example, a pK of 4.56, determined by titration with base⁴⁰. This is not an unusual pK. The acidity of phthalaldehydic acid can be compared with that of o-acetoxybenzoic acid⁴¹ (pK = 4.57). The pK's of p-formylbenzoic acid (3.98) and p-acetoxybenzoic acid⁴¹ (3.89) are close, showing these substituents to have similar effects on acidity in both ortho and para positions. The compound has been shown to undergo the Cannizzaro reaction⁴², a typical reaction of aldehydes lacking α -hydrogens. Both of these latter observations point to the ring-open aldehyde rather than the ring-closed 3-hydroxyphthalide. However, there is chemical behaviour of a very striking kind that can only be accommodated by the ring-closed compound³⁹. Alcohols, such as methanol, ethanol etc., react without a catalyst in a few hours to give a 3-alkoxyphthalide and water. The reactivity of phthalaldehydic acid has been stated to approach that of an acid chloride or anhydride for every reactant except water.

Phthalaldehydic acid is not alone in this behaviour. On the basis of infrared and N.M.R. spectra it was shown⁴³ that o-acetylbenzoic acid exists in methylene chloride solution as 3-hydroxy-3-methylphthalide. The precision of these experimental techniques did not rule out the possibility of an equilibrium between the ring-open and the ring-closed form but it shows that the equilibrium strongly favours the latter. In this case also, there is chemical evidence^{44,45} favouring the ring-open structure so that an equilibrium is more likely.

Examination of the curves shown in Figure IX (as well as comparing them with those of Wiberg and Stewart³⁷) reveals that we are dealing in this instance with two rather typical aldehyde oxidations. The magnitude of the rate constants and the shape of the rate versus pH plot is not in accord with a ring-close structure which, in view of the pK, would have to be ionized in the pH region considered.

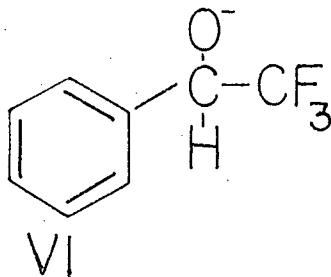


IV



V

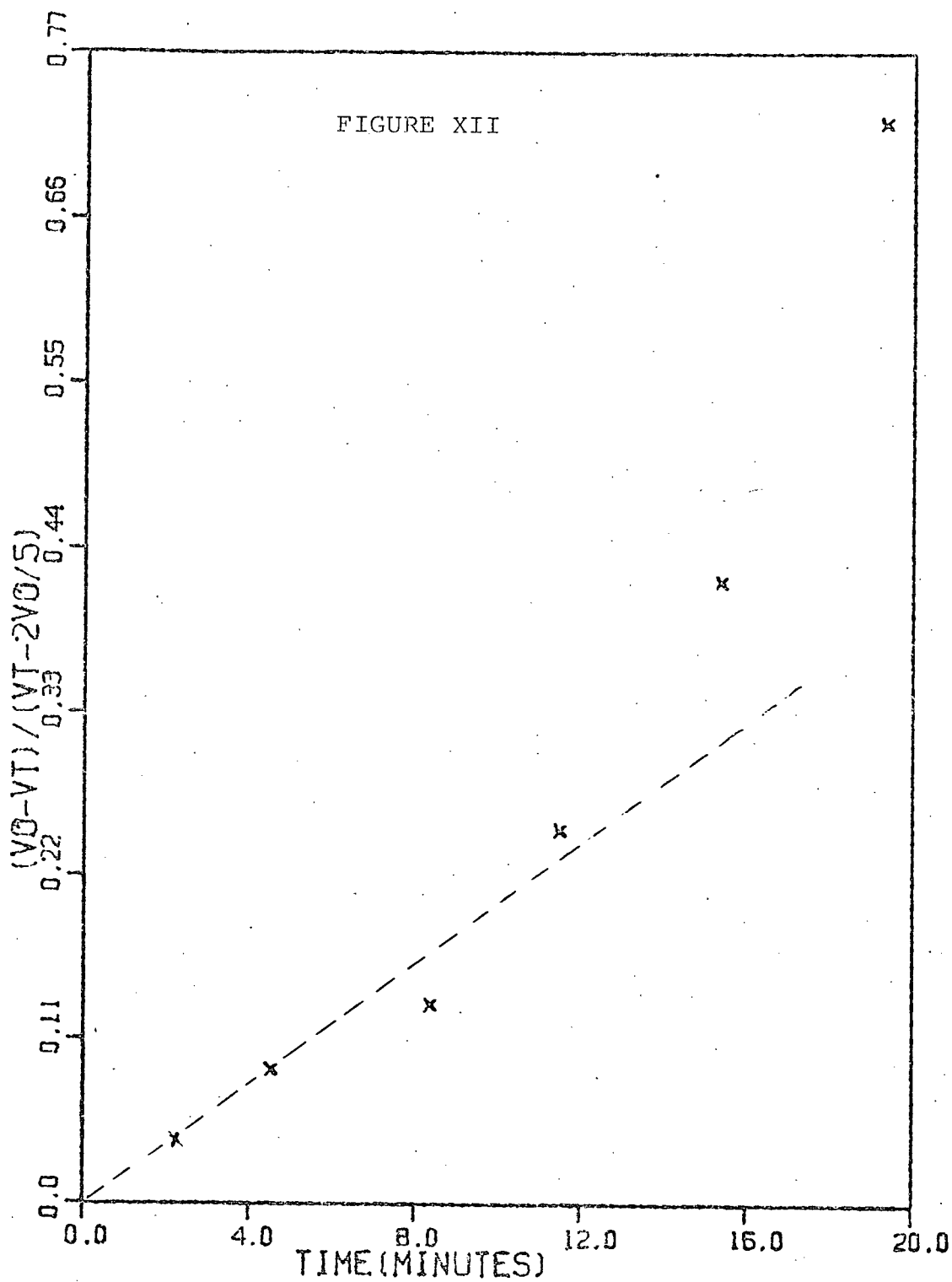
The ion IV resembles alkoxide ion and presumably would have the large reactivity of these ions. The second order rate constant for the oxidation of the ion VI



by permanganate is about 7.2 L/M/Sec while the rate constant referring to the oxidation of the anion of phthalaldehydic acid is about 0.2 L/M/Sec in the pH range studied.

Kinetic experiments on phthalaldehydic acid at acidities greater than pH 5 show curvature and it was not possible to determine rates in this region except approximately using the initial slopes. Tompkins⁴⁶ studied the initial rates of oxidation of benzaldehyde from pH 4.1 to 0.4 observing a rate increase by a factor five towards the more strongly acidic side. In the present work, rate studies were attempted at pH 3.7 and the rate plot was found to be curved as in Figure XII. No accurate rate constant can be extracted from such data but an approximate one would be about 8 L/M/Min. The straight line corresponding to this value has been sketched in.

However, when the acidity is increased to pH 1.55



Phthalaldehydic Acid Oxidation pH = 3.68

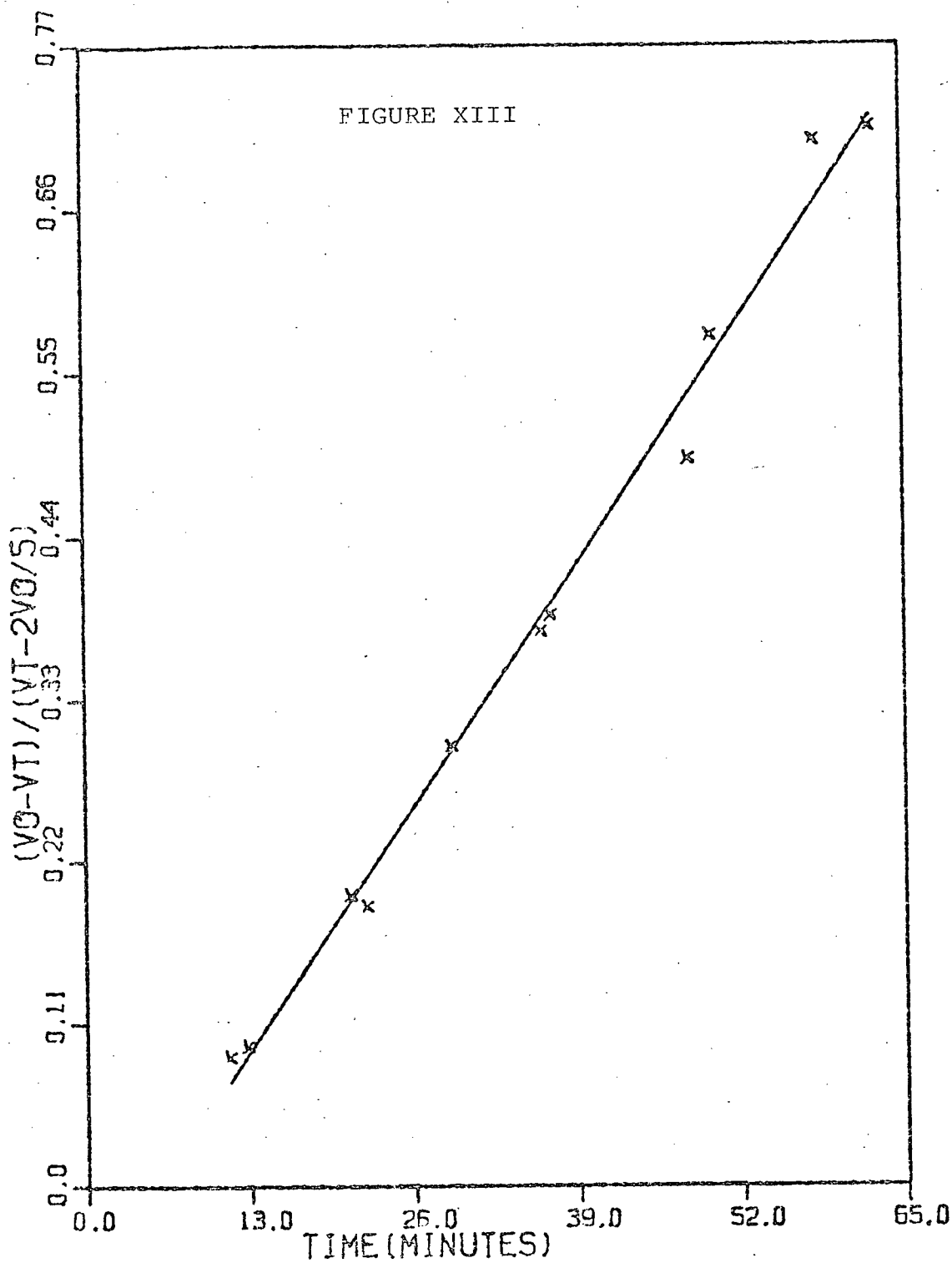
T = 25°C

Straight line corresponds to $k = 8.04 \text{ M/MIN}$

a new behaviour is observed. Instead of the reaction being autocatalytic it appears to be a true second order reaction whose rate plot remains a straight line up to about 50% reaction. This is not the usual behaviour of aldehydes. The work of Tomkins shows that the autocatalytic nature of the reaction continues to higher acidities⁴⁶. Moreover, Tomkins has found that the initial rate increases about five-fold on raising the acidity from pH 4.1 to 0.4. In the case of phthalaldehydic acid this is not observed. The rate at pH 1.55 is in fact smaller, by a factor of three, than the rate determined at pH 6.1. The rate plot for two separate runs displayed on the same graph is shown in Figure XIII.

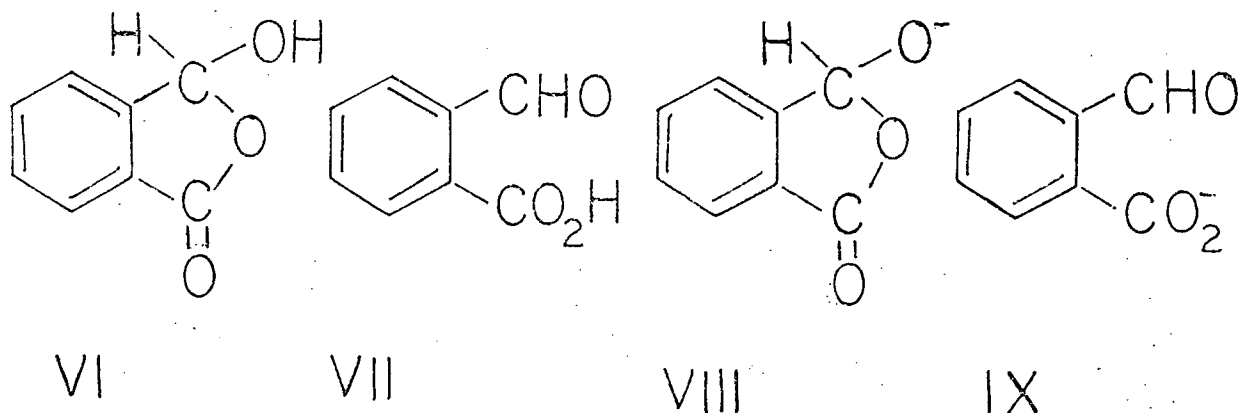
The validity of the run at pH 1.55 was checked by repetition as well as by using a sample of the same stock solution used at pH 1.55 at higher pH (6.1). The behaviour at pH 1.55 is found to be reproducible and the rate constants determined at higher pH agree with those previously determined in this work. The unexpected behaviour at pH 1.55 thus appears to be a valid observation.

The behaviour of phthalaldehydic acid can be explained in terms of the species which are present in solutions of various acidities. For the sake of argument there are four species:



Phthalaldehydic acid oxidation pH = 1.55

$k = 4.95 \text{ L/M/MIN}$



Since the pK is 4.56 the curves in Figure IX refer to the oxidation of the anion. It has already been indicated that the similarity of these curves to those already investigated for other aldehydes as well as the similarity of the activation parameters indicates an aldehyde to be reacting³⁷. At pH 3.7 the curved rate plot is indicative of an aldehyde oxidation as well. The initial rate at this pH ($\sim 8 \text{ L/M/MIN}$) is smaller than the rate determined at pH 6.1 where second order kinetics prevails. Since the compound is only $\sim 9\%$ ionized the lowering in rate could mean either a smaller reactivity of the neutral aldehyde (VII) or the absence of any aldehyde other than the ionized species (IX).

The behaviour at pH = 1.55 is more characteristic of an alcohol or alcohol-like compound. The good second order kinetics and the lower rate constant (4.95 L/M/MIN), close to that of benzhydrol ($\sim 2 \text{ L/M/MIN}$)¹, are more in accord with the behaviour expected for the alcohol-like VI than the aldehyde VII.

This ineluctably leads one to say that unionized phthalaldehydic acid exists almost entirely as VI, while the anion exists as the aldehyde IX. Considering the

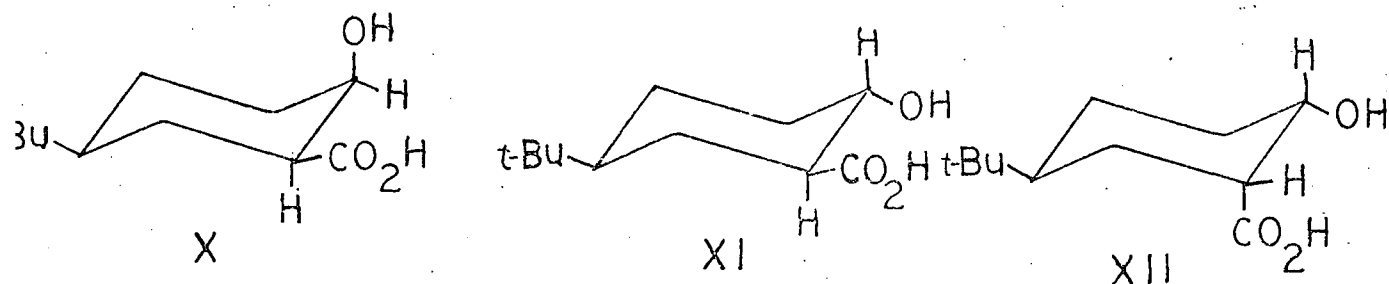
reactivity of alkoxide ion, any appearance of the ion VIII would result in a much higher rate than has been observed. This explains why phthalaldehydic acid undergoes the Cannizzaro reaction which is carried out in strong base. It also indicates that the neutral molecule would react as 3-hydroxyphthalide rather than as 2-formylbenzoic acid.

SECTION C

THE CYCLOHEXANOL SYSTEM

Experimental

In this study, some of the compounds were sufficiently soluble in water to permit the preparation of stock solutions directly. Thus aqueous solutions (0.03 M) of cyclohexanol, cis-2-hydroxycyclohexanecarboxylic acid and trans -2-hydroxycyclohexanecarboxylic acid were prepared. The compounds bearing a t-butyl substituent were in general much less soluble than compounds without this group. In the case of cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X), cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid (XI) and trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (XII) stock solutions of about 0.03 M were prepared by mixing the organic acid and an equivalent amount of potassium hydroxide in warm distilled water.



Since the t-butyl substituted alcohols are not very soluble their concentration in the reaction mixture could not be very much greater than about 0.005 M and was generally kept close to this value. The more soluble alcohols were usually concentrated to the extent of 0.015 M for the kinetic experiments although some runs at concentrations comparable to those used for the less soluble alcohols were carried out.

Kinetic runs on cis-2-hydroxycyclohexanecarboxylic acid were performed in deuterium oxide solvent as well as protium oxide. The deuterium oxide used was 99.7 atom per cent deuterium and stock solutions of the various components involved in the reaction mixture were prepared in this solvent. As buffer K_2DPO_4 was used and the pH was adjusted using 10M D_2SO_4 . The measurement of the pH of the medium was accomplished according to the directions of Gary, Bates and Robinson⁴⁷ using the glass electrode and the saturated calomel electrode. To avoid using excessive amounts of deuterium oxide the reactions were followed spectrophotometrically rather than by titration.

A series of runs in basic solution on cis-2-hydroxycyclohexanecarboxylic acid were performed using a substrate concentration of 0.018 M and an initial concentration ratio of substrate to permanganate of 1 to 2. The rate constants were determined spectrophotometrically by measurement of optical densities at two wavelengths.

Products

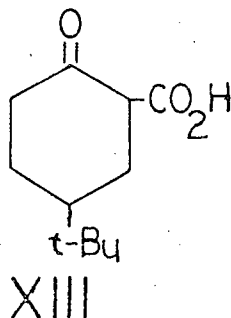
The oxidation of cyclohexanol by permanganate in neutral solution under conditions in which three moles of substrate are consumed for every two moles of permanganate can reasonably only give rise to cyclohexanone as product. Littler³ has made a product study on this reaction and finds that cyclohexanone is obtained in quantitative yield.

In the case of 2-carboxy substituted alcohols the situation is a bit more complicated. The ketone product expected would be a β -keto acid, which species is known to undergo decarboxylation readily⁴⁸. Thus, if the reaction is permitted to proceed in the usual way and a product analysis made, the product found is sure to be a ketone which does not possess a carboxyl function. Analysis at some early stage of the reaction, accomplished in a brief time span so that the β -keto acid is not extensively decomposed, is necessary to prove whether any β -keto acid is formed in the oxidation. Absence of β -keto acid could mean that decarboxylation is concomitant with rather than subsequent to oxidation.

Because permanganate ion and other oxidation states of manganese interfere with spectrophotometric identification of a β -keto acid it was necessary to separate the organic products from the reaction mixture. Extraction with ether was utilized and because of favourable solubility characteristics compound X was used. The product could be more conveniently

extracted if it contained a t-butyl group which reduces its solubility in water.

