

## A MATHEMATICAL MODEL FOR CONCERTED PROTON TRANSFER IN THE HYDROLYSIS OF ETHYLPHENYLBENZALDEHYDE ACETALS

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**Abstract.** The hydrolysis of seven ethyl substituted phenylbenzaldehyde acetals, (2) ( $R = C_2H_5$ ,  $X = H$ ), has been examined in details; the catalytic constants of six buffer acids (pKa ranging from 2.6 to 8) as well as those of hydronium ion and water have been measured. A good Br nsted correlation is obtained for all compounds, the  $\alpha$  coefficient decreasing regularly from 0.7 to 0.5 when the basicity of the leaving group increases. On the contrary the Hammett plots obtained for each acid are bad, excepted those corresponding to hydronium ion and water.

A model of concerted proton transfer is presented which extends and puts in a mathematical form the models previously proposed by Jencks, Kreevoy and Guthrie. With this model we can demonstrate that: *i*) the hydrolysis of a given compound can be either a specific-acid or a general-acid catalysed reaction depending upon the strength of the catalyst, *ii*) The  $\alpha$  Br nsted coefficient is not a measure of the "degree of proton transfer in the transition state" but is rather a measure of the easiness of cleavage of the C - OAr bond, *iii*) It is possible to predict the kind of catalysis which a reaction will be submitted to when we know the two rate constants,  $k_0$  and  $k_{H^+}$ , of the "spontaneous" and of the hydronium ion catalysed hydrolyses.

### INTRODUCTION

Acid - and base-catalysed reactions, - that is reactions involving a proton transfer between the substrate and the external medium -, are of the utmost importance in organic chemistry and biochemistry. Since the very beginning of physical organic chemistry searchers in this field have been busy trying to find out the intimate mechanism of this proton transfer particularly in those reactions involving the formation and the decomposition of tetrahedral intermediates.

Broadly speaking we can distinguish two classes of acid - and/or base-catalysed reactions: those in which a proton is transferred to or from a carbon atom of the substrate, - such as the hydration of alkenes, the enolization of ketones, etc... -, and those in which the proton transfer takes place between two electronegative atoms of the substrate and of the catalyst. In this paper I'll deal only with this second class of reactions, more specifically with acid-catalysed reactions in which the proton is transferred from the catalyst to the substrate.

Br nsted (1) has, many years ago, subdivided these reactions into two sub-classes, the general-acid catalysed and specific-acid catalysed reactions, depending upon whether the concentration of the weak acid catalyst appears or not in the rate law; it is generally acknowledged that the kind of catalysis actually occurring in a reaction process depends only on the substrate: a given compound will always react with specific-acid or general-acid catalysis whatever the solvent and the acid catalyst.

The specific-acid catalysis 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 of the substrate to give, - in the case of acetals for exemple -, an oxocarbenium ion (Mechanism A1). On the other hand, in its classical interpretation the general-acid catalysis implies a slow proton transfer during the rate-determining step of the reaction to give the oxocarbenium ion and the conjugate base of the catalyst (Mechanism A<sub>SE</sub>2).

The well-known Br nsted catalysis law,  $k_A = G(K_A)^\alpha$ , where  $k_A$  is the specific rate constant for catalysis by the acid whose acid dissociation constant is  $K_A$ , correlates the effectiveness of acids as catalysts with their acid strength. Many evidences have been accumulated, since it was first proposed, in support of its essential validity and it is now generally admitted that all reactions which show general

acid catalysis must conform to the Brønsted relation. Besides its use as a means to make predictions of rate constants the Brønsted relation has received a widespread acceptance as an indicator of reaction mechanism, the most interesting aspect of this later application being that the Brønsted exponent  $\alpha$  provides information about transition state structure : the numerical value of the exponent  $\alpha$ , always between 0 and 1, is usually said as being equal to the "extent of proton transfer" at the reaction transition state (for a review of current ideas on this topic see Kresge, Ref. 2).

