

SOME MECHANISTIC STUDIES ON THE HYDROLYSIS OF ACETALS AND HEMIACETALS

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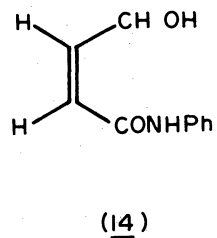
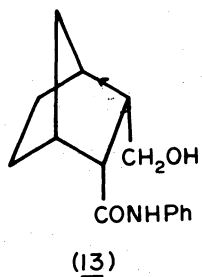
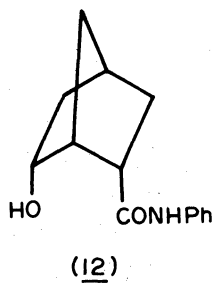
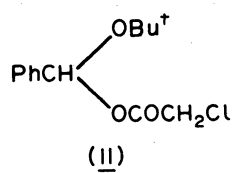
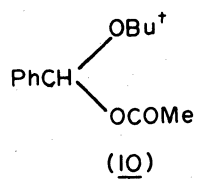
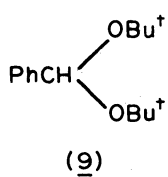
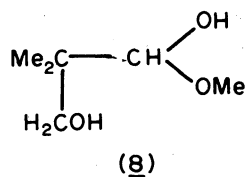
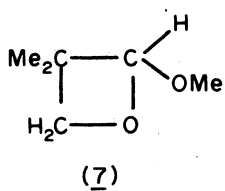
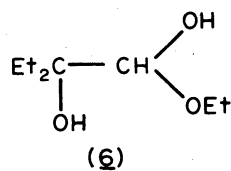
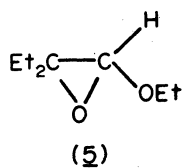
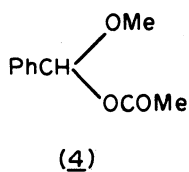
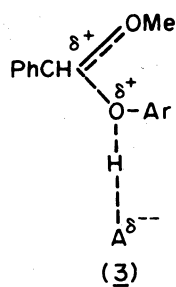
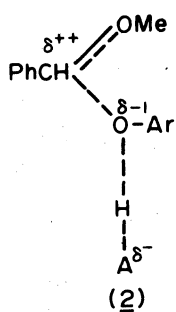
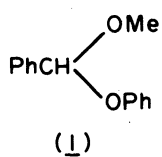
Abstract - The general-acid catalysed hydrolysis of acetals is discussed. It is shown that under certain conditions the rate-limiting step in the hydrolysis of α -acetoxy- α -methoxy-toluene and benzaldehyde di-*t*-butylacetal is decomposition of the hemiacetal. Attempts to study the decomposition of tetrahedral intermediates at the oxidation level of carboxylic acids are described.

The work that I am going to describe today was started about ten years ago and continues until last week. This means that in the early part of my lecture I shall be describing work that is already published or in the course of publication and on which our ideas are reasonably clear, whereas in the second half I shall be describing very recent work upon which our ideas are less clear and for which we have not completed all the experiments we should have liked to have done.

About ten years ago one of my students, Dr. E. Anderson, and I decided that we would try to find an acetal whose hydrolysis was general-acid catalysed, intermolecularly. We had discovered previously examples of intramolecular general-acid catalysis (1) and wondered if it was possible by suitable choice of acetal to observe intermolecular general-acid catalysis. It had been shown by Brønsted and Wynne-Jones that the hydrolysis of diethyl acetal was specific-acid catalysed (2). This has usually been interpreted as indicating that the proton transfer occurs in a rapid and reversible step and is followed by a rate-limiting decomposition of the conjugate acid to give a carbonium-oxonium ion. We considered the free-energy reaction coordinate diagram for such a mechanism and asked the question (3): "what structural changes would be necessary to cause a change to general-acid catalysis?". For the reaction to be general-acid catalysed it would be necessary for the proton transfer step to be rate-limiting and we considered that it would be possible to achieve this by making the conjugate acid less stable and/or the carbonium-oxonium ion more stable. We therefore studied the hydrolysis of benzaldehyde methyl phenyl acetal (1) and found this reaction to be general-acid catalysed. This work was published in 1969 (3), shortly after Fife and Jao's report of the first well authenticated example of general-acid catalysis in the hydrolysis of an acetal, *p*-nitrophenoxy-tetrahydropyran (4).