Accordingly, 5-t-butyl-2-oxocyclohexanecarboxylic acid (XIII)



was prepared using the procedure of Sicher³². This compound is the supposed product in the permanganate oxidation of X. Some spectral properties of this compound were examined for analytical use. In ether saturated with water these are

$$\lambda_{\max} = 254 \text{ m}\mu, \quad \epsilon = 5570$$

The extraction procedure was checked using known amounts of XIII dissolved in water. The aqueous solution was extracted with ether and the concentration of XIII determined by measuring the optical density at 254m μ . The amount of XIII thus determined was usually greater than 90% of the theoretical amount but never completely quantitative. Allowing the aqueous solution to stand for several hours in neutral buffer revealed on analysis, that most of the compound was decarboxylated. The product of decarboxylation, 4-t-butylcyclohexanone, has a very small absorption ($\epsilon = 15.8, \lambda_{\max} = 288\text{m}\mu$) and is not observed in the analysis.

In an actual run aliquots (5 ml) were withdrawn from time to time and extracted with a quantity of ether (10 ml). Some of this ether extract was placed in a quartz cell and the optical density at 254m μ recorded.

The results show that the expected β -keto acid is actually produced but the agreement is only semi-quantitative. At about 25% reaction the amount of XIII observed accounts for 81% of the theoretical maximum and falls off after this point. It is reasonable that at later stages in the reaction the quantity of β -keto acid found should be less than quantitative because of its decomposition. Earlier on the agreement should be better. Because of the nature of XIII the analytical technique cannot produce quantitative results but must fall somewhat short of this. It is shown, however, that substantially the expected product is produced and there is no reason to believe that it is not the sole product. The analysis leads to the conclusion that the immediate oxidation product is 5-t-butyl-2-oxocyclohexanecarboxylic acid which later decarboxylates to give 4-t-butylcyclohexanone.

Results

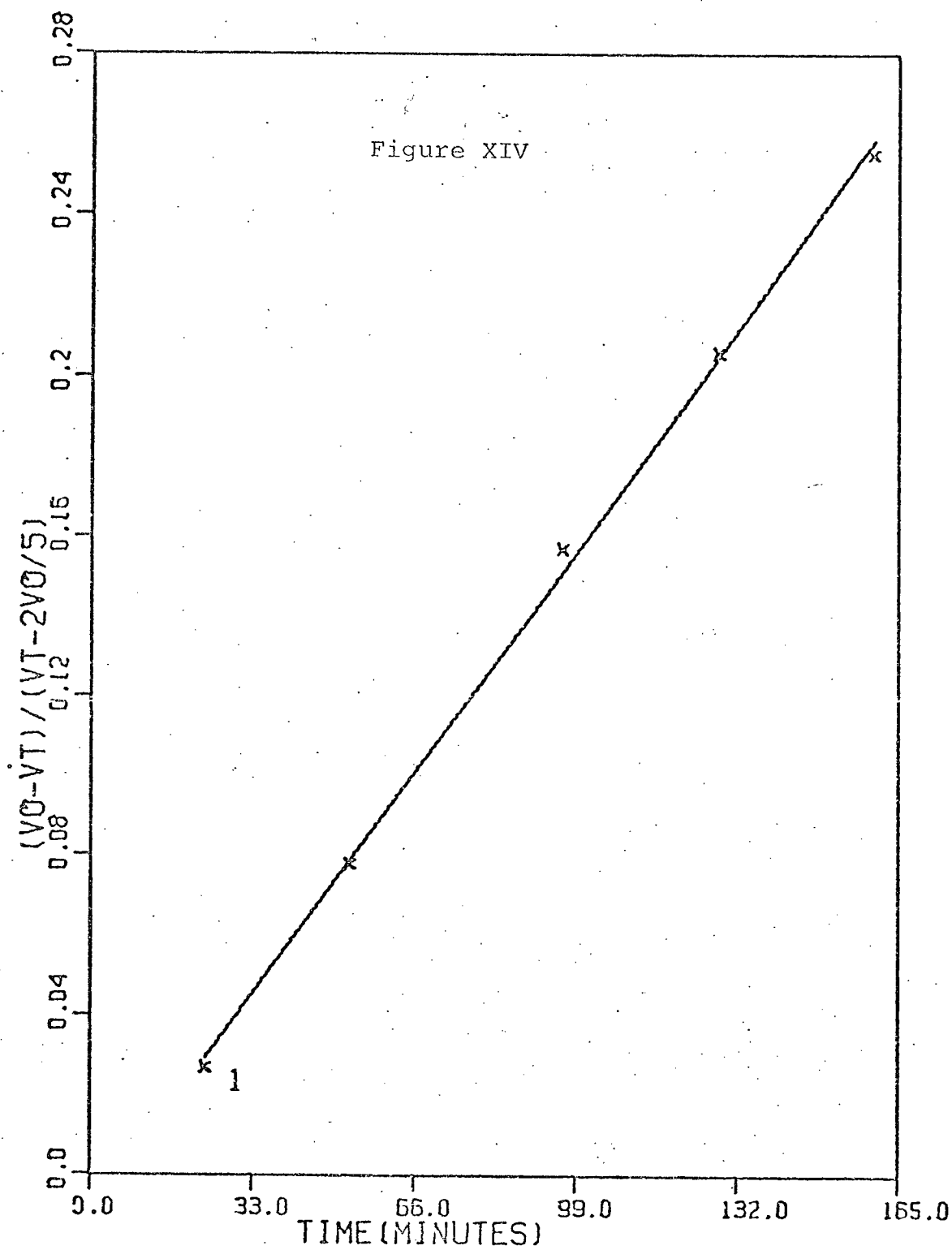
For the case of secondary alcohols which possess hydrogen atoms in the 2- position, the oxidation has one complicating feature. The product is a ketone bearing α hydrogens and therefore is enolizable. Enols are readily

attacked by permanganate and the second order rate plots will not remain straight lines over a very large extent of reaction owing to the reactivity of the product. In neutral solution it is possible to observe good second-order kinetics up to 50% reaction ($(V_o - V_t)/(V_t - \frac{2}{5}V_o) = 1$). In solutions more acidic than pH 7 it is found that straight lines are observed for smaller extents of reaction because of the enolization of the product ketone which is catalyzed by acid.

It must be pointed out that a true straight line whose slope can be determined reproducibly is observed and not a curve whose limiting slope is used to calculate the rate.

Cyclohexanol

A representative rate plot for the oxidation of cyclohexanol is given in Figure XIV. The pH-rate profile for this oxidation over the pH range 1-10.5 is given in Figure XV and the corresponding data are found in Table VII.



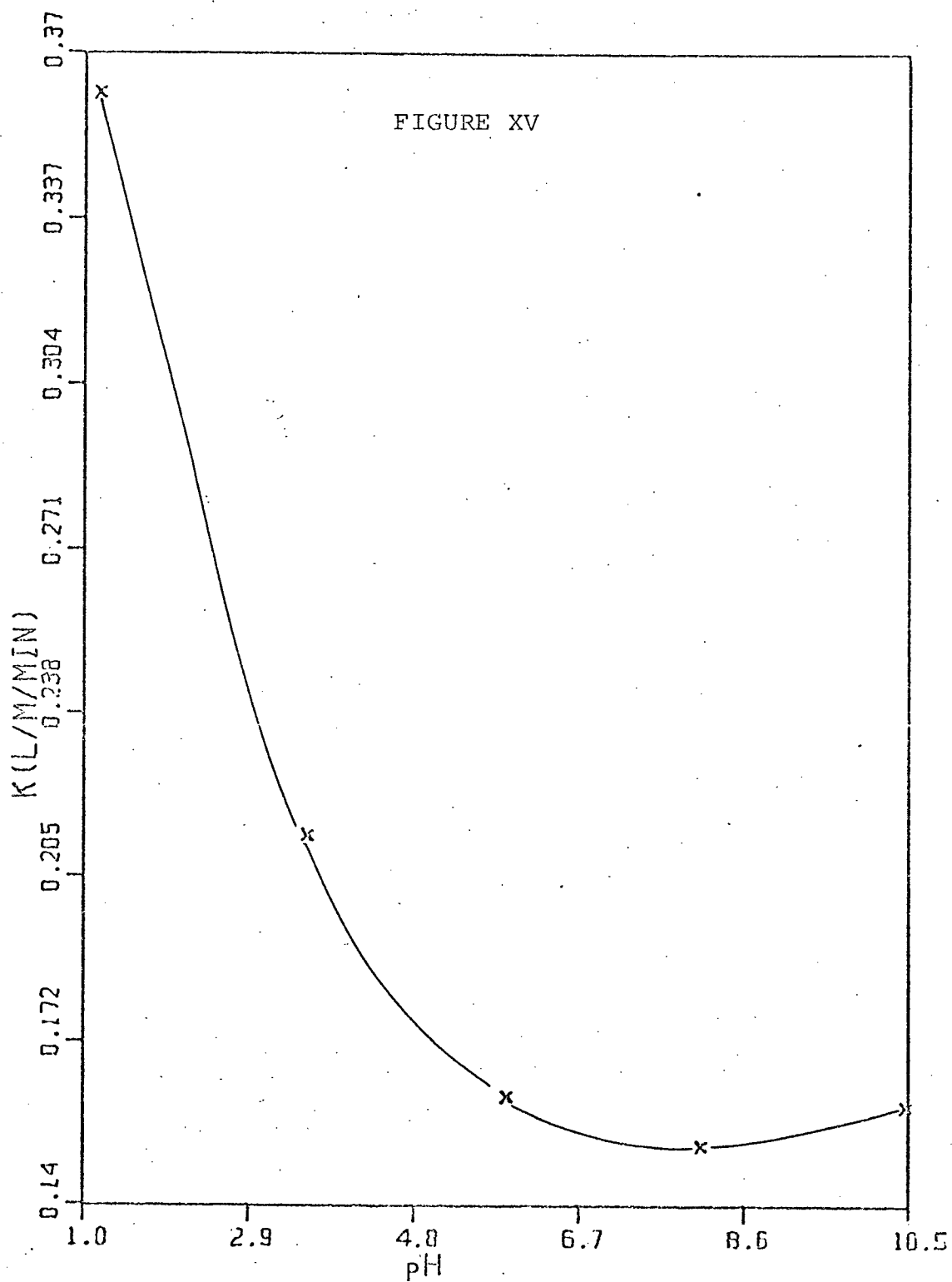
Cyclohexanol oxidation $T = 25^{\circ}\text{C}$ $\text{pH} = 5.88$

$[\text{cyclohexanol}]_0 = 0.00993\text{M}$

Ionic Strength = 0.43

$[\text{MnO}_4^-]_0 = 0.00662\text{M}$

$k = 0.162\text{L/M/MIN}$



Cyclohexanol pH-rate profile $T = 25^{\circ}\text{C}$

$[\text{cyclohexanol}]_0 = 0.00993\text{M}$ Ionic Strength = 0.43

$[\text{MnO}_4^-]_0 = 0.00662\text{M}$

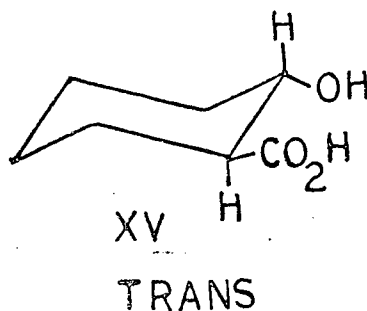
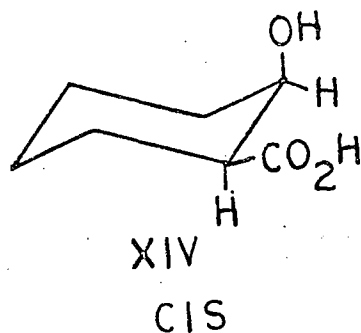
TABLE VII

Permanganate oxidation of Cyclohexanol

pH	k (L/M/MIN)	T = 25°C
1.19	0.362	[cyclohexanol] ₀ = 0.00993M
3.58	0.214	
5.88	0.162	[MnO ₄ ⁻] ₀ = 0.00662M
8.11	0.152	
10.48	0.160	Ionic Strength = 0.43

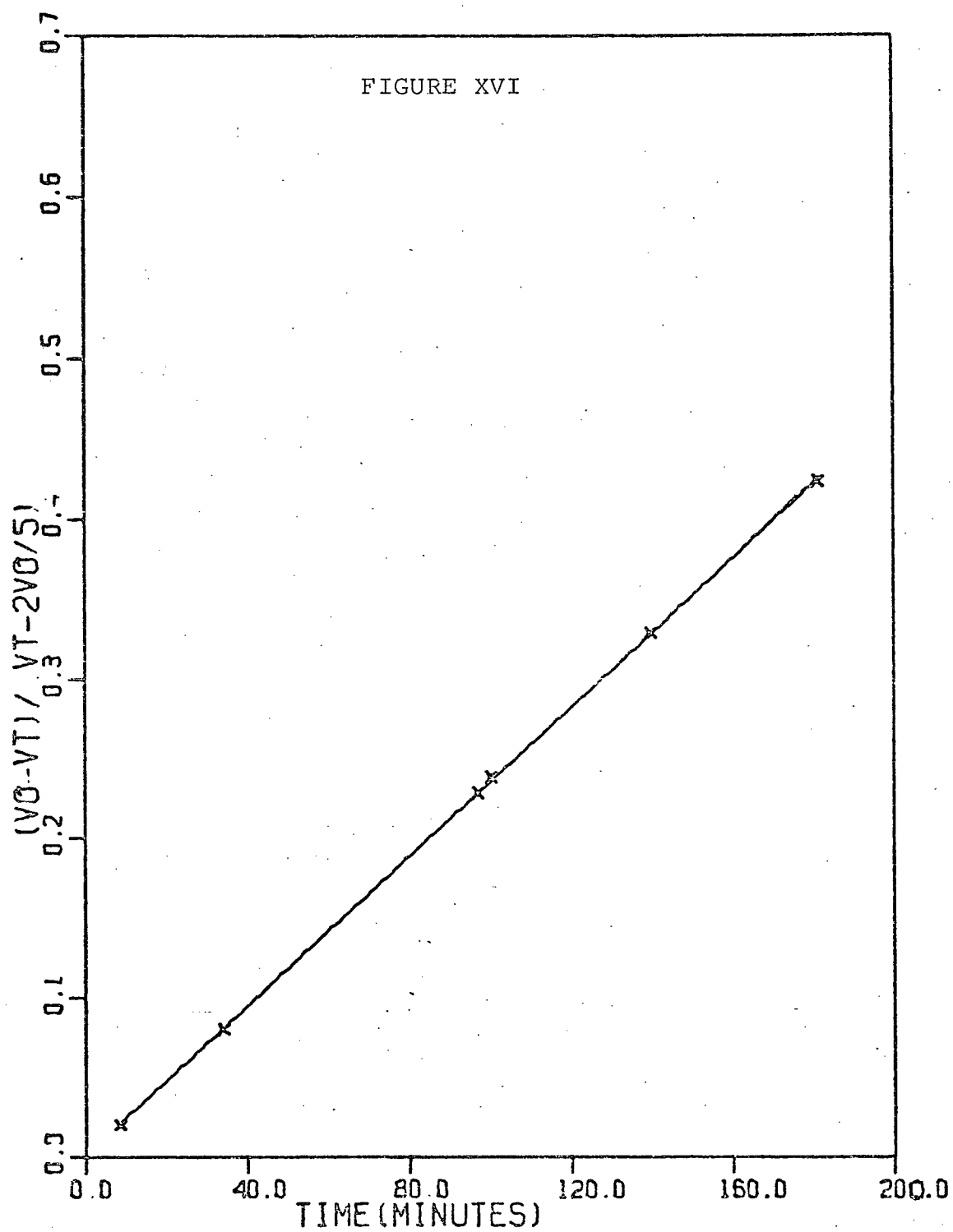
The pH-rate profile is quite unremarkable in the region investigated. The very gentle increase in the rate towards higher acidity and the flat portion in the region of neutrality are similar to the profile observed for the benzhydrol oxidation¹. The exact explanation of this behaviour has not been obtained but the similarity in behaviour is evident.

Cis-and Trans-2-hydroxycyclohexanecarboxylic acids



A typical rate plot for the cis-compound is given in Figure XVI and for the trans-compound in Figure XVII.

The pH-rate profiles for both these compounds are plotted in Figure XVIII and the data presented in Tables VIII and IX.

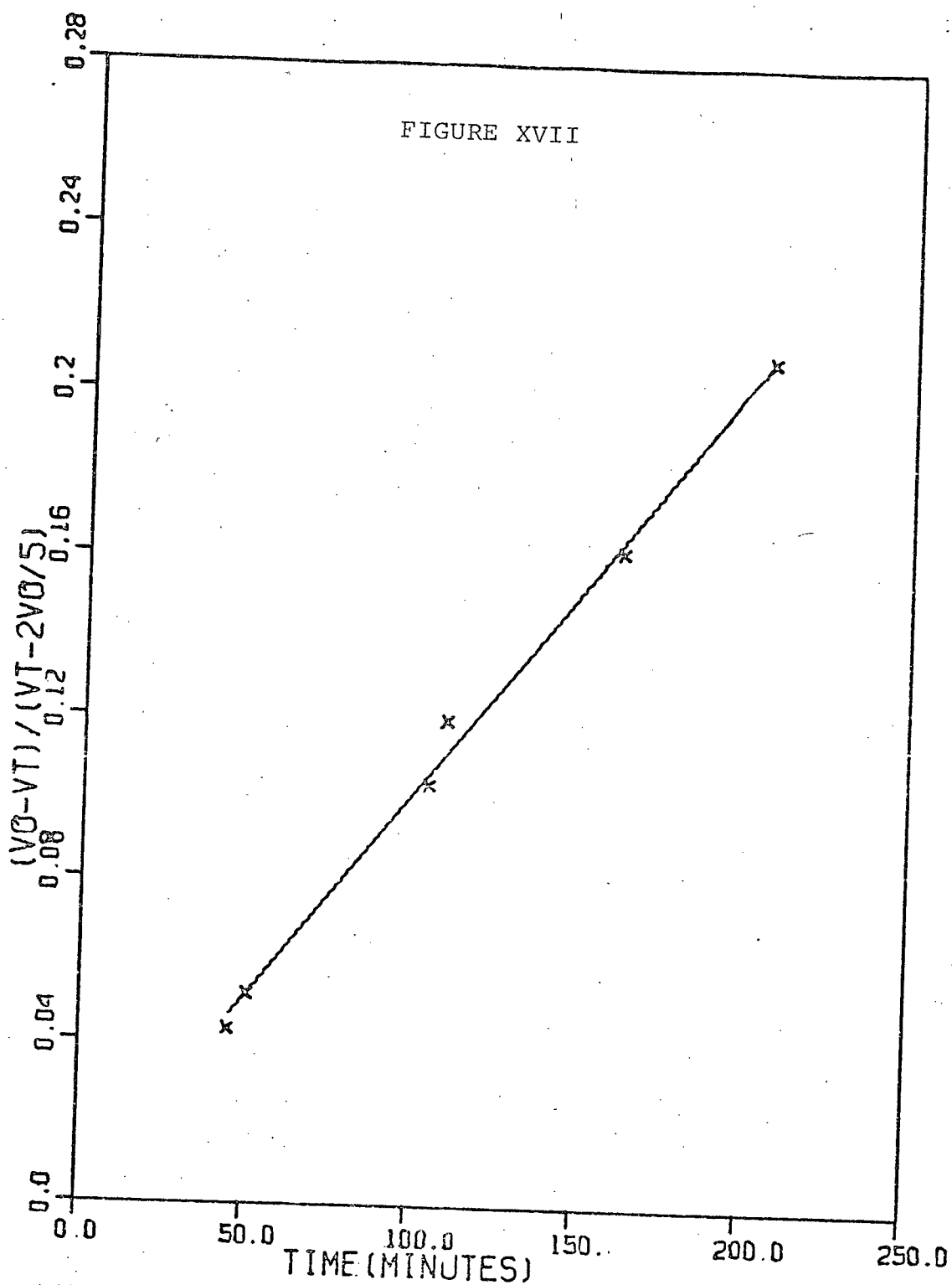


Cis-2-hydroxycyclohexanecarboxylic acid oxidation

$[\text{Substrate}]_0 = 0.002481\text{M}$ $T = 25^\circ\text{C}$ $\text{pH} = 6.20$