The purpose of this article is to show :

- i) that the clear-cut distinction between the two types of catalysis is not necessarily imposed by the nature of the substrate and that systems can exist, - at least the system we have in hands -, which belong to one kind or the other of mechanisms depending upon the circumstances,
- ii) that the Brønsted exponent  $\alpha$  has nothing to do with the "degree of proton transfer at the transition state" ; it is rather a measure of the "easiness of cleavage" of the C - O bond which is broken during the slow step of the reaction.

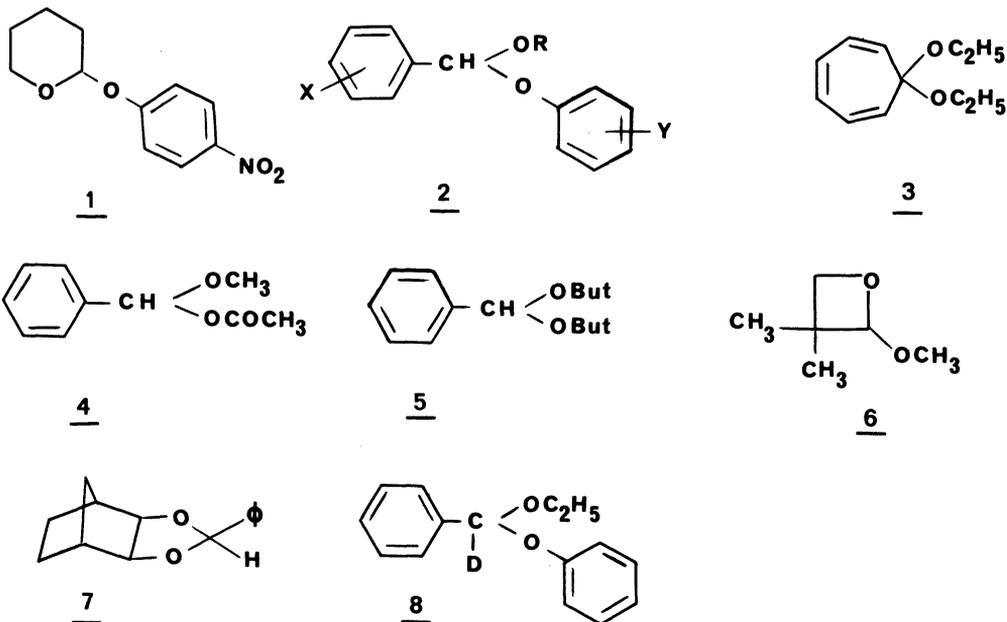
#### PREVIOUS WORKS

In connection with the mechanism of action of the lysozyme we have been interested for several years by the general-acid catalysis in the hydrolysis of acetals, a class of compounds most often known to react via an A1 mechanism.

Prior to 1968 the acetals hydrolysis was believed to be a specific-acid catalysed reaction ; in that year however Fife and Jao (3) reported the first well-authenticated example of general-acid catalysis in the hydrolysis of an acetal, the p-nitrophenoxytetrahydropyran (1). Since then several other systems have been found to obey the same catalysis law and we have now a good idea of the structural features of the substrate which are necessary to cause a change from specific-acid to general-acid catalysis (for a review see Ref. 4). To give some examples, the acetals 1 - 6 have been found to react via an A<sub>SE</sub>2 mechanism ; the reasons for this special behaviour are :

- a good leaving group (1, 2, 4)
- a stable oxocarbenium ion (2, 3, 4, 5)
- a relief of ground state strain (5, 6).

Of all these systems the more versatile is the system number 2, since it is possible to vary at will the nucleofugacity of the leaving group and/or the stability of the oxocarbenium ion by introducing suitable substituents X and Y in the phenyl rings of the benzaldehyde and of the phenol.