Another way of looking at this change from specific- to general-acid catalysis on going from diethyl acetal to benzaldehyde methyl phenyl acetal is that with the former compound complete proton transfer is necessary for bond cleavage to occur, whereas with the latter partial proton transfer is sufficient.

After this work Dr. Anderson departed for California to continue his work on acetals very successfully in Professor Fife's laboratory and the investigation was continued in our laboratory by Dr. Nimmo. Dr. Nimmo studied the effect of substituents on the rate constants for the general-acid catalysed hydrolysis of benzaldehyde methyl phenyl acetal. His most interesting result was that both electron-withdrawing and electron-releasing substituents in the phenoxy group caused an increase in catalytic constants for hydrolysis when the catalyst was a carboxylic acid. This result puzzled us for a long time but eventually we hit on what we think is the correct explanation (5). The general-acid catalysed hydrolysis of benzaldehyde methyl phenyl acetal is an electrophilic substitution on oxygen which involves breaking of a carbon-oxygen bond and formation of a hydrogen-oxygen bond. If the former runs ahead of the latter the oxygen upon which the substitution takes place will carry a net negative



charge (2) whereas if the latter runs ahead of the former it will carry a net positive charge (3). Thus the experimental observations could be explained if compounds with electron-withdrawing substituents in the phenoxy group had a transition state of type (2) whereas compounds with electron-releasing substituents had a transition state of type (3). That this is reasonable is seen by consideration of the contour diagram of the type introduced by Dr. More O'Ferrall (6) and used widely by Professor Jencks (7). In this diagram (Fig.1) proton transfer is plotted on the x-axis and C-O bond breaking on the y-axis. If the transition state saddle point lies above the positively sloping diagonal there is more C-O bond breaking than O-H bond forming and increasing the electron-withdrawing power of the substituent would cause the transition state to move towards the left and top of the diagram and its energy to decrease. Conversely increasing the electron-releasing power of the substituent will cause the transition state to move towards the right and bottom of the diagram and increase until the diagonal is passed. The saddle point then lies below the diagonal with more O-H bond forming than C-O bond breaking and while increasing the electron-releasing ability of the substituent still causes the saddle point to move to the right and bottom of the diagram, it now causes a decrease in the energy of the transition state, because the oxygen now carries a net positive charge.

This behaviour is not found in the hydronium-ion catalysed reaction for which electron-releasing substituents are rate enhancing and electron-withdrawing substituents rate decreasing. This suggests that the transition state saddle point always lies below the positively sloping diagonal when the hydronium ion is the catalyst and that O-H bond forming always runs ahead of C-O bond breaking.

We were interested to note that a similar effect appeared to be occurring in the decomposition of the addition compounds of alcohols with the N,O-tri-methylene phthalimidium ion studied by Gravitz and Jencks (8).

Before completing his Ph.D. Dr. Nimmo carried out a brief investigation of the hydrolysis of α -acetoxy- α -methoxy-toluene (4). This compound was originally made in our laboratory by Dr. Anderson but he did not have time to carry out a kinetic investigation. We were interested in studying this compound because on going from benzaldehyde dimethyl acetal to benzaldehyde methyl phenyl acetal the hydrolysis changes from being specific-acid catalysed to general-acid catalysed and we wondered what the effect would be of having a still better leaving group, acetoxy, instead of phenoxy.