$[\text{MnO}_4^-]_0 = 0.001654\text{M}$ Ionic Strength = 0.43

$k = 0.944\text{L/M/MIN}$



Trans-2-hydroxycyclohexanecarboxylic acid oxidation

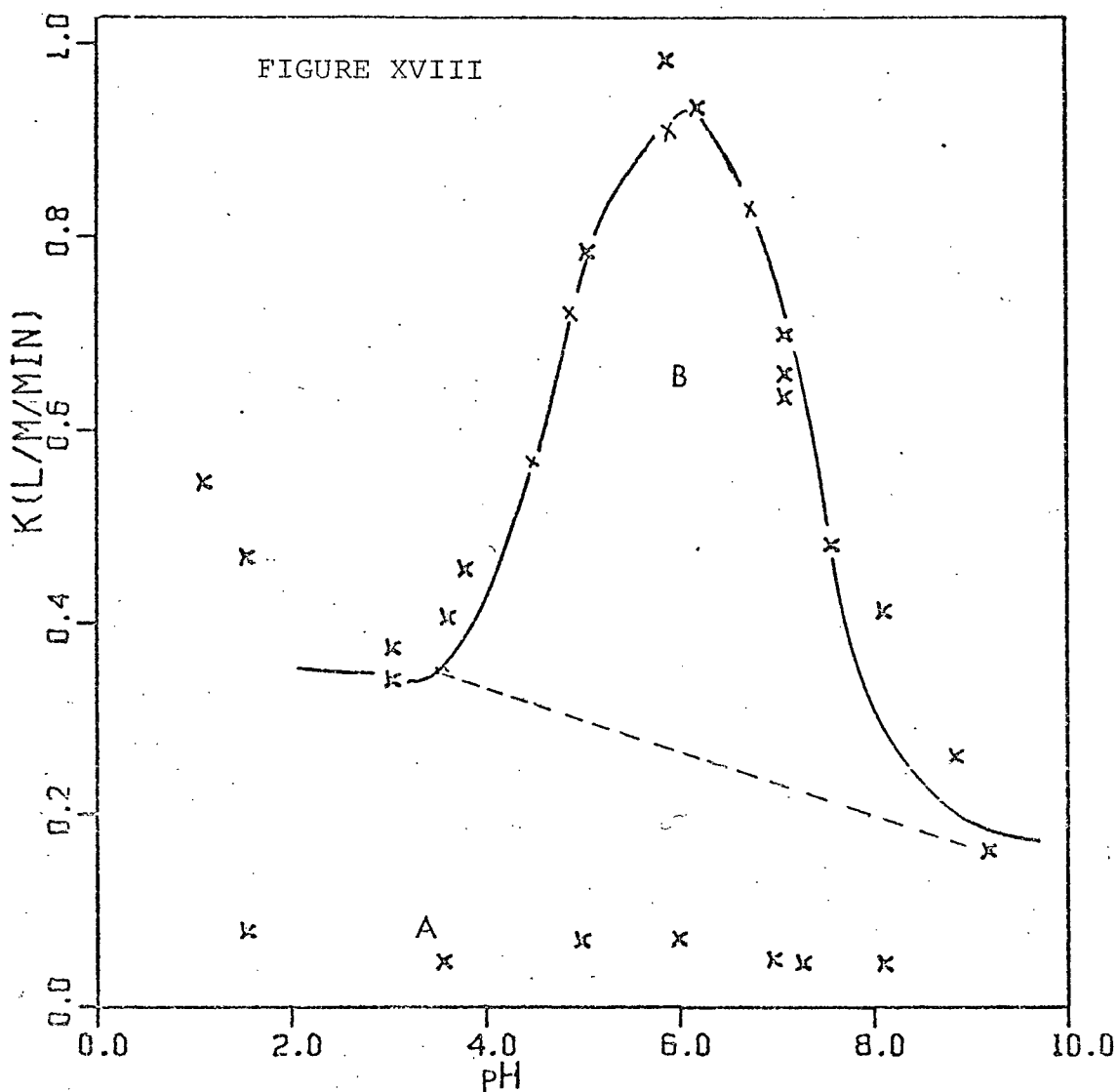
$[\text{Substrate}]_0 = 0.01499\text{M}$

$T = 25^\circ\text{C}$ $\text{pH} = 5.00$

$[\text{MnO}_4^-] = 0.01000\text{M}$

Ionic Strength = 0.43

$k = 0.0671\text{L/M/MIN}$



pH -- rate profiles.

A -- trans-2-hydroxycyclohexanecarboxylic acid

B -- cis-2-hydroxycyclohexanecarboxylic acid

The solid line is obtained from the analysis of the data of Table VIII according to Equation 15 of the Discussion section. The constants used in the calculation are from Table XV.

The x's represent the experimental points.

TABLE VIII

Cis-2-hydroxycyclohexanecarboxylic acid

pH	k (L/M/MIN)	T = 25°C	
1.11	0.548	$[\text{MnO}_4^-]_0 = 0.00333 \text{ M}$ $[\text{Substrate}]_0 = 0.00500 \text{ M}$ Ionic Strength = 0.43	
1.55	0.470		
3.05	0.341		
3.05	0.375		
3.62	0.407	$[\text{OH}^-]$ k (L/M/MIN)	
3.80	0.457		
4.45	0.560		
4.90	0.730		
5.05	0.786	0.016	2.80
5.88	0.985	0.045	3.20
6.20	0.935	0.080	3.60
6.65	0.820	0.126	4.80
7.10	0.700	0.158	7.40
7.10	0.660	0.305	9.80
7.10	0.635		
7.58	0.482		
8.11	0.413		
8.86	0.262		
9.20	0.163		
10.48	0.160		
11.03	0.206		
5.88	0.975 ^a		
5.88	0.980 ^b		

- a. phosphate concentration reduced by a factor of two and ionic strength maintained with sodium perchlorate.
- b. buffer concentration reduced by a factor of five.

TABLE IX

Trans-2-hydroxycyclohexanecarboxylic acid

pH	k (L/M/MIN)	T = 25°C	
1.55	0.0785	$[\text{Substrate}]_0 = 0.015 \text{ M}$ $[\text{MnO}_4^-]_0 = 0.010 \text{ M}$	
3.58	0.0470		
5.00	0.0671	$[\text{MnO}_4^-]_0 = 0.010 \text{ M}$ = 0.43	
6.00	0.0718		
6.97	0.0490		
7.28	0.0442		
8.11	0.0452		

Two facts are immediately evident from Figure XVIII - firstly, the striking bell-shape profile for the cis-compound and secondly, the absence of such an effect for the trans-compound and its lower reactivity.

These effects will receive a discussion further on when other relevant information has been presented.

Kinetic studies on the cis-compound were carried out in deuterium oxide solvent as well. The second order rate constants (spectrophotometric) as a function of pD are given in Table X and Figure XIX.

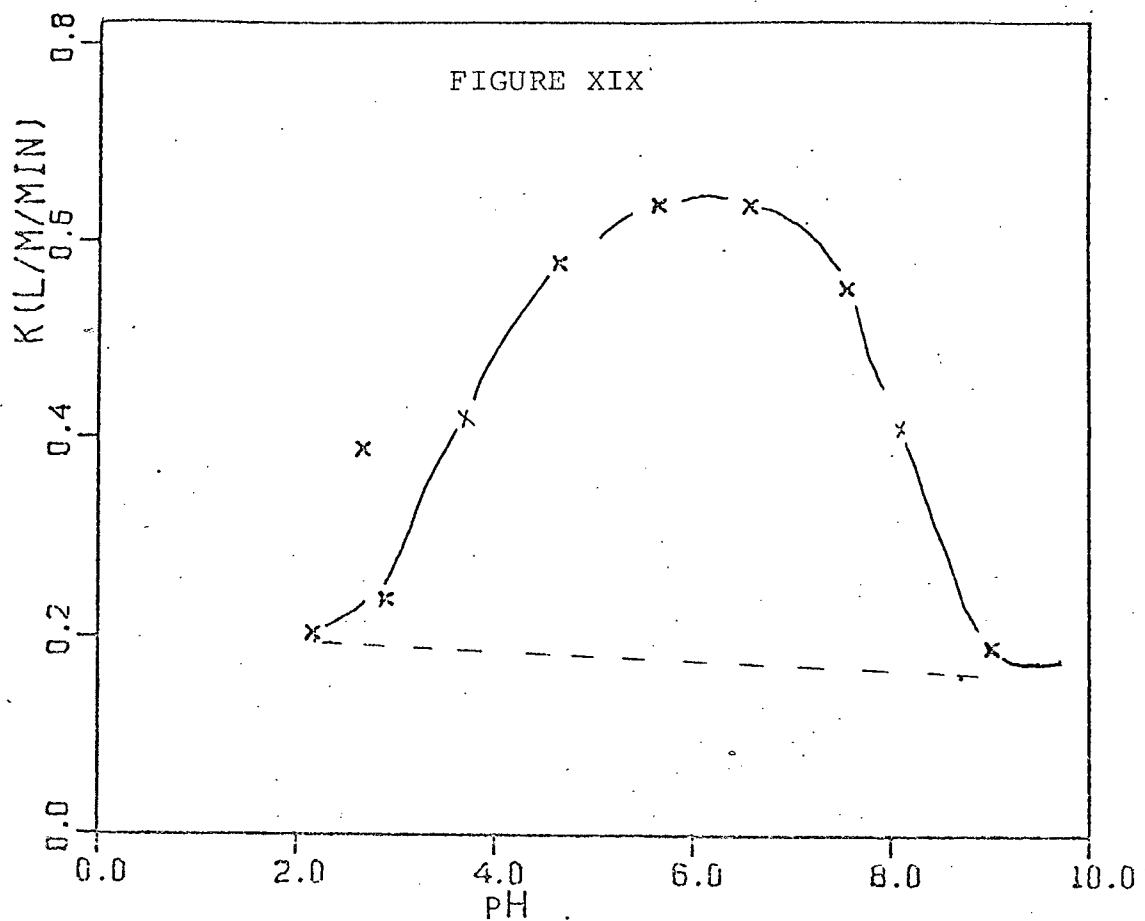
TABLE X

Cis-2-hydroxycyclohexanecarboxylic acid

Oxidation in deuterium oxide

pD	k (L/M/MIN)	$T = 25^{\circ}\text{C}$ $[\text{Substrate}]_0 = 0.00292\text{M}$ $[\text{MnO}_4^-]_0 = 0.00195\text{M}$ Ionic Strength = 0.43
2.18	0.206	
2.91	0.240	
3.70	0.430	
4.65	0.58	
5.65	0.640	
6.58	0.640	
7.56	0.555	
8.10	0.420	
9.03	0.190	

As mentioned in the General Experimental section trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid was prepared. The oxidation rate of this compound was measured using a titration method. The data are given in Figure XX and Table XI.



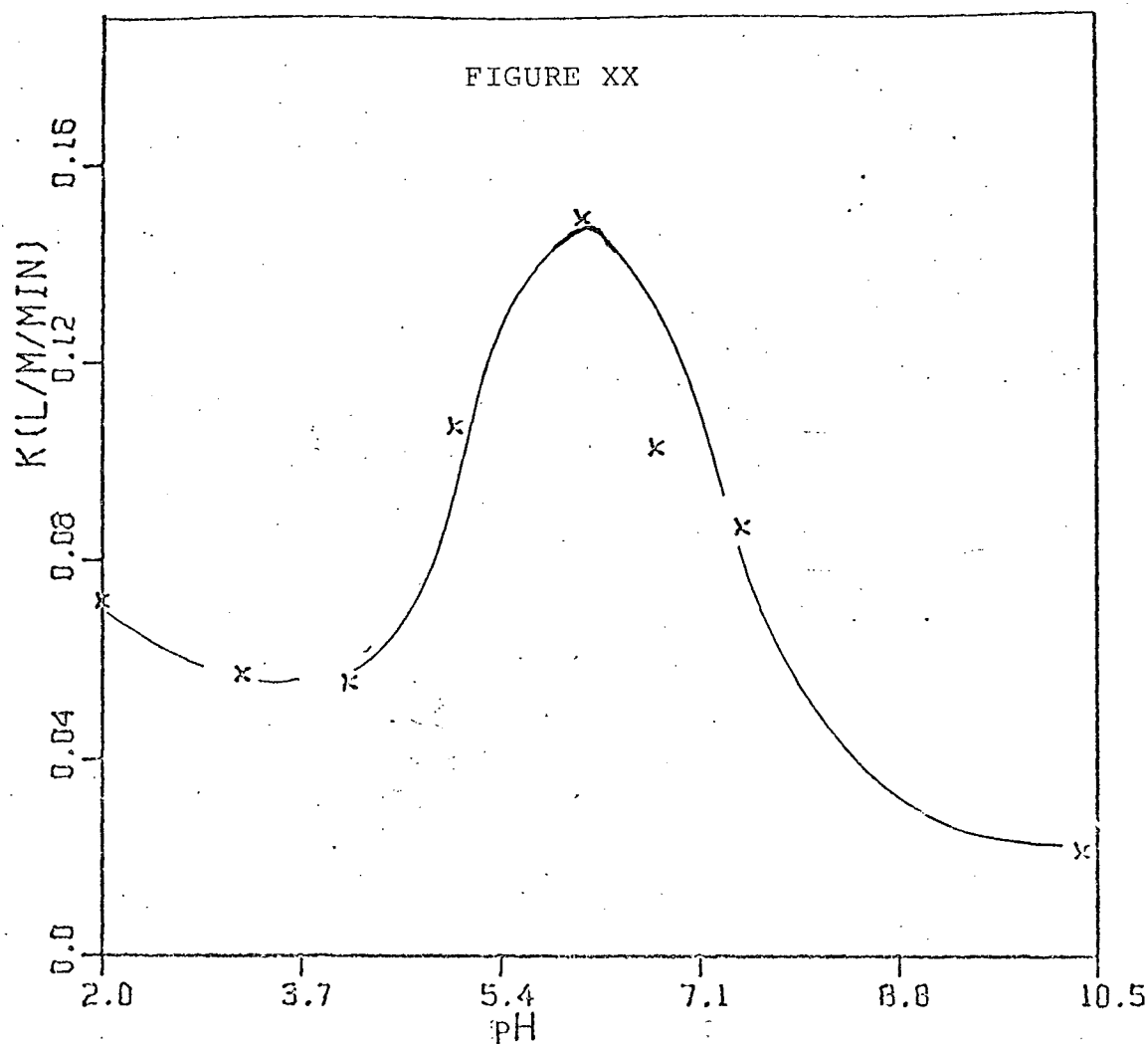
pH - rate profile

cis-2-hydroxycyclohexanecarboxylic acid

Oxidation in deuterium oxide.

The solid line was derived from the data of Table X using Equation 15. The constants used in this Equation are from Table XVI.

The x's represent the experimental points.



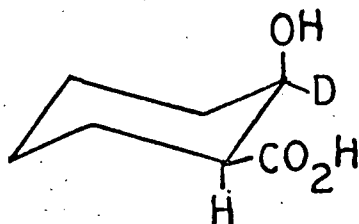
pH - rate profile

Trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid

Unfortunately the attempted correlation according to Equation 15 did not work. The correlation coefficient was not higher than 0.93 which is too low to be meaningful. Presumably the error in the rate constants is too great to permit correlation.

TABLE XI

Trans-2-deuterio-cis-2-hydroxycyclohexanecarboxylic acid



pH	k (L/M/MIN)	
2.00	0.0719	T = 25°C
3.20	0.0575	
4.11	0.0560	[Substrate] ₀ = 0.0104 M
5.01	0.107	
6.11	0.149	[MnO ₄ ⁻] ₀ = 0.00693 M
6.73	0.103	
7.46	0.0872	Ionic Strength = 0.43
10.38	0.0214	

The 5-t-butyl-2-hydroxycyclohexanecarboxylic acids

Of the four isomers possible (each having the t-butyl group in the equatorial position) three are used in the present work. As mentioned earlier they are cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X), cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid (XI) and trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (XII).

Because of the large conformational energy of the t-butyl group it must remain almost exclusively in the equatorial position⁴⁹. Because of this the conformations of each of the three isomers exist predominately (99.9%)

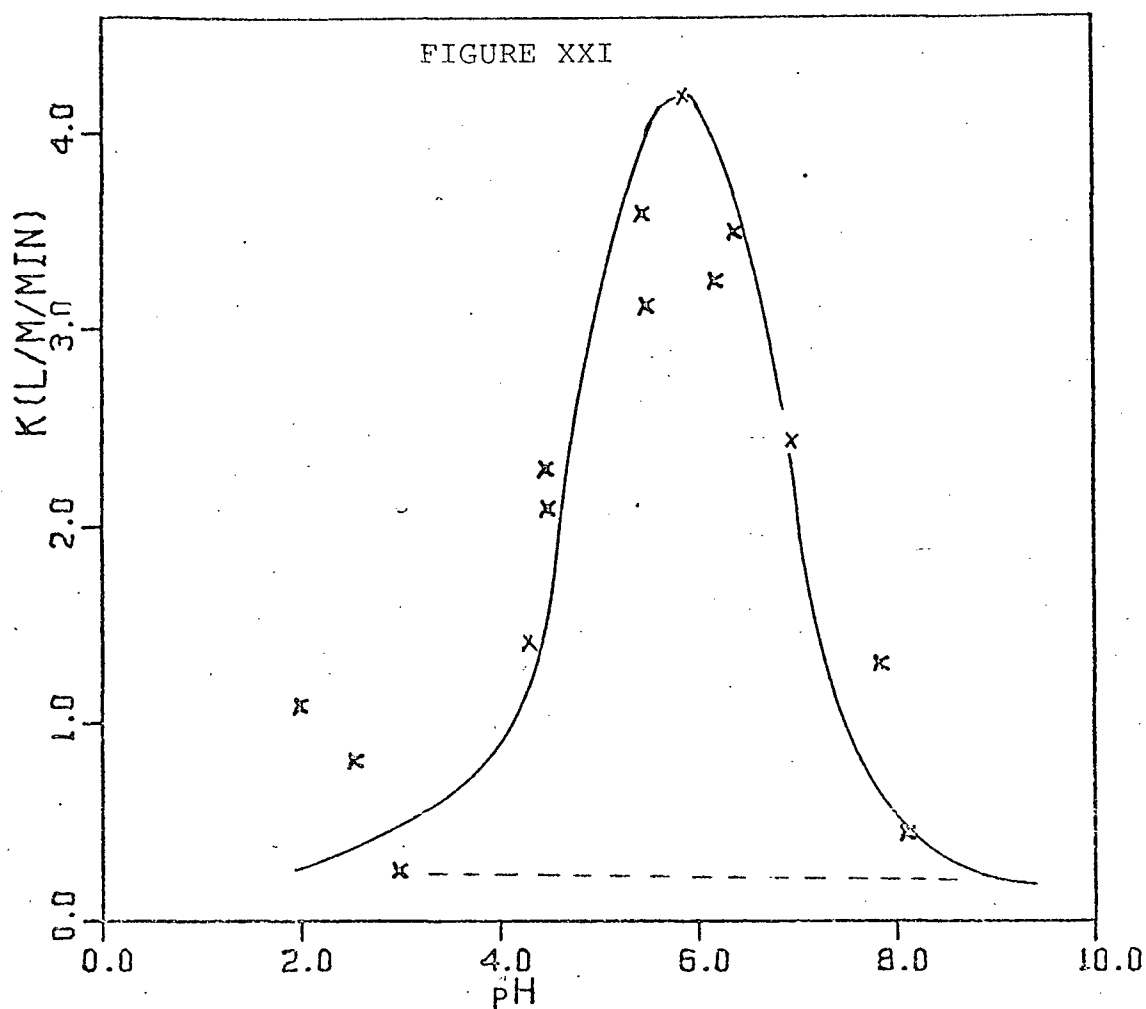
in the preferred conformation. This is contrasted with the two isomers of 2-hydroxycyclohexanecarboxylic acid whose configurations are not so rigidly biased in favour of one conformation. Evidence will be presented to indicate that compounds X, XI, XII, XIV and XV do actually have the conformations already implied.