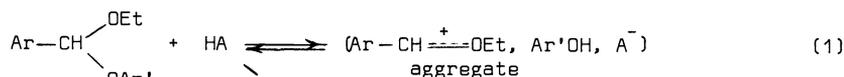
Slightly after we had started to study this system Capon and Nimmo (5) published their results on the hydrolysis of methyl substituted-phenylbenzaldehyde acetals; they showed that the reaction was indeed general-acid catalysed, that the leaving group was always the phenoxide and confirmed the interest of these compounds to study the process of concerted proton transfer. We decided nevertheless to continue our researches (Ref. 6) on these substrates in extending as much as possible the range of pK of the acid catalyst and in working

out the theoretical aspect of this problem.

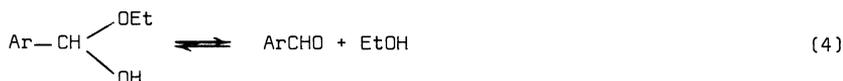
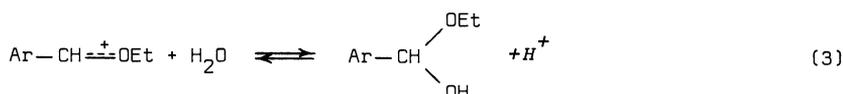
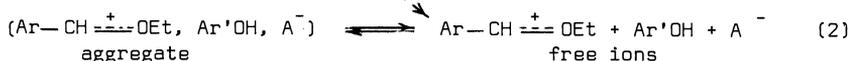
The reaction, whose stoichiometry is :



occurs in 3, and possibly 4, steps :



or



The proton transfer occurs during the first step of the reaction and is "concerted" with the cleavage of the C-OAr' bond ; since we were interested by the mechanism of this proton transfer it was important for us to be certain that the rate-limiting step of the reaction was actually the first one and not the step 2,3 or 4.

Step 4 is the decomposition of a hemi-acetal ; it has been found to be the rate-determining step in the hydrolysis of compound (4) (Ref. 7) and has been suggested as the rate-determining step in the hydrolysis of substituted benzaldehyde diethylacetals (Ref. 8 and 9) ; this later suggestion has been very recently infirmed by Przystas and Fife (10) who have shown that for these acetals the formation of the oxocarbonium ion was indeed the rate-determining step at all pH values.

Step 3 is the nucleophilic attack of water on the oxocarbonium ion ; this step can be rate-determining only in very special circumstances, for example when the intermediate oxocarbonium ion is very stable as in the hydrolysis of tropone diethylacetal, (3) (Ref. 11), or when there is a possibility of internal return as in compound (7) (Ref. 12) ; it is most improbable that step 3 could be rate-limiting in our system.

Step 2 is the diffusional separation of the conjugate base of the catalyst from the oxocarbonium ion ; a slow diffusional separation process has been invoked by Jensen et al. (13) in the acid-catalysed hydrolysis of dialkylbenzaldehyde acetals and has been shown by Jensen and Jencks (14) to be the rate-determining step in the "water reaction" (uncatalysed or spontaneous hydrolysis) of benzaldehyde O-ethyl S-phenylacetal (C - S cleavage). The findings of Jensen have not been confirmed by later experiments made by Przystas and Fife (10) and it seems unlikely that this step could be rate-determining in the hydrolysis of compounds of type (2) ; the case of the thioacetal is very peculiar : the high nucleophilicity of the thiophenoxide anion, ArS<sup>-</sup>, makes the return reaction,  $k_{-1}$ , very fast and causes a shift of the rate-determining step from step 1 to step 2. We believe that in our case step 2 cannot be rate-limiting, if it exists at all ; we think that in most hydrolysis reactions this step is bypassed and that the system goes directly from the reactants to the free ions pair.

#### PRELIMINARY EXPERIMENTS

To make sure that the rate constants we have measured were indeed the rate constants,  $k_1$  of the first step we have prepared the deuterated acetal (8) and determined the kinetic  $\alpha$ -isotope effect in weak acid buffer solutions. The results obtained are listed in Table 1.