Would the reaction still be general-acid catalysed or would we get a reaction that follows the pathway of the left-hand side and the top of the More O'Ferrall-Jencks diagram (Fig.1)? Now of course we know on the basis of Jencks' rule (9) that the latter is what would be expected for catalysis by carboxylic acids because there would be no thermodynamic advantage for the transfer of a proton from a catalyst to the leaving group. Dr. Nimmo just carried out a series of reactions in several carboxylic-acid buffers but only used one buffer ratio for each acid. He followed the formation of benzaldehyde spectrophotometrically (280 nm) and observed catalysis by the components of the buffer. We assumed that by analogy to benzaldehyde methyl phenyl acetal that general-acid catalysis was occurring and calculated catalytic constants on this basis. These showed very little variation with structure of the carboxylic acid. This result was subsequently confirmed by Mr. Gordon Reid and although we were able to find an explanation for this result we were not entirely happy with it and checked to see if the reaction was also general base catalysed. This was found to be so in acetate buffers and we obtained catalytic constants $k(\text{HOAc}) = 0.0771 \text{ l/mole/s}$ and $k(\text{AcO}^-) = 0.180 \text{ l/mole/s}$ at 15° . The value of $k(\text{HOAc})$ was not unreasonable but that of $k(\text{AcO}^-)$ was very much larger than $k(\text{AcO}^-)$ for the hydrolysis of *p*-nitrophenyl acetate which is $5.64 \times 10^{-6} \text{ l/mole/s}$ at 25° . It seemed to us that this catalysis could not be nucleophilic or general-base catalysis of a reaction at the acetoxy group of the starting material since *p*-nitrophenoxy should be a much better leaving group than α -methoxy- α -phenoxy-methoxy. It is also difficult to see how a catalytic constant of this magnitude could arise from attack at the pro-acyl carbon. After quite a long time we realised what must be happening. The acetoxy-group is such a good leaving group that the step in which it leaves is not the rate determining step which has become decomposition of the hemiacetal. Hemiacetal decomposition is similar to the dehydration of aldehyde hydrates (11) and the mutarotation of glucose (12) both of which show general-acid and general-base catalysis. To test whether decomposition of the hemiacetal were rate-determining we studied the hydrolysis of α -chloroacetoxy- α -methoxy-toluene

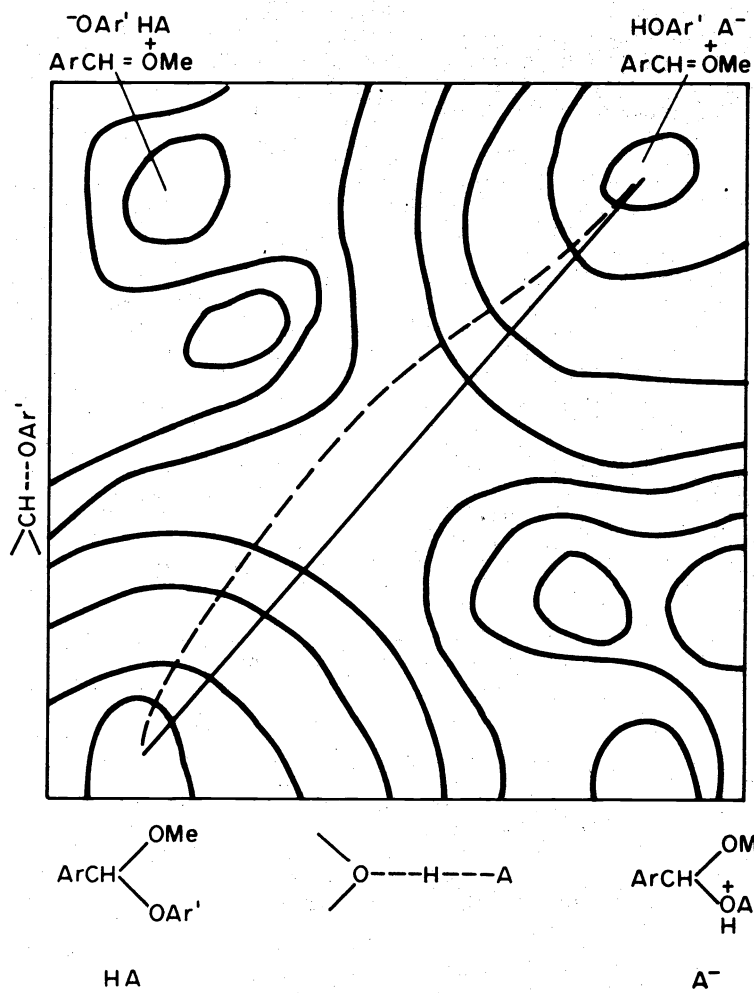
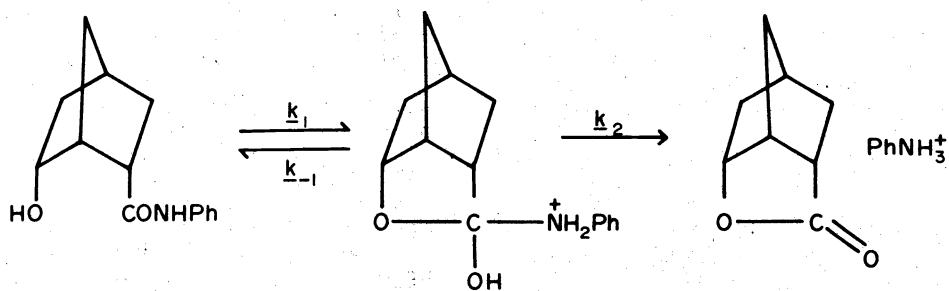