Compound X has the pH-rate profile given in Figure XXI and Table XII. The data for compounds XI and XII is presented in Table XIII. Here it is noted that the bell-shape

TABLE XII

Cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid

pH	k (L/M/MIN)	T = 25°C
2.00	1.1	[Substrate] ₀ = 0.00100 M
2.55	0.820	
3.00	0.255	
4.30	1.45	[MnO ₄ ⁻] ₀ = 0.000667 M
4.50	2.10	
4.48	2.30	
5.46	3.59	Ionic Strength = 0.43
5.50	3.12	
5.80	4.25	
6.19	3.25	
6.39	3.50	
7.00	2.50	
7.85	1.31	
8.11	0.447	



pH - rate profile

Cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid

Solid line represents the fit of Equation 15 to the data of Table XII. The constants used in Equation 15 are tabulated in Table XVII.

The x's represent the experimental points.

TABLE XIII

Cis-5-t-butyl-trans-2-hydroxycyclohexanecarboxylic acid (XI)

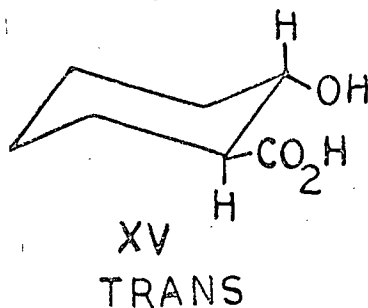
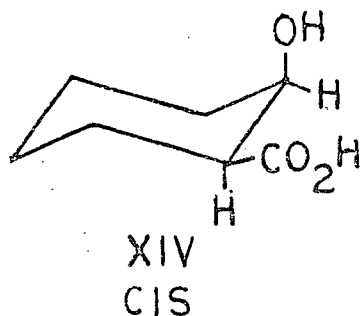
Trans-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (XII)

pH	k (L/M/MIN)	Compound	T = 25°C
4.68	1.55	XII	[Substrate] ₀ = 0.00293 M
6.01	1.11	XII	
7.53	0.863	XII	
1.36	0.242	XI	[MnO ₄ ⁻] = 0.00195 M
3.13	0.130	XI	
3.60	0.133	XI	
5.05	0.183	XI	Ionic Strength = 0.43
5.98	0.183	XI	
6.67	0.150	XI	
7.88	0.084	XI	
9.18	0.043	XI	

for compound X rises, at its maximum, to a higher rate than does the bell-shape corresponding to cis-2-hydroxycyclohexanecarboxylic acid oxidation. Compound XI exhibits a very slight maximum which is scarcely outside of experimental error. Compound XII does not appear to give a bell-shape effect at all.

Conformations

The conformations of all the compounds used in this work are believed to be known with a reasonable degree of certainty. We will consider first the pair of isomers cis- and trans-2-hydroxycyclohexanecarboxylic acids.



The fact that in the presence of strong base one isomer changes to the other indicates clearly that the former is the cis-compound and the latter the trans-compound. The available information concerning the conformational energies of the hydroxyl and the carboxyl group indicate that the conformation written above for the cis-isomer is predominant. It is difficult to imagine the trans isomer as adopting any conformation other than that with both substituents equatorial.

In addition to this Sicher³² et al. have studied the chromic acid oxidation of this isomeric pair and observe that the cis-isomer is about three times as reactive as the trans-isomer. This is similar to the effect noted by other workers in the chromic acid oxidation of cis- and trans-4-t-butyl-cyclohexanols - namely, that the axial hydroxyl reacts faster than the equatorial by a factor of approximately three.⁵²

The NMR spectra of the cis-isomer together with the compound (of similar melting-point) obtained from the sodium borodeuteride reduction of ethyl 2-oxocyclohexanecarboxylate are given in Figures XXII and XXIII. The protons

FIGURE XXII

100 MHz Spectrum

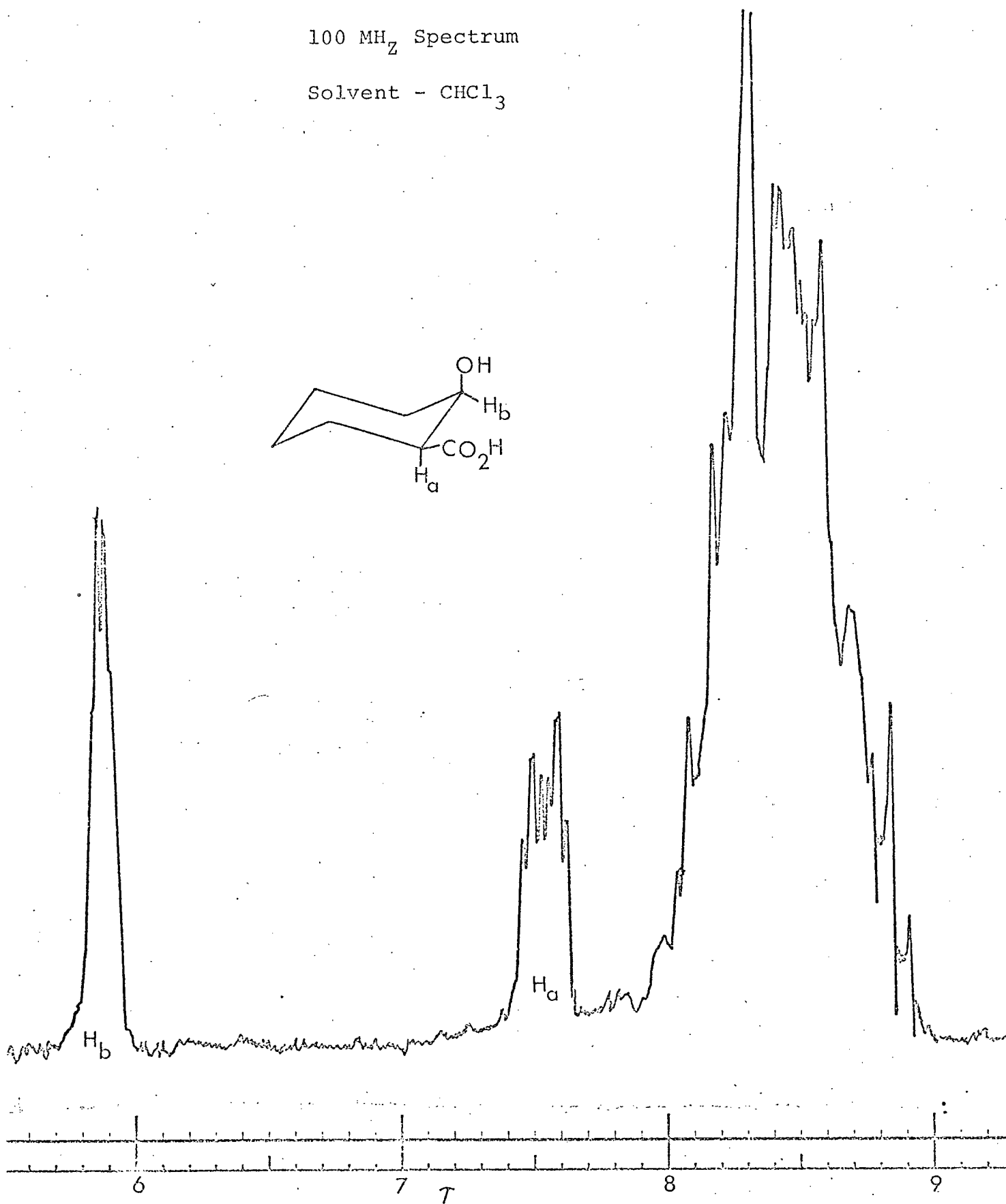
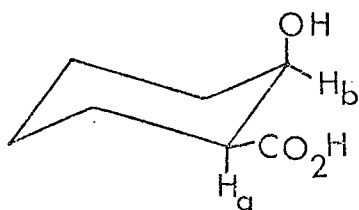
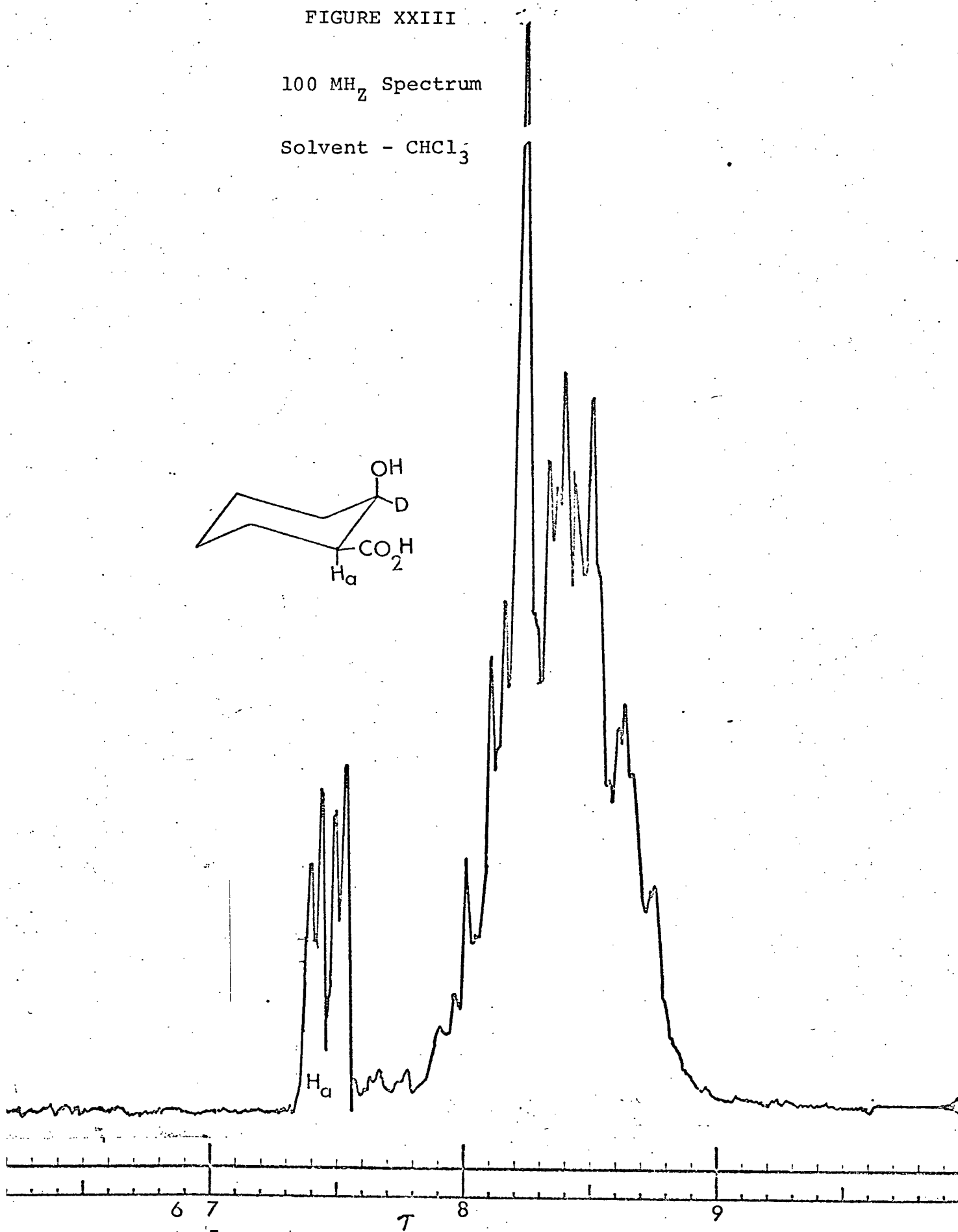
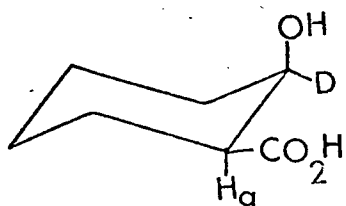
Solvent - CHCl_3 

FIGURE XXIII

100 MHz Spectrum

Solvent - CHCl_3 

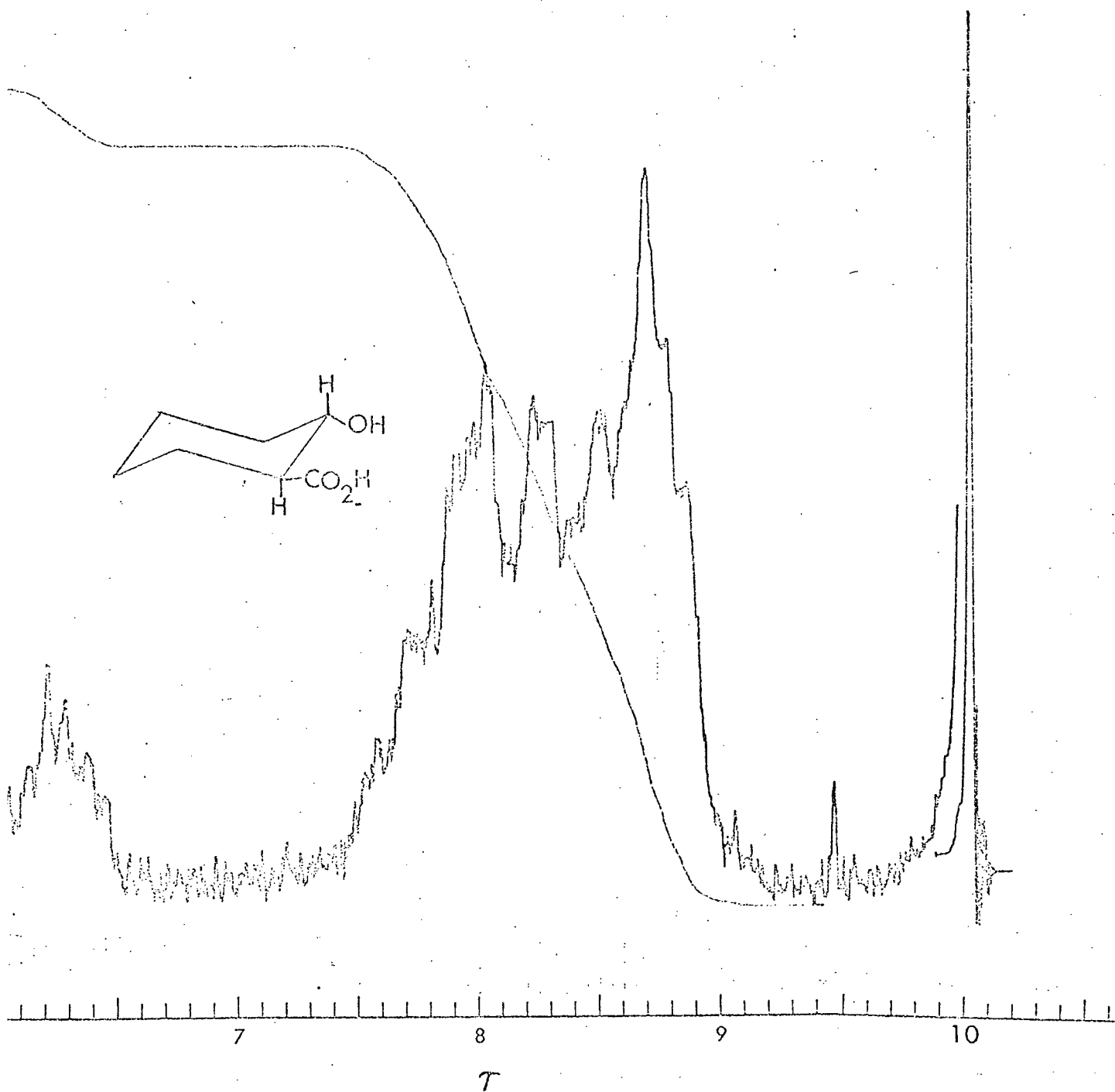
involved in the hydroxyl and carboxyl groups are not shown. A glance at the spectrum of Figure XXII indicates an axial and an equatorial proton. Axial-axial couplings⁵⁰ are well-known to be larger than axial-equatorial and equatorial-equatorial couplings. The latter two are quite small and of comparable magnitude. The NMR spectrum of the deuterio derivative clearly indicates that the equatorial proton is the one attached the carbon bearing the hydroxyl group because of the disappearance of the absorption of this proton and the corresponding loss of coupling in the resonance of the axial proton.

The predominant conformation of the cis-isomer may then be taken as represented by XIV.

The trans-isomer can be taken as given by XV. On the basis of pK measurements in solvents other than water previous authors⁵¹ have concluded that this isomer might exist in a di-axial conformation in solvents of lower dielectric constant than water. In water however this is not the case and the NMR spectrum bears this out (Figure XXIVa). Only one ring proton is observable separated from the remaining protons. This proton - presumably adjacent to the hydroxyl or carboxyl group - has a broad resonance composed of two large couplings and one smaller coupling. This proton must then be axial and the molecule have the configuration XV.