TABLE 1. Secondary kinetic  $\alpha$ -isotope effect for acid-catalysed and pH-independent hydrolysis of ethylphenylbenzaldehyde acetal in water at 25°C.  $\mu = 0.3$  M

Acid	pH	$k^H/k^D$
$10^{-3}$ M HCl	3.43	$1.06 \pm 0.02$
HCOOH	3.54	$1.14 \pm 0.03$
CH <sub>3</sub> COOH	4.61	$1.17 \pm 0.03$
(CH <sub>3</sub> ) <sub>2</sub> AsOOH	6.33	$1.20 \pm 0.03$
H <sub>2</sub> O		$1.24 \pm 0.06$

It is well established that for those reactions in which the central carbon atom changes from tetrahedral towards trigonal geometry in the transition state the value of  $k^H/k^D$  is significantly greater than unity; the larger the value of  $k^H/k^D$  the more oxocarbenium ion character in the transition state. Despite rather large experimental errors the trend is perfectly clear: the Deuterium  $\alpha$ -isotope effect increases when the strength of the acid catalyst decreases; for the pH-independent hydrolysis, the "water reaction", the value is near the maximum we can expect for a limiting SN<sub>1</sub> reaction (Ref. 15). These results prove beyond any reasonable doubt that step 1 is indeed the slow step of the hydrolytic reaction: if step 2 or 3 would have been rate-limiting the central carbon atom would have had a near trigonal geometry in the transition state, then we could have expected an almost constant isotope effect with the ratio  $k^H/k^D$  near its maximum value. Being the rate-determining step actually the first one we can present and discuss in confidence the rate constants of hydrolysis obtained with ethyl substituted-phenyl benzaldehyde acetals.

## RESULTS

Six ethyl substituted-phenyl benzaldehyde acetals have been studied; most of the rate-constants have been measured in water, at 30°C and at a ionic strength of 0.25 M. The catalytic constants,  $k_{AH}$ , of six buffer acids have been determined from measures with at least 5 buffer concentrations; the catalytic constant of the proton came from measurements made in the presence of  $10^{-3}$  M HCl, the one of the water (pH-independent hydrolysis) from the intercepts of the graphs  $k_{obs} = f(HA)$  for the cacodylic, phosphoric and methylphosphonic acids. The compounds and the acid catalysts used in this research are shown in Table 2, the catalytic constants obtained in Table 3.

TABLE 2. Physical characteristics of substrates and catalysts used in this work. The acid pKs are at 30°C and  $\mu = 0.25$  M for a buffer concentration equal to zero.

Substrate		Catalysts	
	$\sigma_Y$	Acid	pK <sub>a</sub>
Y		H <sub>3</sub> O <sup>+</sup>	-1.72
p-OCH <sub>3</sub>	-0.27	CH <sub>2</sub> ClCOOH	2.61
p-CH <sub>3</sub>	-0.17	HCOOH	3.49
H	0.00	CH <sub>3</sub> COOH	4.50
m-OCH <sub>3</sub>	0.12	(CH <sub>3</sub> ) <sub>2</sub> AsOOH	6.01
m-Cl	0.37	PO <sub>4</sub> H <sub>2</sub> <sup>-</sup>	6.58
m-NO <sub>2</sub>	0.71	CH <sub>3</sub> -PO <sub>3</sub> H <sup>-</sup>	7.38

An additional proof of the rate-limiting formation of the oxocarbenium ion is given by the fact that the proton catalytic constant,  $k_{H^+}$ , is the same, -within experimental error -,

whatever the method of determination ;  $k_{H^+}$  can be estimated in two ways : *i*) from measurements in hydrogen chloride solutions, *ii*) from the intercepts of the graph  $k_{obs} = f(HA)$  providing we can neglect the contribution of the "water reaction" which is always the case for acids as strong as, or stronger, than formic acid ; both values of  $k_{H^+}$  agree within a few percent and there is no systematic trend in the small difference between the two rate constants .

TABLE 3. Specific catalytic constants for the acid-catalysed hydrolysis of ethylphenyl benzaldehyde acetals  $k_{AH}$  in  $M^{-1}s^{-1}$  at 30°C.