Fig. 1. More O'Ferrall - Jencks Diagram.



Scheme 1

since if a reaction of the starting material were rate-determining different rate constants would be expected for the α -acetoxy and α -chloroacetoxy compounds whereas if the decomposition of the hemiacetal were rate-determining, the rate constants should be identical within experimental error. The experimental results show that the latter is occurring. Further evidence that decomposition of the hemiacetal was slower than its formation was obtained by following the reaction in an acetate buffer (0.1M NaOAc, 0.1M DOAc) in a mixture of deuterated dimethyl sulphoxide and deuterium oxide (1:1 v/v) at 2° by NMR spectroscopy (Varian HA 100). The chemical shift of the signal of the pro-acyl CH proton of the starting material was determined about one minute after dissolving to be $\delta=6.48$ ppm downfield from internal sodium 2,2-dimethyl-2-silapentane-5-sulphonate. In this spectrum there was a very small signal at $\delta=5.44$ ppm which was ascribed to the pro-acyl CH proton of the hemiacetal since its chemical shift was close to that of the CH proton of benzaldehyde dimethyl acetal for which $\delta=5.35$ ppm. This signal increased in intensity as the signal at $\delta=6.48$ decreased and after about 14 minutes the two signals were of approximately equal intensities. In this spectrum there was also a small signal at $\delta=9.88$ ppm which is the chemical shift of the acyl CH proton of benzaldehyde. After two hours the signals at $\delta=6.48$ and 5.44 ppm had disappeared and only the signal at $\delta=9.88$ remained. Thus under these conditions formation of the hemiacetal is faster than its decomposition to benzaldehyde.

There have been relatively few previous investigations of the decomposition of hemiacetals (13, 14, 15, 16) and to our knowledge none of those derived from aromatic aldehydes. In the hydrolysis of acetals the decomposition of the hemiacetal is normally a fast step (17) and for aromatic aldehydes the equilibrium constant for the formation of hemiacetals is normally unfavourable unless electron-withdrawing substituents are present (18). The generation of hemiacetals of aromatic aldehydes as intermediates in the hydrolysis of their *O*-acetates therefore provides for the first time a general method for studying their decomposition. In the pH-range 3.69 to 6.27 there is no indication of a change in the rate-determining step to formation of the hemiacetal but this may occur at higher pHs.