FIGURE XIVa

60 MHz Spectrum

Solvent - D₂O

The conformations of the three 5-t-butyl-2-hydroxycyclohexanecarboxylic acids used in this work have been deduced by Sicher. His technique involved the determination of hydroxyl conformation using as criterion the rate of chromic acid oxidation and the conformation of carboxyl according to the molecule's ability to isomerize in base. An axial hydroxyl group will be more reactive to chromic acid oxidation than an equatorial one. An axial carboxyl group will change to an equatorial conformation by vigorous treatment with strong base while an equatorial one will remain unchanged. Thus the three compounds below have the properties shown

Chemical Behaviour of Three Isomers of

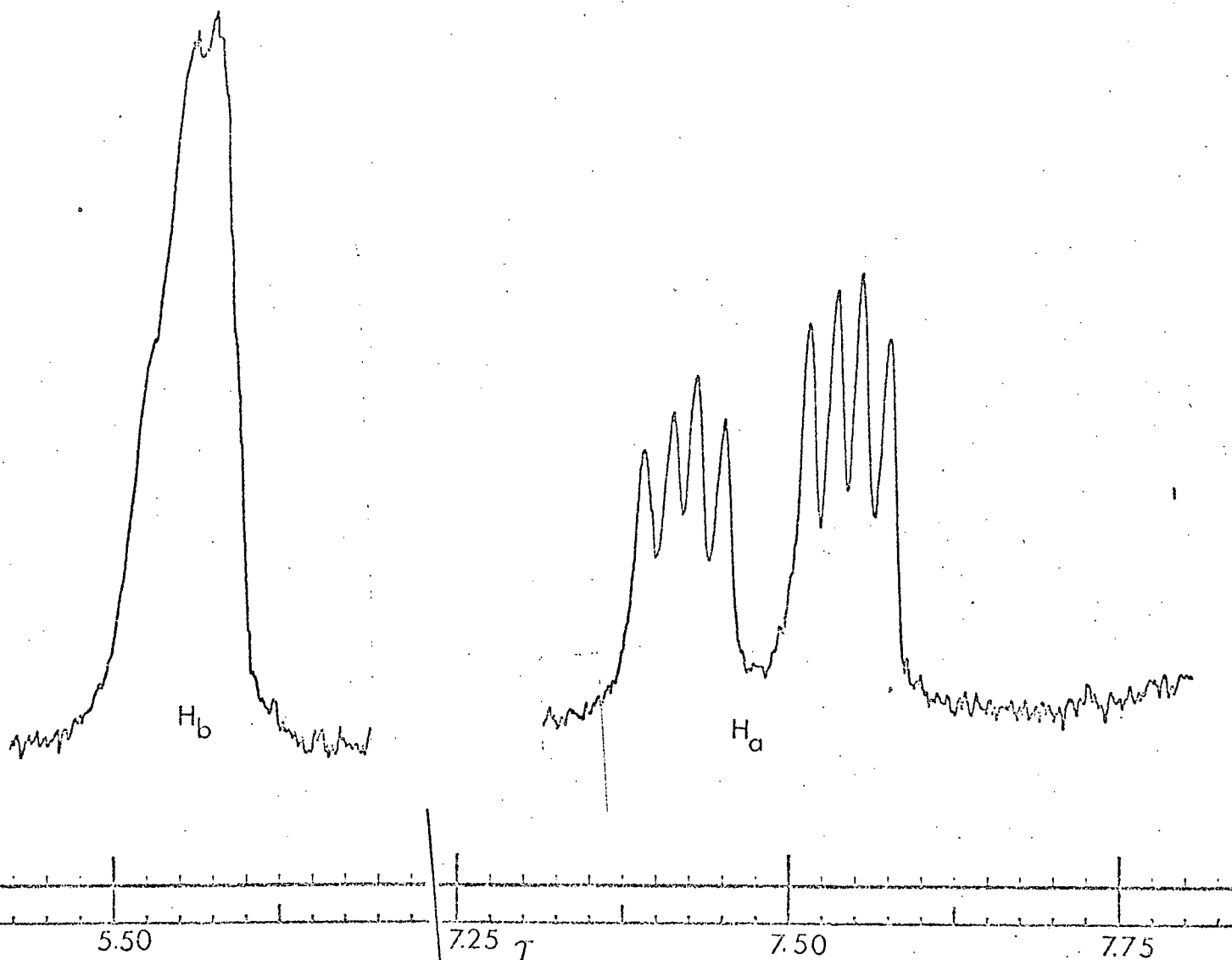
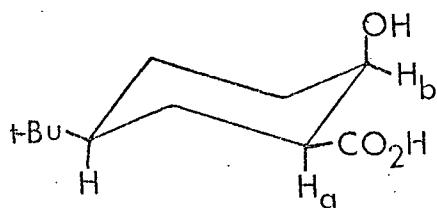
5-t-Butyl-2-hydroxycyclohexanecarboxylic Acid

COMPOUND	X	XI	XII
Relative Rate of Chromic Acid Oxidation	3	1	1
Isomerization with base	-	-	+

Such chemical properties unambiguously determine the conformations of these three isomers. If this is correct and the previous conclusion concerning the conformation of XIV is correct this

FIGURE XXIVb

100 MHz Spectrum

Solvent - CHCl_3 

compound and compound X should have rather similar NMR spectra. This is so. Two protons are observable separated from the remaining ring protons in the NMR spectrum. These are recorded in Figure XXIVb which is a time-averaged spectrum of 19 scans and considerably expanded. The NMR spectrum of X supports the conformational assignments made by Sicher for this particular compound and by implication the conformations assigned to the other two isomers.

Activation Parameters

The temperature-rate dependence of cis-2-hydroxycyclohexanecarboxylic acid was studied at three pH values (2.0, 5.88, 10.38). These rates along with the activation parameters calculated from them are given in Table XIV.

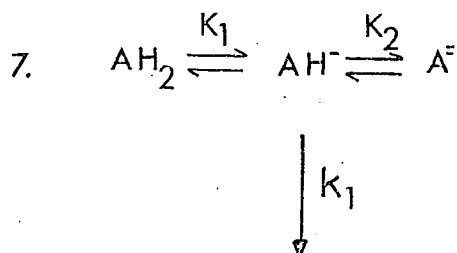
TABLE XIV

Cis-2-hydroxycyclohexanecarboxylic acid oxidation

pH	2.00	5.88	10.38
k (L/M/SEC)			
T			
5	---	0.00230	---
15	0.00325	0.00597	0.000950
25	0.00817	0.0156	0.002670
35	0.01535	0.0332	0.005155
45	0.02400	---	0.01630
ΔH^\ddagger (Kcal/ $^\circ$ mole)	$11.5^{+1.1}$	$15.9^{+0.4}$	$16.1^{+1.3}$
ΔS^\ddagger (eu)	$-29.7^{+2.0}$	$-13.9^{+1.1}$	$-16.4^{+2.1}$
Corr. coeff.	0.991	0.999	0.993

Discussion

The bell-shape pH-rate profiles observed in this work, although they appear to be novel for oxidation reactions, are rather common in certain areas of mechanistic investigation⁵³. Indeed, as far as enzyme containing systems are concerned, such behaviour is encountered with remarkable frequency⁵⁴. The literature is replete with studies on such systems. A thorough discussion of enzyme systems and how they give rise to bell-shape curves is given by Dixon and Webb⁵⁴. According to these authors as well as several standard texts dealing with the subjects of enzyme reactions⁵⁵ and chemical kinetics⁵⁶ this behaviour comes about for the following reason. There exist two equilibria (or more) involving hydrogen ions in which the enzyme takes part. The enzyme species involved in these equilibria are not all of the same enzymatic activity; in fact, one species which can exist only at intermediate pH values and not at higher and lower acidities is more active than the rest. In terms of Equation 7.



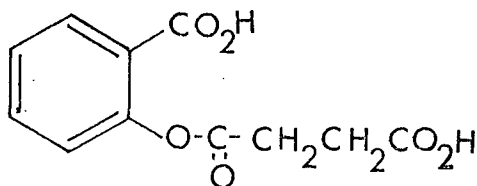
we would say that species AH^- is more reactive than either AH_2 and A^- and that the rate of reaction is properly given by $k_1[AH^-]$. In terms of the total amount of species present, $[AH_2]_t$, the rate would be represented as

$$\text{Rate} = \frac{k_1[AH_2]_t}{1 + \frac{[H^+]}{K_1} + \frac{K_2}{[H^+]}}$$

the observed rate constant (k_{OBS}) then would be

$$8. \quad k_{OBS} = \frac{k_1}{1 + \frac{[H^+]}{K_1} + \frac{K_2}{[H^+]}}$$

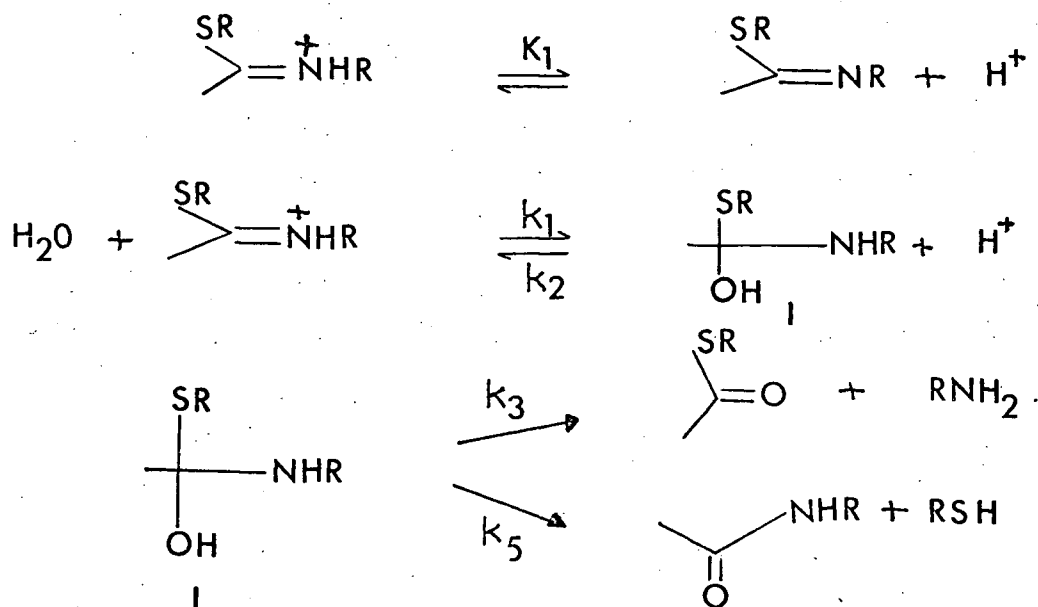
which has the proper mathematical form to result in a bell-shape curve. The case with enzyme reactions is very complex involving many equilibria which usually cannot all be sorted out. There are, however, on record a considerable number of reactions not involving enzymes which exhibit maxima in their pH-rate plots^{57,58,59,23}. A number of these reactions involve two ionizable carboxyl functions and are admirably accounted for in terms of Equations 7. and 8. For example, the hydrolysis of XVI⁵⁷



XVI

exhibits the bell-shape behaviour under consideration. The reaction of 2,2'-dicarboxytolan⁶⁰ to form 3-(2-carboxybenzylidene)-phthalide also behaves in this way. Kinetic deportment of this kind is adequately covered by Equation 8. and no other considerations seem to be involved.

There are reactions which yield bell-shape pH-rate profiles in which two clearly definable protonic equilibria are not evident^{23,58}. In these cases the form of Equation 8. is found to hold but one or both of the K's are replaced by functions involving two or more rate constants. The studies of Chaturvedi⁶¹ on thioimide ester hydrolysis illustrate this point. A bell-shape pH-rate profile is observed for this reaction whose reaction sequence, as a consequence of this, is thought to be the following:

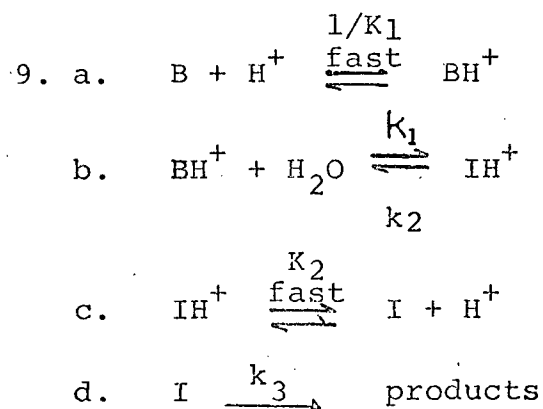


Assuming that a steady-state concentration of the intermediate I exists, leads to the expression for the observed rate constant:

$$k_{\text{OBS}} = \frac{k_1}{\frac{k_2 [\text{H}^+]}{k_5 + k_5} + \frac{K_1}{[\text{H}^+]} + \frac{K_1 k_2}{k_3 + k_5}}$$

The descending limb of the bell is controlled by the equilibrium represented by K_1 ; the ascending limb by the collection of rate constants $k_2/(k_3+k_5)$.

A careful consideration of the ways in which hydrolysis reactions may give rise to bell-shape pH-rate profiles has been made by Zerner and Bender²³. These authors list five different reaction sequences which can result in a bell-shape pH-rate profile. The first of these situations is that represented by Equation 7. This is the most commonly observed case and where enzymes are concerned Equation 7 is usually believed to represent an adequate explanation of events. One reaction sequence, cited by Zerner and Bender, that will concern us to some extent is the following:



B is the substrate and can participate in the reversible rapid equilibrium whose constant is $1/K_1$. A hydrated intermediate is formed (IH^+) which can decompose to give product only after it has lost a proton in the rapid equilibrium represented by K_2 . If we take the rate to be given by $k_3[I]$ and apply the steady-state assumption to $[I]$ and $[IH^+]$ the result is

$$\text{Rate} = \frac{k_3 k_1 [BH^+] [H_2O]}{k_3 + \frac{[H^+]}{K_2}}$$

If $[BH^+]$ is expressed in terms of the total amount of substrate species $[B]_t$ the result is

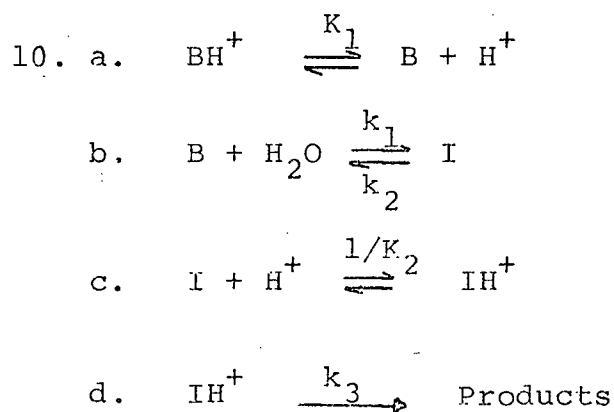
$$\text{Rate} = \frac{k_3 k_1 [B]_t [H_2O]}{\left(k_3 + \frac{k_2 [H^+]}{K_2} \right) \left(1 + \frac{K_1}{[H^+]} \right)}$$

This equation, of course, describes a bell-shape pH-rate profile.

A glance at the reaction sequence of Equation 9. shows qualitatively that this should be the case. At low acidities the substrate B will not be sufficiently protonated for reaction to occur readily. At high acidities the intermediate will be completely protonated and the equilibrium will lie too far to the left. At intermediate acidities

there should be an optimum pH at which both equilibria may contribute to the overall reaction. It is precisely this opposition of equilibria in the cases examined by Zerner and Bender which produces the bell-shape pH-rate profile and in general this is probably quite true²³.

A situation kinetically indistinguishable from Equation 9. would be one in which each species is substituted by its conjugate giving:



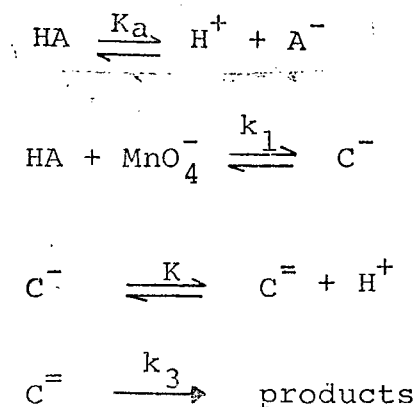
the form of the kinetic expression is the same in this case as it is for Equation 9.

With this preamble we can begin an examination of the reactions involved in this work. The discussion will follow lines similar to those mentioned above and the reaction sequences will involve two protonic equilibria acting in opposed directions.

The reactions consist of the permanganate oxidations of 2-carboxy substituted cyclohexanols and undoubtedly in

those cases in which the pH-rate profile is bell-shaped the ionization of the carboxyl group is important. Abbreviating the substrate as HA, we can write the following sequence which will be referred to as Reaction Scheme I.

Reaction Scheme I



According to Reaction Scheme I the neutral alcohol HA reacts with permanganate to form an intermediate; this intermediate dissociates; and the resulting di-anion decomposes to products. For the moment the identity of the intermediates will be left open and we will pursue the kinetic consequences of the reaction scheme.

The overall rate is given by

$$\text{Rate} = k_3 [\text{C}^=]$$

Assuming the equilibria involving protons to be rapid we make use of the steady-state assumption regarding $[C^=]$ and $[C^-]$ to obtain

$$-\frac{d([C^-] + [C^=])}{dt} = k_3 [C^=] + k_2 [C^-] - k_1 [HA] [MnO_4^-] = 0$$

Because $[C^-] = [C^=] [H^+] / K$ we have

$$[C^=] = \frac{k_1 [HA] [MnO_4^-]}{k_3 + k_2 [H^+] / K}$$

thus the rate is given by

$$\text{Rate} = \frac{k_1 k_3 [HA] [MnO_4^-]}{k_3 + k_2 [H^+] / K}$$

If we now express the rate in terms of the permanganate concentration and the total substrate concentration

($[HA]_t = [HA] + [A^-]$) we get

$$\text{Rate} = \frac{k_1 k_3 [HA]_t [MnO_4^-]}{(k_3 + k_2 [H^+] / K) (1 + K_a / [H^+])}$$

The observed second order rate constant, k_{OBS} , becomes

$$11. \quad k_{OBS} = \frac{k_1 k_3}{(k_3 + k_2 [H^+] / K) (1 + K_a / [H^+])}$$

This equation (11) has the requisite form to result in a bell-shape pH-rate profile. The pH corresponding to the maximum rate can be obtained by differentiating k_{OBS} with respect to $[H^+]$ and is

$$12. \quad \text{pH}_{\text{max}} = \frac{1}{2} \log(k_2/k_3 K K_a) .$$

Equation 11. may be rearranged to give

$$\frac{1}{k_{\text{OBS}}} = \frac{1}{k_1} \left[1 + \frac{k_2 K_a}{k_3 K} \right] + \frac{1}{k_1} \left[\frac{K_a}{[H^+]} + \frac{k_2 [H^+]}{k_3 K} \right] \quad \text{and}$$

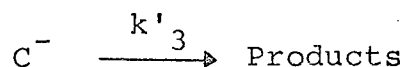
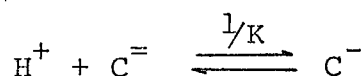
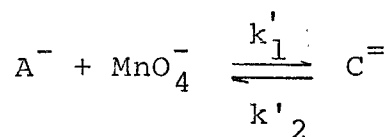
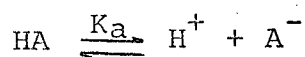
$$\frac{1}{k_{\text{OBS}}} = \frac{1}{k_1} (1+C) + \frac{1}{k_1} (A+B)$$

with $C = k_2 K_a / k_3 K$, $A = K_a / [H^+]$ and $B = k_2 [H^+] / k_3 K$.

A plot of $1/k_{\text{OBS}}$ against $A+B$ should then give a straight line of slope $1/k_1$ and intercept $(1+C)/k_1$. Thus we can obtain k_1 and the term $k_3 K / k_2$ from the values of k_{OBS} .

It is also possible to consider the same kind of reaction sequence in terms of the conjugates of the acid and base species in Scheme I. This gives us Reaction Scheme II.

Reaction Scheme II



Following the same procedure as previously we get

$$\text{Rate} = \frac{k'_1 k'_3 [\text{HA}]_t [\text{MnO}_4^-]}{(k'_3 + k'_2 K / [\text{H}^+]) (1 + [\text{H}^+] / K_a)}$$

and

$$13. \quad k_{\text{OBS}} = \frac{k'_1 k'_3}{(k'_3 + k'_2 K / [\text{H}^+]) (1 + [\text{H}^+] / K_a)}$$

The pH corresponding to maximum k_{OBS} is

$$14. \quad \text{pH}_{\text{max}} = \frac{1}{2} \log(k'_3 / k'_2 K K_a)$$

We also have

$$15. \quad \frac{1}{k_{\text{OBS}}} = \frac{1}{k'_1} \left[1 + \frac{k'_2 K}{k'_3 K_a} \right] + \frac{1}{k'_1} \left[\frac{[\text{H}^+]}{K_a} + \frac{k'_2 K}{k'_3 [\text{H}^+]} \right]$$

and

$$16. \quad \frac{1}{k_{\text{OBS}}} = (1 + C')/k'_1 + (A' + B')/k'_1$$

with $C' = k'_2 K / k'_3 K_a$, $A' = [H^+] / K_a$ and $B' = k'_2 K / k'_3 H^+$.

In this case as well we can plot $1/k_{\text{OBS}}$ against $(A' + B')$ and obtain as slope $1/k'_1$ and as intercept $(1 + C')/k'_1$. From the value of pH_{max} we can obtain the term $k'_3 / K k'_2$.

The kinetic analysis resulting from Schemes I and II was applied to the experimental rate data for Cis-2-hydroxycyclohexanecarboxylic acid. A word about the computational procedure is in order before the actual results are given.

It was found that the raw experimental data as recorded in Table VIII could not be made to correlate (correlation coefficient ~ 0.9) according to the equations derived from Reaction Scheme I. A glance at Figure XVIII as well as the behaviour of cyclohexanol with changing pH indicate that the "normal" reaction and that involving the bell-shape behaviour take place simultaneously. A separation of the two effects must be made in order to analyse numerically the actual bell-shape reaction. Several attempts were made but the one represented in Figure XVIII seemed the simplest and best solution. The area below the dotted line represents "normal" behaviour and that above the line

"bell-shape" behaviour. This procedure was followed for the bell-shape curves of Figures XIX and XXI as well. In the work of Zerner and Bender⁵³ it was also found that the data had to be "corrected" to eliminate extraneous effects.

The most critical item involved in the calculation is the determination of the value of pH_{max} . This number can of course be estimated from the experimental results but a sufficiently precise value cannot be obtained in this way. The procedure followed was to estimate a value and see how closely the plot of $1/k_{\text{OBS}}$ against $(A+B)$ approached a straight line. The criterion used for this was the correlation coefficient of the line. It appeared that the correlation coefficient went through a maximum as the pH was varied over a certain interval. The pH corresponding to this maximum correlation could be determined to any desired degree of accuracy. This pH_{max} was consistent with the value estimated from the bell-shape plot by inspection.

Once the appropriate pH_{max} is determined the next step is to adjust K_a such that k_1 determined from the slope is consistent with that determined from the intercept. This can be done to any desirable degree of accuracy as well - the limiting feature being the standard error in k_1 . A change in K_a is found not to produce any change in the correlation coefficient or pH_{max} . Consequently K_a and pH_{max} can be

adjusted quite independently, with pH_{max} being determined first of course. These calculations were carried out using a computer least-squares program. The result of the calculations for cis-2-hydroxycyclohexanecarboxylic acid are given in Table XV.

TABLE XV

Cis-2-hydroxycyclohexanecarboxylic acid (XIV) in protium oxide

pH_{max}	=	6.020
pK_a	=	4.70
k_1	=	315 ± 24 (L/M/MIN)
C	=	429.86
k_3^K/k_2	=	4.61×10^{-8}

k'_1	=	0.730 ± 0.050 (L/M/MIN)
C'	=	2.326×10^{-3}
k'_2^K/k'_3	=	4.61×10^{-8}

Correlation Coefficient = 0.984

The same was done to the data for the oxidation of compound XIV in deuterium oxide. The results are given in Table XVI.

TABLE XVI

Cis-2-hydroxycyclohexanecarboxylic acid (XIV) in deuterium oxide

pD_{\max}	=	6.378
pK_a	=	4.96
k_1	=	288 ± 5 (L/M/MIN)
C	=	689.89
k_3K/k_2	=	1.59×10^{-8}
<hr/>		
k'_1	=	0.416 ± 0.006 (L/M/MIN)
C'	=	1.450×10^{-3}
k'_2K/k'_3	=	1.59×10^{-8}
Correlation Coefficient	=	0.995

A comparison of the results in protium oxide and in deuterium oxide for Compound XIV can be made. The k_1 values are nearly the same in the two solvents, $k_1(H_2O)/k_1(D_2O)$ being 1.09.

The k'_1 values however do show some change with

$k'_1(H_2O)/k'_1(D_2O) = 1.75$. This difference is significant and will be considered in due course. The quantity

k_3K/k_2 (or k'_2K/k'_3) shows some variation with

$k_3K/k_2(H_2O)/k_3K/k_2(D_2O) = 2.90$. In the light of well known work^{15,62} concerning the behaviour of acid strength in

deuterium oxide and protium oxide, this isotope effect can be explained adequately. If k_3 and k_2 are not influenced,

or influenced to the same extent, by the isotopic change in the solvent, then the effect observed is due entirely to a change in K . Acid weakening by a factor of from two to three or changing from protium oxide to deuterium oxide has been observed in a great many cases⁷⁹. This is presumably what is happening here, although it appears impossible to distinguish this from more complicated behaviour arising from changes in all three components of the factor k_3K/k_2 .

It is possible to explain the difference in the maximum values in k_{OBS} between Compound XIV in protium oxide and deuterium oxide quite simply. Making use of Equations 6. and 11. the following relationship is obtained.

$$k_{OBS(max)} = \frac{k_1}{(1 + \frac{K_a}{[H^+]_{max}})}$$

The difference can be explained in terms of the failure of $[H^+]_{max}$ and K_a to change to the same extent when the solvent is changed from protium oxide to deuterium-oxide. The ability to calculate the ratio $k_{OBS(max)}(H_2O)/k_{OBS(max)}(D_2O)$ from the data in Tables XV and XVI reflects only internal consistency in the calculated parameters. The relationship above does however indicate the origins of the isotope effect observed.

The data for the other compound showing a bell-shape pH-rate profile were subjected to the same mathematical treatment. The results for Cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X) are given in Table XVII.

TABLE XVII

Cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X)

pH_{max}	=	5.964	
pKa	=	4.85	
k_1	=	559 ± 27	(L/M/MIN)
C	=	166.06	$k_3K/k_2 = 8.42 \times 10^{-8}$
<hr/>			
k'_1	=	3.33 ± 0.16	(L/M/MIN)
C'	=	6.022×10^{-3}	$k'_2K/k'_3 = 8.42 \times 10^{-8}$

Correlation Coefficient = 0.991

At this point we shall assemble the relevant calculated parameters into a single table for more convenient referral. This is Table XVIII.

TABLE XVIII

Compound	pH _{max}	pKa	k ₁	k' ₁	k ₃ K/k ₂ (k' ₂ K/k' ₃)
XIV(H ₂ O)	6.020	4.70	315	0.730	4.61 x 10 ⁻⁸
XIV(D ₂ O)	6.378	4.96	288	0.416	1.59 x 10 ⁻⁸
X	5.964	4.85	559	3.33	8.42 x 10 ⁻⁸

The difference in the value of pH_{max} between Compound XIV in protium oxide and deuterium oxide is of some importance. This is so because the value of pH_{max} in each case is derived from the experimental numbers quite irrespective of mechanistic assumptions. Admittedly the values of pH_{max} in Table XVIII are determined by a mathematical procedure involving an assumption of mechanism but these values do not vary significantly from those that would be obtained from an inspection of Figures XIX and XVIII. The difference is 0.358. If we consider the expression derived previously, in connection with Reaction Scheme I, which relates pH_{max} to the equilibrium constants and rate constants in that reaction sequence we have

$$\text{pH}_{\text{max}} = \frac{1}{2} \log(k_2/k_3 K K_a) \quad .$$

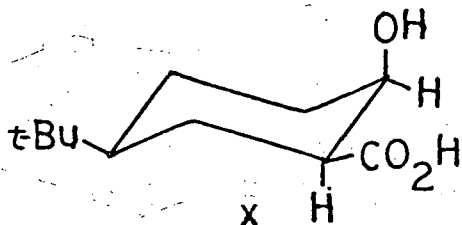
On the assumption that k₂ and k₃ are not subject to a deuterium solvent isotope effect we are left to consider the two ionization constants K and K_a. The effect on acid strength of changing from protium oxide to deuterium oxide is well-documented⁶³ to be a weakening on by a factor of from two to three. Considering the above expression then, we would expect

the pH_{max} to be greater in deuterium oxide by about 0.30 to 0.47. Thus it can be said that the expression derived from Reaction Scheme I predicts the direction and roughly the magnitude of the shift in pH_{max} on changing from protium oxide to deuterium oxide. Of course, the corresponding expression derived from Reaction Scheme II, having the same mathematical form, predicts exactly the same thing.

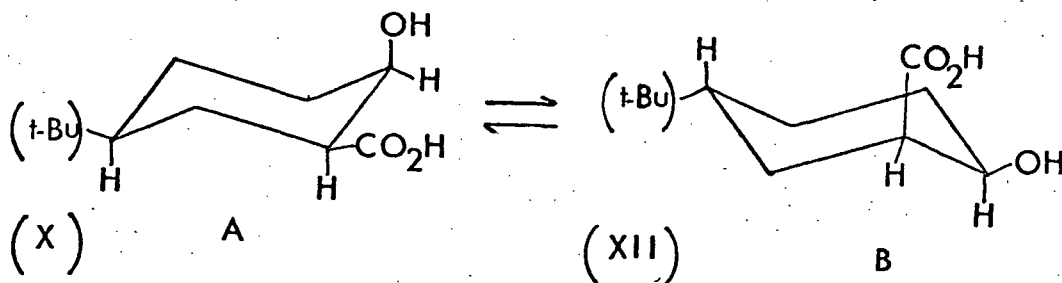
The values of k_1 and k'_1 and the deuterium isotope effect have already been mentioned. The fact that $k_1(\text{H}_2\text{O})/k_1(\text{D}_2\text{O})$ is 1.09 while $k'_1(\text{H}_2\text{O})/k'_1(\text{D}_2\text{O})$ is 1.75 is probably informative. In view of considerable work on solvolysis reactions in both deuterium and protium oxides⁶⁴, it is safe to say that processes which do not involve proton or deutron exchange and which do not involve the solvent (other than its role as such) do not have deuterium solvent isotope effects significantly different from one. In the present context we might say that anywhere from 0.8 to 1.2 is not significantly different from unity. In other contexts these small observed differences, usually obtained from very precise measurements, are of course significant and worthy of careful scrutiny. The nature of the step described by k_1 or k'_1 is such that it is unlikely to be influenced by a solvent change from protium oxide to deuterium oxide. No protons are involved and the solvent presumably plays only

a solvation role. As a consequence of the large value of $k'_1(\text{H}_2\text{O})/k'_1(\text{D}_2\text{O})$, derived from analysis of the experimental data, Reaction Scheme II would appear to be discredited in favour of Reaction Scheme I for which $k_1(\text{H}_2\text{O})/k_1(\text{D}_2\text{O})$ is near unity.

As a means of differentiating between Reaction Scheme I and Reaction Scheme II the data for compound X are pertinent. It must be recognized that compound X is fixed in a single conformation because of the presence of the t-butyl group. Its conformation is described, as before, by X.

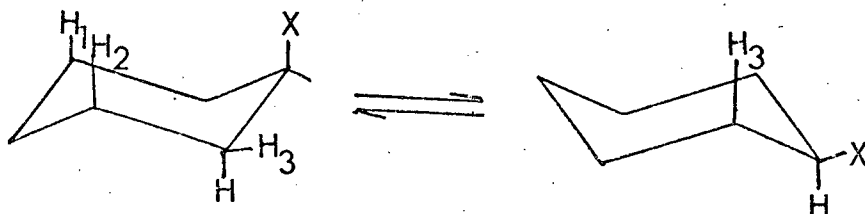


Cis-2-hydroxycyclohexanecarboxylic acid (XIV), although favouring one conformation more than another, is not constrained in the same way, the conformational equilibrium can be represented in the following way:



The experimental results for compound XII indicate that a compound fixed in a configuration of the kind represented by B does not exhibit the bell-shape pH-rate profile under consideration. On the other hand the data for compound X indicate that a conformation like A does give this effect.

This indicates that as far as the bell-shape profile is concerned conformation A is reactive and conformation B is inert. An estimate of the fraction of compound XIV which exists as A and B is now required. This can be done from a consideration of the conformational energies of the hydroxyl and carboxyl groups. The conformational energy⁶⁵ of a substituent X is defined as $-\Delta G^{\circ}$ of the following process:



To use conformational energies in considering di-substituted cyclohexanes would then seem to be quite incorrect. In the present case it cannot be a very bad approximation however. The conformational energy of X is determined by its steric interactions with the hydrogens marked 1, 2 and 3. The disposition of X towards hydrogen 3 is the same in both conformations so that replacement of it by some other group should not prevent us from considering the conformational energies of the two groups separately. This is, of course, provided that the repulsion between the two cis substituents is not so great that the molecule is distorted. This state of affairs comes about because of the symmetry of cis-1,2-disubstituted cyclohexanes. Because the two substituents

are disposed similarly towards each other in both conformations many effects cancel. The same is not true of the trans isomer. This being the case, from a knowledge of the conformational energies of $-OH$, $-CO_2H$ and $-CO_2^-$ we can estimate the fraction of compound existing as A or B or the anions obtainable from these (A^- or B^-).

In Reaction Scheme I the value of k_1 includes only unionized substrate as reactant. If that part of the unionized substrate in conformation B does not participate in the reaction the value of k_1 is reduced*. The factor by which it is reduced is $[A]/([A] + [B])$. This factor can be calculated once values for the conformational energies are obtained. The values used here are the "best values" given in the compilation of conformational energies made by Hirsch⁶⁵ ($-OH = 0.87$ Kcal/mole; $-CO_2H = 1.35$ Kcal/mole; $-CO_2^- = 1.92$ Kcal) as they seem most appropriate to the present experimental conditions. An array of values^{65,66,67} does exist however which makes the estimation something of an approximation.

The above conformational energies give a value of 0.690 for the ratio $[A]/([A] + [B])$. It was mentioned that the value of k_1 was reduced by this factor for compound XIV but was not in the case of compound X. This

* The value of k_1 is lower than expectation because all unionized substrate is regarded as reactive, while only that part of the unionized substrate in conformation A is in fact reactive. This is not the case for compound X however.

would mean that the following relationship should hold

$$17. \quad \frac{k_1(\text{XIV})}{k_1(\text{X})} = \frac{[\text{A}]}{[\text{A}] + [\text{B}]}$$

The value of $k_1(\text{XIV})/k_1(\text{X})$ is 0.565 ± 0.072 . This value is sufficiently close to that calculated from conformational energies to say that agreement exists.

In the case of Reaction Scheme II we are dealing with the anions of the acids considered in Reaction Scheme I. The ratio $[\text{A}^-]/([\text{A}^-] + [\text{B}^-])$ is 0.85, calculated from the conformational energies. The ratio $k'_1(\text{XIV})/k'_1(\text{X})$ is 0.22. There is no reasonable adjustment of the conformational energies that can be made to give this figure. Even if this were possible, the NMR information tells quite convincingly that A or A^- is the predominant conformation making 0.22 appear a patently incorrect evaluation of the conformational equilibrium constant. Thus Reaction Scheme I appears to be the more valid from a comparison of the reactivities of compounds XIV and X.

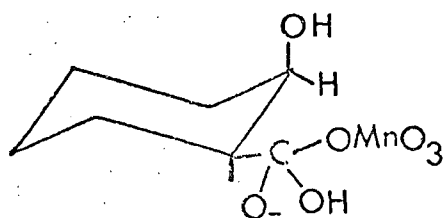
Nature of the Intermediate

Before considering the structure of the intermediate it should be pointed out that such a species has not been directly observed. The visible spectrum of permanganate does not change in any way as a result of addition of any of the substrates associated with bell-shape pH-rate profiles-other than to

diminish with time. The steady-state assumption, besides requiring that the concentration of intermediate does not change with time usually carries the added implication of low concentration⁵⁶.

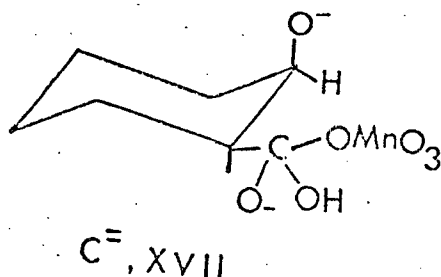
The NMR spectrum of XIV was recorded in deuterium oxide at pD 6 and 2. The two spectra were virtually identical to that of Figure XXII, except for a slight shift towards higher field of the spectrum at pD 6 relative to that at pD 2.

It is clear from the disparity between the pH-rate profiles for cyclohexanol and cis-2-hydroxycyclohexanecarboxylic acid (XIV) that the carboxyl group is implicated mechanistically. This consideration and the behaviour shown by the three isomers bearing a t-butyl substituent specifies more precisely the role that conformation plays in the reaction. With this in mind a more exact mechanistic view can be provided in terms of Reaction Scheme I. The first step of importance is the formation of the species C^- from the neutral alcohol and permanganate ion. The intermediate C^- may be represented by structure XVI,



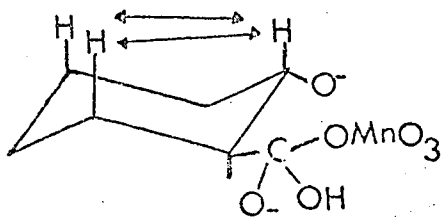
C^- , XVI

in which the permanganate ion has intruded into the carboxyl group. A complex similar to this in which permanganate ion adds to a carboxyl has been considered in the case of formate oxidation⁶⁸. (It can be seen that the "permanganate ion" in XVI is favourably placed with regard to the hydrogen which must be removed during the rate controlling step of the oxidation. The data of Figures XVIII and XX show that a sufficiently large deuterium isotope effect operates ($k_H/k_D = 6.6$) in the vicinity of pH_{max} to justify the conclusion that this hydrogen is removed in the rate controlling step.) The following step indicated in Reaction Scheme I is the dissociation of C^- to give $C^=$. The scheme also requires that $C^=$ be considerably more reactive than C^- . There are in C^- only two protons at all likely to be removed in a dissociation step. One of these is attached to an oxygen atom which has a negative charge very close by; the other is part of the alcoholic OH. If this latter proton is removed, $C^=$ would then be XVII.



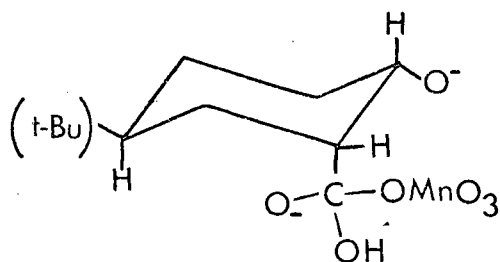
In XVII, the hydrogen to be removed in the rate controlling step is activated towards oxidation by being part of an alkoxide ion. The rate enhancing influence of alcohol ionization has been laboured sufficiently in the introduction of this thesis to show that $C^=$ would necessarily be significantly more reactive than C^- , given the structures XVI and XVII^{1,2,5}.

In terms of the intermediate structures presented, the role of conformation in the reaction becomes explicable. For compound XV the intermediate equivalent to $C^=$ would be -



The removal of the appropriate hydrogen atom in the transition state would involve surmounting steric interactions of the kind indicated in the above figure. Compound XV, in Figure XVIII, does show a very slight maximum around pH 6. This behaviour may be due to a minute contamination with compound XIV or it may be real. In either case it indicates that an intermediate of compound XV of type $C^=$ is less likely to proceed to products than an isomeric intermediate of compound XIV.