This work indicates that if one had a very reactive acetal there is a possibility that decomposition of the hemiacetal might be the rate-limiting step. In recent years two examples of this type of behaviour have been discovered (15, 16). Thus Schaleger and his co-workers found that at low pHs decomposition of the hemiacetal (6) was rate-limiting in the hydrolysis of acetal (5) and Atkinson and Bruce found that decomposition of hemiacetal (8) was rate-limiting in the hydrolysis of acetal (7). The rate-limiting step changed to formation of the hemiacetal at high pHs with both compounds. We wondered if there were any further examples of this type of behaviour that had not been recognised and remembered the hydrolysis of benzaldehyde di-*t*-butyl acetal (9). It had been shown by Cawley and Westheimer that bond fission occurs between the pro-acyl carbon and the oxygen and not between the *t*-butyl group and the oxygen (19) and Anderson and Fife reported that it was hydrolysed rapidly with general-acid catalysis (20). This was considered to arise from the sterically crowded ground state which caused the acetal bond to be broken easily. It seemed to us that a similar rate enhancement would not be expected with the hemiacetal as it is much less sterically crowded and hence there might be a change in the rate-limiting step to decomposition of the hemiacetal. Mr. Duncan Grieve in our laboratory has studied the hydrolysis of compounds (9), (10) and (11). At pH 4.6 the rate constants of formation of benzaldehyde were identical from all three compounds. At pH 7.5 the rate constants for the formation of benzaldehyde from compounds (10) and (11) were identical and about 35 times greater than the rate constant for the formation of benzaldehyde from (9). At intermediate pHs the formation of benzaldehyde from (9) no longer followed the first-order rate law but that from (10) and (11) did. At some pHs a definite induction period could be seen in the formation of benzaldehyde from (9) while at others the non-first order behaviour was indicated by the first, second and third half lives not being equal. This behaviour is very similar to that reported by Atkinson and Bruce (16) for the hydrolysis of (7). We interpret these results to indicate that under our conditions, with the buffer concentration less than 0.025M, the rate-limiting step is decomposition of the hemiacetal at pHs less than 4.6 and formation of the hemiacetal at pHs greater than about 7. At intermediate pHs formation and decomposition of the hemiacetal occur at comparable rates. Anderson and Fife (20) used higher buffer concentrations and we are not sure at present whether this conclusion applies to these conditions as well.

We next asked ourselves if it would be possible to go to a higher oxidation level and generate the tetrahedral intermediate of an acyl-transfer reaction by hydrolysis of its O-acetate. Several tetrahedral intermediates at the oxidation level of a carboxylic acid have been prepared or detected spectroscopically (21) and two fairly detailed kinetic investigations have been reported (22). All these compounds have fairly complex structures however and there has been no kinetic investigation of the decomposition of a tetrahedral intermediate formed from a simple formate, acetate, or benzoate.

There have recently been some very interesting calculations by Guthrie on the stability of this type of tetrahedral intermediate (23). On the basis of these one can calculate that the tetrahedral intermediate in the hydrolysis of methyl formate, $\text{HC(OH)}_2(\text{OMe})$, would be most stable in aqueous solution at pH ca 5 and at this pH would decompose mainly through its monoanion with a half life of 1 to 5 seconds at 25°. We are currently trying to generate the very similar tetrahedral intermediate $\text{HC(OH)}(\text{OMe})_2$ by hydrolysis of $\text{HC(OAc)}(\text{OMe})_2$.

Finally I should like to turn to the question of whether any carboxylic acid derivative reacts through a detectable concentration of a tetrahedral intermediate. Dr. Cleland studied the hydrolysis of amides (12), (13) and (14) in aqueous perchloric acid of concentration greater than 0.1M. He followed the decrease in absorbance at 242 nm at which wave length the extinction coefficient of the anilinium ion is much smaller than that of the amide. He found that the variation of absorbance with time did not follow the first-order rate law but consisted of two phases, one fast and one slow. We checked the purity of the starting materials and the reaction products and considered that this behaviour could not be from the starting material being impure or from it undergoing two reactions. We also considered the possibility that it arose from a slow cis-trans isomerisation of the starting amide, but the reaction appears to be too slow for this to be happening. In 0.01M perchloric acid and in imidazole buffers the hydrolyses of these compounds shows simple first-order behaviour. This behaviour was checked for compound (12) by Mr. I. McCaffer. The most reasonable explanation seems to be that there is accumulation of an appreciable concentration of a tetrahedral intermediate. We have analysed the kinetics of hydrolysis of compound (12) on the basis of Scheme 1 on the assumption that the extinction coefficient at 242 nm of the protonated tetrahedral intermediate (15) would be similar to that of the anilinium ion, i.e. small compared to that of the starting amide. The value of k_2 , the rate constant for decomposition of the tetrahedral intermediate decreases with increasing acid concentration. This behaviour is similar to that found for the decomposition of a carbinolamine derived from a Schiff base (24). The rate constants k_1 and k_{-1} increase with increasing acid concentration up to about 4M and then decrease at higher concentrations.

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