Compound XII and the B conformation of compound XIV are conformationally identical. The corresponding $C^{\equiv-}$ type intermediate would be as follows

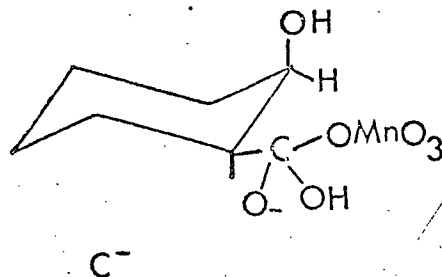
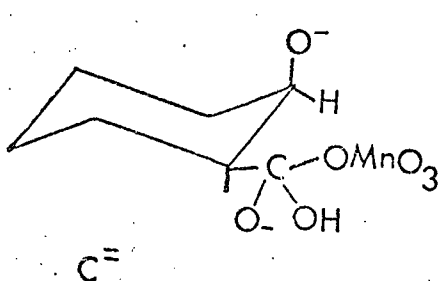


in which it appears physically impossible for this intermediate to react by removal of the required hydrogen atom. As well as being unable to react in the necessary manner, this intermediate would be of high energy relative to a similar intermediate with the complexed carboxyl group in the equatorial position.

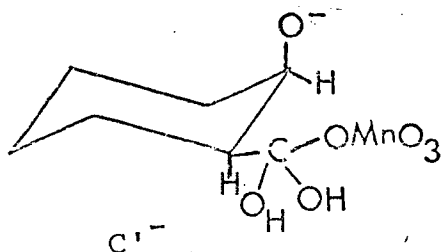
Thus both in terms of the conformational data for these compounds and the known high reactivity of alkoxide ion the intermediates $C^{\equiv-}$ and C^{\equiv} and Reaction Scheme I may be said to be consistent.

Earlier Reaction Scheme II was found to be discredited on several counts. It is found that the proposed structures for $C^{\equiv-}$ and C^{\equiv} cause difficulties in terms of this scheme. The difficulty comes from the fact that the intermediates have the same structure in both reaction schemes-but for Reaction Scheme II it becomes necessary to

reverse the previous decision as to which is the more reactive.



It is not easy to imagine C^- being more reactive than $C=$ as they are represented above. However C^- may not exist as drawn but as C'^-



in which case an argument can be made in favour of C'^- being more reactive than $C=$. In such an argument it would be observed that $HMnO_4$ is a considerably more reactive species than MnO_4^- ^{1,5} and that the manganese containing moiety in C'^- resembles the former more than does the manganese containing moiety in $C=$. A distinction between the two reaction schemes might be difficult if the only consideration was the structure of the intermediates necessary to rationalize them. However, with the evidence presented previously it would appear that Reaction Scheme I and intermediates $C=$

and C^- are more in accord with the total results than Reaction Scheme II and intermediates $C^=$ and C^- or C'^- .

Dissociation Constants

The dissociation constant of cis-2-hydroxycyclohexanecarboxylic acid has been determined under conditions of ionic strength directly comparable to that used in the present work⁵¹. The value of the pK is 4.80. This value is to be compared to the corresponding value (4.70) necessitated by the treatment of the kinetic data according to Reaction Schemes I and II. A comparison with the work of Zerner and Bender²³ indicates that this agreement between indirect kinetic determination and direct determination is quite good. The agreement indeed, argues quite forcefully that the ionization of the acid is important in determining the overall kinetic character of the oxidation. Were this not the case agreement referred to would be quite diabolical.

The pK required by the kinetic analysis for cis-2-hydroxycyclohexanecarboxylic acid in deuterium oxide is, as expected⁷⁹, larger than the corresponding value found in protium oxide. The limit of error which should be placed on this pK difference is quite uncertain. In any event, the difference is of the right order.

The pK(4.85) of cis-5-t-butyl-cis-2-hydroxycyclohexanecarboxylic acid (X) is not exactly as might be expected. The work of Stolow⁹³ clearly indicates that, in

cyclohexanecarboxylic acids, the equatorial carboxyl group is more acidic than the axial carboxyl group by about 0.4 pK units. Cis-2-hydroxycyclohexanecarboxylic acid (pK = 4.70) has a conformation with the carboxyl group in the axial position in which, according to our previous calculation, it spends about 30% of its time. Freezing the molecule in the more acidic conformation (by the introduction of a t-butyl group) would lower the pK by 0.1 units. This assumes that the pK difference between an axial carboxyl and an equatorial carboxyl is 0.4. Consequently the pK of compound X is slightly higher than expectation. The discrepancy, however, is slight.

Variation of Buffer Concentration

Because the actual composition of the buffer alters considerably in the pH range studied (although not the ionic strength) and the second ionization constant of 0-phosphoric acid is near the pH_{max} value ($\text{pK}_2 = 7.12$), it was considered necessary to carry out some oxidation runs at various buffer concentrations. Table VIII shows that at pH 5.88 the second order rate constant for the oxidation of compound XIV remains constant over a five-fold change in buffer concentration. Thus, effects due to the buffer (e.g. general base catalysis) are not important.

Activation Parameters

Enthalpies and entropies of activation for cis-2-hydroxycyclohexanecarboxylic acid at three pH values (2.00, 5.88, 10.38) are given in Table XIV. To this can be added the values determined by Barter and Littler⁴ for cyclohexanol at pH 4.6 ($\Delta H^\ddagger = 14.0 \pm 0.4$ Kcal/mole, $\Delta S^\ddagger = -23.3 \pm 1.2$ eu). At first glance it is evident that the parameters for compound XIV at pH 2.00 are similar to those for cyclohexanol at pH 4.6. This is an expected

result since both sets of parameters refer to the oxidation of a neutral cyclohexanol under conditions in which the "neutral" reaction is occurring. In the case of compound XIV, the reaction at pH 2.00 is as far away from the bell-shape behaviour as is experimentally feasible, without being in the region in which catalysis by strong acids takes place.

The activation parameters determined at pH 5.88, which are significantly different from those at pH 2.00, are not easy to interpret. Before considering these quantities some comments concerning their validity should be voiced. The oxidation experiments were carried out at all temperatures using the same buffer stock solution diluted appropriately by the solutions of reactants. The pH of the reaction mixture was 5.88 at 25°C. At all other temperatures (5°C to 35°C) the pH of the medium would be subject to a temperature effect on the buffer system. The data tabulated by Robinson and Stokes⁶⁹ for solutions 0.025M in both K_2HPO_4 and NaH_2PO_4 (pH = 6.860 at 25°C) indicate that the total change in pH between 5°C and 35°C should be about 0.10 pH-units. The small standard error in the activation parameters probably means that this small pH change is of no consequence.

A change in pH_{max} with temperature would tend to invalidate the measurement as well but again the small standard error in the calculated activation probably means that this is not the case. A significant change in pH_{max} with temperature

would place the position of rate measurement on the steep slope of the bell-shape curve and the resulting $\log(k/T)$ against I/T plot would show curvature or be otherwise badly behaved. That this is not the case indicates that pH_{max} changes but slightly in the temperature range considered.

The value of $k_{\text{OBS (max)}}$ can be related both to k_1 and k'_1 . The two equations are

$$k_{\text{OBS (max)}} = \frac{k_1}{\left(1 + \frac{k_a}{[\text{H}^+]_{\text{max}}}\right)^2}$$

and

$$k_{\text{OBS (max)}} = \frac{k'_1}{\left(1 + \frac{[\text{H}^+]_{\text{max}}}{K_a}\right)^2}$$

If it is assumed that K_a is not very temperature dependent, it is possible to calculate activation parameters corresponding to steps k_1 and k'_1 . This assumption is acceptable if one considers the temperature dependence of the $\text{pK}'\text{s}$ of organic acids tabulated by Robinson and Stokes⁷⁰.

The squared term in the second equation is very close to unity so that the activation parameters for this step are nearly the same as those determined for the overall

reaction. The parameters corresponding to k_1 have been calculated and are given in Table XIX along with the other values relevant to this discussion.

TABLE XIX

cis-2-hydroxycyclohexanecarboxylic acid

Activation Parameters pH 5.88

	Overall Reaction	k'_1 step	k_1 step
ΔH^\ddagger (Kcal/ $^\circ$ mole)	15.9	15.9	14.7 ± 0.4
ΔS^\ddagger (eu)	-13.9	-13.9	-5.3 ± 1.1

According to Reaction Scheme I the step described by k_1 is the formation of an intermediate from permanganate ion and unionized substrate. The step described by k'_1 refers to the formation of an intermediate from permanganate ion and substrate anion. Disregarding the actual magnitude of the entropies for the moment it can be said that the entropy for the k_1 step should be more positive than the entropy for the k'_1 step by an amount equal to the contribution from electrostatic repulsions between the reacting ions⁷¹. This figure is regarded as about 20 eu but is obtained from substantial approximations⁵⁶. Both entropy values may be considered, relative to one another, in accord with expectation. Of course it should not be forgotten that Scheme I and Scheme II

are mutually exclusive. Either the reaction step corresponding to k'_1 is fictitious or that corresponding to k_1 is.

The absolute value of these calculated parameters is another matter. A diligent perusal of the literature for activation parameters of reactions reasonably similar to steps k_1 and k'_1 reveals a very wide spread. Basic hydrolysis of esters, basic hydrolysis of aryl sulfonyl chlorides⁷² and nucleophilic substitution reactions (S_N2) of various kinds^{73,74} possess activation parameters (in water) which are exceedingly dependent on substrate structure and substitution. In the face of this it would be futile to try to decide which set of activation parameters is the more realistic.

A comparison of the activation parameters at pH = 5.88 with those at pH 2.00 shows that the faster reaction has a much higher activation enthalpy (3.8 Kcal) but this is counteracted by a much less negative entropy of activation (13.9 eu). It is difficult to comment on the actual magnitude of these parameters. The reaction at pH 5.88 is complicated by several steps prior to the rate controlling step, all of which will have some influence on the entropy and enthalpy. The entropy of activation at pH 2.00 is not unusual and compares with values already determined⁴.

The activation parameters at pH 10.38 are similar to those at pH 5.88. This is probably a coincidence. One would expect the parameters at pH 10.38 to be similar to those at pH 2.00. That they are not probably indicates that at pH 10.38 the neutral reaction is not the only reaction taking place. The rate at higher pH's is found to depend on the first power of the hydroxide ion concentration. At pH 10.38 this base assisted reaction may be taking place along with the neutral reaction to give the observed activation parameters. This would render the determined values quite meaningless.

There are several studies in the literature dealing with the permanganate oxidation of hydroxy substituted carboxylic acids^{75,76,77}. Bakore and Rama Shankar have studied the oxidation of citric acid, tartaric acid and mandelic acids in weakly acidic solutions (pH = 2 to 4). These authors present evidence for complex formation between permanganate and tartrate ion, and permanganate and citrate ion. It is clear, however, from the evidence presented by these workers that such oxidations are not related closely to the present work. Firstly they consider α -hydroxy acids while in the present case β -hydroxy acids are involved. The stoichiometry of the reactions is quite dissimilar - the

manganese product is Mn(II) and the organic products include carbon dioxide. The reactions are very strongly autocatalytic necessitating the evaluation of initial slopes to obtain kinetic data. The present work involves quite different behaviour.

There does not appear to be any observation of a "bell-shape" pH-rate profile dealing with an oxidation between a transition metal ion and an organic substrate other than as has been reported herein.

The structures proposed for the intermediates do not involve the formation of permanganate esters. This possibility was considered unlikely because of what is known about permanganate oxidations, because of the difficulty in conforming such a possibility with the reaction schemes necessary to give the observed behaviour and because of the difficulty with which permanganate ion exchanges its oxygen with solvent⁷⁸.

Summary

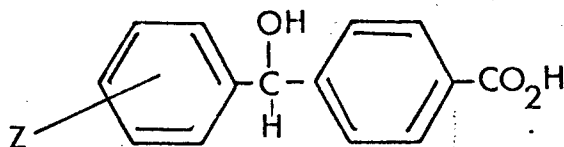
The data for the oxidation of compound XIV in water and deuterium oxide, and compound X in water were found amenable to treatment in terms of a kinetic scheme involving two acid ionization equilibria. Two mechanistic schemes were proposed and the data were discussed with regard to distinguishing between them. The structure of the intermediate proposed was consistent with the oxidation

behaviour of different conformations, as well as the behaviour of compound XIV in deuterium oxide. The distinction between hydride-transfer and hydrogen atom transfer in the rate controlling step does not enter these considerations and the results presented herein do not impinge upon this problem.

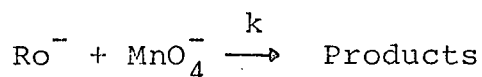
SUGGESTIONS FOR FURTHER WORK

The decision between hydride-transfer and hydrogen-atom transfer in permanganate oxidations has been a subject for speculation^{2,7,16} since the substituent-effect work of Stewart and Van der Linden. Because the ρ value for borohydride reduction of substituted acetophenones⁹⁰ and fluorenones⁹¹ is about +2 it was anticipated that the removal of hydride should involve a similar ρ with changed sign.⁸ The results for the oxidation of aryltrifluoromethyl carbinols did not bear this out. To distinguish between a legitimate result and a special effect caused by the proximity of the $-\text{CF}_3$ group to the reacting centre it might prove fruitful to study the borohydride reduction of α,α,α -trifluoroacetophenone. The interpretation of the oxidation results might then be clear.

Attempts have been made to evaluate substituent effects for permanganate oxidation in basic solution⁹² but failed because of solubility difficulties. This difficulty could be surmounted by using a benzhydrol of the following composition -



The ionized carboxyl group would provide reasonable solubility and the substituents could be varied in the other ring. A plot of the experimental rate constant versus hydroxide ion concentration such as is given in Figure V. would enable one to determine kK from the slope. The product kK comes from the following reaction sequence



It should be simple to separate the effect of substituents for the ionization of the alcohol from the experimental results to give the effect for the rate controlling step. In fact the ρ value for the ionization of aryltrifluoromethyl carbinols⁷ is known to be very close to 1.

OBSERVATIONS

In the Introduction the deuterium isotope effect determined in the permanganate oxidation of phenyl trifluoromethyl carbinol was mentioned². One explanation of this large effect ($k_H/k_D = 16$, at 25°C) was proton-tunnelling^{2,80}. This point will now be considered further.

To say that proton-tunnelling accounts for the large isotope effect is to imply that tunnelling is more significant for the protium containing compound than for the deuterio compound⁶³. The consequence of this is to make k_H "unnaturally" large thereby making k_H/k_D larger than it would be in the absence of tunnelling.

Current theories^{63,80} are quite explicit as to the observations which may be interpreted in terms of proton-tunnelling. If the activation energy for the reaction of the protio compound becomes smaller as the temperature is lowered - i.e. the plot of $\log k$ against $1/T$ shows a curvature which tends to make the curve parallel to the $1/T$ axis at low temperatures, this is considered the best evidence for proton tunnelling. In solution work, there is only one case in which such an effect has been found⁸¹. Bell's thorough discussion of the subject indicates that for the narrow temperature ranges available for temperature studies in condensed phases, (most of the relevant work was done in water or ethanol) it

appears unlikely that most reactions which involve proton-tunnelling would show any curvature at all in their Arrhenius plots.

Bell's account of proton-tunnelling leads to a criterion much less stringent than the one just considered. He has been able to set certain limits for the behaviour of the pre-exponential term of the Arrhenius equation on isotopic substitution. When no proton-tunnelling is involved the limits are: $1/\sqrt{2} \geq A_D/A_H \geq 2$. Experimental evaluation of values for this ratio outside these limits provides some justification for the involvement of proton-tunnelling, according to Bell's analysis.

There are two rather significant pieces of experimental work which support this conclusion. The bromination⁸² of 2-carbomethoxycyclopentanone catalyzed by a variety of bases was found to have a A_D/A_H ratio greater than 2 in all the cases studied. In the instance of catalysis of fluoride the value of the ratio is 24, much greater than for the other base catalysts. Hulett later showed,⁸¹ using a larger temperature range than originally considered, that the Arrhenius plot for this reaction with fluoride ion catalyst is curved, in the manner considered above, at lower temperatures. This study and the one to be mentioned next are the result of very careful experimentation and the data cannot be discredited by invoking experimental error.

If the criterion mentioned above is correct, in the absence of tunnelling the ratio of A factors should be within the prescribed range. Shiner and Smith⁸³, and Shiner and Martin⁸⁴ determined the ratios A_D/A_H and A_T/A_D for the ethoxide promoted elimination reaction of 1-bromo-2-phenylpropane. The value of A_D/A_H was 2.53, close to the limit of 2 but within experimental error greater than 2. For the elimination involving deuterium and tritium it is very unlikely that tunnelling is taking place. This, according to Bell's theory, would necessitate having A_T/A_D within the prescribed limits. In fact A_T/A_D is 1.19 bearing out the theoretical predictions. Shiner and Martin have voiced the opinion that these results constitute important support for the theories advanced by Bell. Indeed their results show that A_D/A_H does not vary capriciously but really in accordance with theory.

The two examples considered above do not have large primary isotope effects. In the work of Bell, Fendley and Hulett the k_H/k_D values are from 2 to 3. In the work of Shiner and Smith k_H/k_D at 25°C is 7.8.

The isotope effect for the permanganate oxidation of formate ion is 9.2. A careful kinetic study by Bell and Onwood⁸⁵ revealed A_D/A_H to be 1.12. This might lead

to the conclusion that the limits placed on the permissible variation of A_D/A_H in the absence of tunnelling are too generous and that a value of unity is more likely in solution. This conclusion however would be based on only two pieces of evidence.

For the permanganate oxidation of phenyltrifluoromethyl carbinol the value of A_D/A_H is $3.4^{+1.2}$. Admittedly the standard error in this quantity is large but the ratio is still greater than 2. The conclusion based on what has preceded this is clear. The large isotope effect (16.2 at 25°C) is at least partly accounted for by proton-tunnelling.

This discussion would not be complete without a consideration of the work of Lewis and Robinson⁸⁶. These authors take as a basis from which to attack the question of proton tunnelling what has become known as the Swain equation.

$$k_H/k_T = (k_H/k_D)^{1.442}$$

The Swain equation⁸⁷ was derived without considering tunnelling and the ability of the equation to deal with tunnelling is explored. It would appear from their results that in cases where tunnelling is extensive (A_D/A_H is large) the Swain equation does not hold exactly true. Deviations appear to lead to a conclusion of tunnelling being important but such deviations do not readily occur. In connection with this

the work of Shiner and Martin, in which the values of A_H/A_D and A_D/A_T give clear evidence of tunnelling, shows rather exact agreement with the Swain equation⁸⁴. Lewis and Robinson determined k_H/k_T for the permanganate oxidation of phenyltrifluoromethyl carbinol and find the Swain equation accurately relating k_H/k_D to k_H/k_T . In the light of their conclusions regarding the Swain equation this result neither takes away from nor adds to the previous considerations.

Clearly a great deal more work is required if we are to understand the subtleties of proton tunnelling and its importance in chemical reactions: In accordance with the present understanding of the subject the conclusion made above concerning the permanganate oxidation of phenyltrifluoromethyl carbinol appears justified.

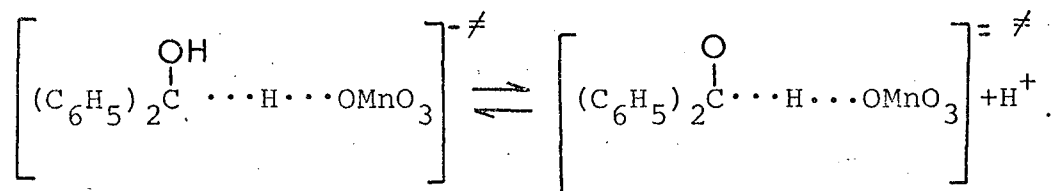
The "Transition State Characterization" theory of Kurz^{17,18} was considered in the Introduction as it was applied to the fluoral hydrate oxidation by Kurz himself. It appears possible to attack the permanganate oxidation of benzhydrol in the same way. Benzhydrol reacts in neutral solution in an acid independent reaction but the reaction is base catalyzed in solutions with pH exceeding ~11.5 11.

The appropriate equation to use is Equation 5.b., where in this case k_1 refers to the bimolecular reaction between permanganate and benzhydrol and k_2 is a third order rate constant for the base catalyzed reaction. That is

$$\text{Rate} = k_1 [\text{H}_2\text{Z}] [\text{MnO}_4^-]$$

$$\text{Rate} = k_2 [\text{OH}^-] [\text{MnO}_4^-] [\text{H}_2\text{Z}]$$

The values for k_1 and k_2^9 give 11.3 for pK_a^\ddagger . This pK_a^\ddagger refers to the following equilibrium



For a hydride transfer reaction 0% bond formation would result in the above equilibrium resembling the ionization of benzhydrol itself ($\text{pK} \sim 16$)¹². At 100% reaction the equilibrium resembles the deprotonation of the conjugate acid of benzophenone ($\text{pK}_{\text{BH}^+} = -6.2$)¹³. A hydrogen atom transfer mechanism would lead to the ketyl radical at 100% reaction ($\text{pK} = 9.2$)¹¹. If the correction to pK_a^\ddagger suggested by Kurz is applied, the result is 29% C-H bond breaking for hydride transfer and 89% for hydrogen atom transfer. The computed pK_a^\ddagger appears to be in accord with both mechanisms.

If one considers the magnitude of the deuterium isotope effect which has been observed for this reaction, a conclusion concerning which mechanism is the more probable can be reached. According to theory⁸⁸ the value of the deuterium isotope effect should reach its maximum value when the hydrogen (or deuterium) is half-transferred in the transition state. This conclusion follows from the

simple theory which describes the isotope effect as originating from the difference in the zero-point energy between the C-H and C-D stretching vibrations.

It has been noted above that large isotope effects occur with fluorinated alcohols^{2,5} and some remarks have been made concerning the interpretation these observations may be given. Alcohols which do not contain fluorine appear to exhibit smaller isotope effects.^{1,3} If it is granted that the isotope effect (Δ) found in the permanganate oxidation of benzhydrol is near its maximum value, then at the same time it must also be granted that the amount of bond-breaking afforded by the hydride-transfer mechanism is more appropriate to this state of affairs than is that which corresponds to a hydrogen-atom transfer mechanism.

The enthalpy of activation for benzhydrol oxidation is quite small^{1,9}. At pH 13 it is 5.6 Kcal/^omole and at pH 7 it is 5.7 Kcal/^omole. In view of the facility of permanganate oxidations and considering the "Hammond Postulate"⁸⁹ it might be concluded that the transition state for the permanganate oxidation of benzhydrol is more reactant-like than product-like. Combining this conclusion with the conclusion relating to the isotope effect in this reaction leads to the favouring of a hydride-transfer mechanism as the more likely alternative.

Bibliography

1. Ross Stewart, J. Am. Chem. Soc. 79, 3057 (1957).
2. Ross Stewart and R. Van der Linden, Discussions Faraday Soc. No. 29, 211 (1960).
3. J.S. Littler, J. Chem. Soc. 2190 (1962).
4. R.M. Barter and J.S. Littler, J. Chem. Soc. B, 205 (1967).
5. Ross Stewart and Michael M. Mocek, Can. J. Chem. 41, 1160 (1963).
6. Fariza Banoo and Ross Stewart, Can. J. Chem. 47, 3199 (1969).
7. Ross Stewart, in Oxidation in Organic Chemistry, Part A, ed. K.B. Wiberg, Academic Press Inc., New York, 1965.
8. R. Van der Linden, Ph.D. Thesis, University of British Columbia, 1960.
9. Fariza Banoo, Ph.D. Thesis, University of British Columbia, 1969.
10. J.S.F. Pode and W.A. Waters, J. Chem. Soc. 717 (1956).
11. G. Porter and F. Wilkinson, Trans. Faraday Soc. 57, 1686 (1961).
12. P. Ballinger and F.A. Long, J. Am. Chem. Soc. 82, 795 (1960).
13. Ross Stewart, M.R. Granger, R.B. Moodie and L.J. Muenster, Can. J. Chem. 41, 1065 (1963).
14. F.R. Duke, J. Phys. Chem. 56, 882 (1952).
15. C.K. Rule and V.K. La Mer, J. Am. Chem. Soc. 60, 1974 (1938).
16. J. Rocek, Oxidation of aldehydes by transition metals, from the Chemistry of the Carbonyl Group, ed. Saul Patai, Interscience, 1966.
17. J.L. Kurz, J. Am. Chem. Soc. 85, 987 (1963).
18. J.L. Kurz, J. Am. Chem. Soc. 86, 2229 (1964).
19. B. Capon, Quart. Revs. 15, 45 (1964).
20. W.P. Jencks, Catalysis in Chemistry and Enzymology, McGraw-Hill Book Company, Inc., 1969.

21. T.C. Bruice and S.J. Benkovic, Bioorganic Mechanisms, Vol. 1, W.A. Benjamin, Inc., New York, 1966.
22. E.F. Caldin and J.H. Wolfenden, J. Chem. Soc. 1239 (1936).
23. B. Zerner and M.L. Bender, J. Am. Chem. Soc. 83, 2267 (1961).
24. K.B. Wiberg and Ross Stewart, J. Am. Chem. Soc. 77, 1786 (1955).
25. S. Glasstone, K.J. Laidler and Henry Eyring, the Theory of Rate Processes, McGraw-Hill Book Company, Inc., New York, 1941.
26. K.B. Wiberg, Physical Organic Chemistry, John Wiley & Sons, Inc., 1964.
27. Arthur I. Vogel, A. Text-Book of Practical Organic Chemistry, 3rd ed. Longmans, Green and Co. Ltd., 1956.
28. Resinger and Thompson, Rec. trav. chim. 82(8), 801 (1953).
29. Handbook of Chemistry and Physics, 43rd ed., the Chemical Rubber Publishing Co., 1961-62.
30. Dictionary of Organic Compounds, 4th ed., Oxford University Press, 1965.
31. J. Pascual, J. Sistare, and J. Regas, J. Chem. Soc., 1943 (1949).
32. J. Sicher, F. Sipos, and M. Tichy, Collection Czech. Chem. Commun. 26, 847 (1961).
33. Inorganic Isotopic Syntheses, Rolf H. Herber ed., W.A. Benjamin, Inc., New York, 1962.
34. Donald G. Lee, in Oxidation, Vol. 1, R.L. Augustine ed., Marcel Dekker, Inc., New York, 1969.
35. G. Kortüm, W. Vogel, and K. Andrussov, Dissociation Constants of Organic Acids in Aqueous Solution, Butterworths, London, 1961.
36. C.D. Ritchie and W.F. Sager, Progr. Phys. Org. Chem. 2, 323 (1964).
37. K.B. Wiberg and Ross Stewart, J. Am. Chem. Soc. 77, 1786 (1955).
38. J. Rocek, Ref. 16, p. 480.
39. D.D. Wheeler, D.C. Young, and D.S. Erley, J. Org. Chem. 22, 547 (1957).

40. J. Tirouflet, *Compt. rend.* 236, 1426 (1953).
41. G.B. Barlin and D.D. Perrin, *Quart. Revs.* XX, 75 (1966).
42. S. Racine, *Ber. deut. chem. Ges.* 19, 778 (1886).
43. D.S. Erley, W.J. Potts, P.R. Jones, and P.J. Desio, *Chem. & Ind.* (London) 1915 (1964).
44. P.R. Jones and S.L. Congdon, *J. Am. Chem. Soc.* 81, 4291 (1959).
45. P.R. Jones and A.A. Lavigne, *J. Org. Chem.* 25, 2020 (1960).
46. F.C. Tompkins, *Trans. Faraday Soc.* 39, 280 (1943).
47. R. Gary, R.G. Bates, and R.A. Robinson, *J. Phys. Chem.* 68, 3806 (1964).
48. Henry Dent Gardiner, William Henry Perkin, jun., and Hubert Watson, *Trans. Chemical Soc. Pt. II*, 1756 (1910).
49. J.A. Hirsch, *Topics in Stereochemistry* 1, 199 (1967).
50. Aksel A. Bothner-By, *Advan. Mag. Resonance*, 1, 195 (1965).
51. M. Kilpatrick and J.G. Morse, *J. Am. Chem. Soc.* 75, 1896 (1953).
52. J.C. Richer, A. Pilato, and E.L. Eliel, *Chem. & Ind.* (London) 2007 (1961).
53. Ref. 21, p. 4, ff
54. M. Dixon and E.C. Webb, *Enzymes*, Academic Press Inc., New York, 1964.
55. K.J. Laidler, *Chemical Kinetics of Enzyme Action*, Oxford University Press, 1958.
56. K.J. Laidler, *Chemical Kinetics*, 2nd ed., McGraw-Hill Book Company, 1965.
57. H. Morawetz and I. Oreskes, *J. Am. Chem. Soc.* 80, 2591 (1958).
58. R.B. Martin, S. Lowey, E.L. Elson, and John T. Edsall, *J. Am. Chem. Soc.* 81, 5089 (1959).
59. L. A. Cohen and W.M. Jones, *J. Am. Chem. Soc.* 82, 1907 (1960).
60. E.N. Oftedahl, Jr., *Ph.D. Thesis*, Northwestern University, 1964.
61. Rama K. Chaturvedi, Andrew E. MacMahon, and Gaston L. Schmir, *J. Am. Chem. Soc.* 89, 6984 (1967).

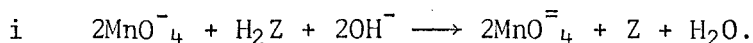
62. E. Högfeldt and J. Bigeleisen, J. Am. Chem. Soc. 82, 15 (1960).
63. R.P. Bell, The Proton in Chemistry, Cornell University Press, 1959.
64. R.E. Robertson, Progr. Phys. Org. Chem. 4, 213 (1967).
65. J.A. Hirsch, Topics in Stereochemistry 1, 199 (1967).
66. Michael Hanach, Conformation Theory, p. 103, Academic Press, 1965.
67. Ernest L. Eliel, Stereochemistry of Carbon Compounds, p. 236, McGraw-Hill Book Company, Inc., 1962.
68. K.B. Wiberg and Ross Stewart, J. Am. Chem. Soc. 78, 1214 (1956).
69. R.A. Robinson and R.H. Stokes, Electrolyte Solutions, Butterworths Scientific Publications, 1959.
70. Ref. 69, pp. 517 and 526.
71. L.L. Schaleger and F.A. Long, Advan. Phys. Org. Chem. 1, 1 (1963).
72. O. Rogne, J. Chem. Soc. B, 1294 (1968).
73. J. Miller, Aromatic Nucleophilic Substitution, Elsevier, 1968.
74. C.A. Bunton, Nucleophilic Substitution at a Saturated Carbon, Elsevier, 1964.
75. G.V. Bakore and Rama Shankar, Indian J. Chem. 1, 108 (1963).
76. G.V. Bakore and Rama Shankar, Indian J. Chem. 1, 268 (1963).
77. G.V. Bakore and Rama Shankar, Indian J. Chem. 1, 331 (1963).
78. J.C. Sheppard and Arthur C. Wahl, J. Am. Chem. Soc. 79, 1020 (1957).
79. Ref. 63, p. 188.
80. J.R.H. Hulett, Quart. Revs. 18, 227 (1964).
81. J.R. Hulett, J. Chem. Soc. 468 (1960).
82. R.P. Bell, J.A. Fendley, and J.R. Hulett, Proc. Royal Soc. 235, 453 (1956).
83. V.J. Shiner, Jr., and M.L. Smith, J. Am. Chem. Soc. 83, 593 (1961).

84. V.J. Shiner, Jr., and Brian Martin, *Pure and Applied Chemistry* 8, 371 (1964).
85. R.P. Bell and D.P. Onwood, *J. Chem. Soc. B*, 150 (1967).
86. E.S. Lewis and J.K. Robinson, *J. Am. Chem. Soc.* 90, 4337 (1968).
87. C.G. Swain, E.C. Stivers, J.F. Reuwer, Jr., and L.J. Schaad, *J. Am. Chem. Soc.* 80, 5885 (1958).
88. F.H. Westheimer, *Chem. Revs.* 61, 265 (1961).
89. G. Hammond, *J. Am. Chem. Soc.* 77, 334 (1955).
90. John A. Muzzio, Ph.D. Thesis, Purdue University, 1965.
91. G.G. Smith and R.P. Bayer, *Tetrahedron* 18, 323 (1962).
92. Michael M. Mocek, Ph.D. Thesis, University of British Columbia, 1962.
93. Robert D. Stolow, *J. Am. Chem. Soc.* 81, 5806 (1959).

APPENDIX A

The derivations of Equations 10. and 13. from the General Experimental section are presented here.

Equation 10. refers to the reaction in basic solution in which the stoichiometry is as follows--



The rate constant k is defined by Equation ii.

$$\text{ii} \quad - \frac{d[\text{MnO}_4^-]}{dt} = k[\text{MnO}_4^-][\text{H}_2\text{Z}]$$

If permanganate and substrate are initially present in the stoichiometric concentration ratio, a special integrated form of Equation ii is obtained, which is Equation 9. However, if the initial ratio, which will be called $1/a$, is not 2, a different integrated form results.

Beginning with Equation ii then, the rate may be expressed entirely in terms of the instantaneous permanganate concentration ($[\text{MnO}_4^-]$), the initial permanganate concentration ($[\text{MnO}_4^-]_0$) and a , where a has been defined as $[\text{H}_2\text{Z}]_0/[\text{MnO}_4^-]_0$. The result is Equation iii.

$$\text{iii} \quad - \frac{d[\text{MnO}_4^-]}{dt} = k[\text{MnO}_4^-] \left\{ a[\text{MnO}_4^-]_0 - \frac{1}{2} ([\text{MnO}_4^-]_0 - [\text{MnO}_4^-]) \right\}$$

Equation iii simplifies to iv.

$$\text{iv} \quad - \frac{d[\text{MnO}_4^-]}{dt} = \frac{1}{2} k[\text{MnO}_4^-] \left\{ [\text{MnO}_4^-] + (2a-1)[\text{MnO}_4^-]_0 \right\}$$

Integration of iv between the limits of $[\text{MnO}_4^-]_0$ to $[\text{MnO}_4^-]$ and $t = 0$ to t leads to Equation v.

$$\text{v} \quad \frac{1}{2}kt = \frac{1}{(2a-1)[\text{MnO}_4^-]_0} \ln \frac{[\text{MnO}_4^-] + (2a-1)[\text{MnO}_4^-]_0}{2a[\text{MnO}_4^-]}$$

The concentration terms within the logarithmic function in Equation v can be expressed in terms of the volume of thiosulfate needed to titrate an aliquot of the reaction mixture. Let us assume for simplicity that the volume of the aliquot and the thiosulfate concentration are unity,

since these factors will cancel out eventually. Bearing in mind that the analysis measures the oxidizing power of the solution for all manganese species above oxidation state two, we have at $t = 0$

$$\text{vi} \quad [\text{MnO}_4^-] = \frac{V_0}{5}.$$

At times other than the beginning of the reaction we must rely on the known stoichiometry to determine $[\text{MnO}_4^-]$. At time t the volume of titrant (V_t) is related to the composition of the solution by Equation vii.

$$\text{vii} \quad V_t = 5[\text{MnO}_4^-] + 4[\text{MnO}_4^{=}]$$

the manganate concentration ($[\text{MnO}_4^{=}]$) can be related to the concentration of permanganate by Equation viii.

$$\text{viii} \quad [\text{MnO}_4^{=}] = [\text{MnO}_4^-]_0 - [\text{MnO}_4^-]$$

Combining Equations vi, vii and viii to eliminate the manganate concentration gives finally Equation ix.

$$\text{ix} \quad [\text{MnO}_4^-] = V_0 - \frac{4}{5} V_t$$

Substitution of vi and ix into Equation v leads to Equation x.

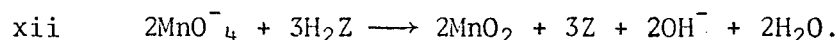
$$\text{x} \quad \frac{1}{2}kT = \frac{1}{(2a-1)[\text{MnO}_4^-]_0} \ln \left[\frac{V_t + V_0(2a-5)/5}{2a(V_t - \frac{4}{5}V_0)} \right]$$

Expressing Equation x in terms of the decadic logarithm and $[\text{H}_2\text{Z}]_0$ gives Equation xi after slight rearrangement.

$$\text{xi} \quad kt = \frac{4.606 a}{(2a-1)[\text{H}_2\text{Z}]_0} \log \left[\frac{V_t + V_0(2a-5)/5}{2a(V_t - \frac{4}{5}V_0)} \right]$$

Equation xi is identical to Equation 10, quoted in the General Experimental section.

Equation 13 is used when the following stoichiometry obtains:



Expressing Equation ii in terms of permanganate concentration, while considering the stoichiometry of Equation xii, gives Equation xiii.

$$\text{xiii} \quad \frac{-d[\text{MnO}^-_4]}{dt} = k[\text{MnO}^-_4] \left\{ a[\text{MnO}^-_4]_0 - \frac{3}{2} ([\text{MnO}^-_4]_0 - [\text{MnO}^-_4]) \right\}$$

Simplification of xiii gives xiv

$$\text{xiv} \quad \frac{-d[\text{MnO}^-_4]}{dt} = \frac{3}{2} k [\text{MnO}^-_4] \left\{ [\text{MnO}^-_4] + \left(\frac{2}{3}a - 1\right) [\text{MnO}^-_4]_0 \right\}$$

By integration of Equation xiv between the limits of $[\text{MnO}^-_4]_0$ to $[\text{MnO}^-_4]$ and $t = 0$ to t Equation xv is obtained.

$$\text{xv} \quad \frac{3}{2} kt = \frac{1}{(2a-1)[\text{MnO}^-_4]_0} \ln \frac{[\text{MnO}^-_4] + \frac{2}{(3a-1)}[\text{MnO}^-_4]_0}{\frac{2a}{3}[\text{MnO}^-_4]}$$

Again we have

$$\text{xvi} \quad [\text{MnO}^-_4] = \frac{V_0}{5}$$

and because of the new stoichiometry

$$\text{xvii} \quad V_t = 5[\text{MnO}^-_4] + 2[\text{MnO}_2]$$

and

$$\text{xviii} \quad [\text{MnO}_2] = (\text{MnO}^-_4) - [\text{MnO}^-_4] .$$

Eliminating $[\text{MnO}_2]$ from xvi, xvii and xviii leads to xix

$$\text{xix} \quad [\text{MnO}^-_4] = \frac{1}{3} (V_t - \frac{2}{5} V_0)$$

After substitution of xix and xvi into xv, Equation xx is obtained.

$$\text{xx} \quad \frac{3}{2} kt = \frac{1}{(2a-1)[\text{MnO}^-_4]_0} \ln \left[\frac{3}{2a} \cdot \frac{V_t + V_0(2a-5)/5}{V_t - 2V_0/5} \right]$$

Expressing xx in terms of $[\text{H}_2\text{Z}]_0$ and the decadic logarithm leads to Equation xxi after slight rearrangement.

$$\text{xxi.} \quad kt = \frac{4.606 a}{2a-3} \frac{1}{[\text{H}_2\text{Z}]_0} \log \left[\frac{3}{2a} \cdot \frac{V_t + V_0(2a-5)/5}{V_t - 2V_0/5} \right]$$

Equation xxi is Equation 13 considered in the General Experimental section.