Y = Acid	p-OMe	p-Me	H	m-OMe	m-Cl	m-NO <sub>2</sub>
H <sub>3</sub> O <sup>+</sup> a)	234	172	160	133	108	74
CH <sub>2</sub> ClCOOH <sup>a</sup> )	0.84	0.58	0.78	0.77	0.91	1.70
HCOOH	0.36	0.19	0.25	0.23	0.26	0.54
CH <sub>3</sub> COOH	4.0x10 <sup>-2</sup>	2.9 x 10 <sup>-2</sup>	4.9 x 10 <sup>-2</sup>	5.8 x 10 <sup>-2</sup>	7.3 x 10 <sup>-2</sup>	23 x 10 <sup>-2</sup>
(CH <sub>3</sub> ) <sub>2</sub> AsOOH	4.1x10 <sup>-3</sup>	3.3 x 10 <sup>-3</sup>	5.2 x 10 <sup>-3</sup>	6.5 x 10 <sup>-3</sup>	8.8 x 10 <sup>-3</sup>	35 x 10 <sup>-3</sup>
PO <sub>4</sub> H <sub>2</sub> <sup>-</sup>	3.3x10 <sup>-3</sup>	2.6 x 10 <sup>-3</sup>	4.3 x 10 <sup>-3</sup>	6.6 x 10 <sup>-3</sup>	10.2 x 10 <sup>-3</sup>	42 x 10 <sup>-3</sup>
CH <sub>3</sub> PO <sub>3</sub> H <sup>-</sup>	5.4x10 <sup>-4</sup>	3.5 x 10 <sup>-4</sup>	-	10.9 x 10 <sup>-4</sup>	10.3 x 10 <sup>-4</sup>	53 x 10 <sup>-4</sup>
H <sub>2</sub> O b)	9.9x10 <sup>-8</sup>	3.4 x 10 <sup>-7</sup>	4.6 x 10 <sup>-7</sup>	1.4 x 10 <sup>-6</sup>	5.9 x 10 <sup>-6</sup>	6.8 x 10 <sup>-5</sup>
α c)	0.70	0.68	0.64	0.61	0.56	0.51
(s.d.)	(0.03)	(0.02)	(0.02)	(0.01)	(0.03)	(0.03)

a) Constants extrapolated at 30°C from measurements made at lower temperature (10°C, 18°C, 25°C)

b)  $k_{H_2O} = k_o/55.5$

c) Brønsted exponent : calculated from the slope of the graphs  
 $\text{Log}(k_{AH}/p) = -(\rho k_a + \text{Log } p/a)$

From the rate constants of Table 3, we can draw two types of correlations : *i*) A Brønsted correlation by plotting  $\text{Log}(k_{AH}/p)$  against  $-(\rho k_a + \text{Log } p/q)$ ,  $p$  being the number of equivalent dissociable protons of the acid,  $q$  the number of sites of protonation of its conjugate base. We have a Brønsted plot for each substrate and we can see Fig. 1 that in every case, the correlation is fairly good (correlation coefficient  $r = 0.997$  or better) if we take into account the six weak acids only ; the points corresponding to the methylphosphonic acid is slightly below the line for the m-Cl and m-NO<sub>2</sub> compounds : the reason for this particular behaviour will become clear later.

The slopes  $\alpha$  of the Brønsted lines are given in Table 3 : they decrease significantly when the electron attracting character of the substituent Y increases. As usual the points corresponding to the catalytic constants of proton and water fall off the lines, the hydronium ion being slightly below, the water strongly above. This is not a surprise since, as we will see later, the hydronium ion and water do not behave as the other acid catalyts do.

*ii*) A Hammett correlation by plotting, for a same acid,  $\text{Log } k_{AH}$  against the  $\sigma_Y$  constants of the substituents. Four Hammett plots are presented on Fig. 2a-2d, (the graphs for chloroacetic and acetic acids are very much like that of formic acid, those for cacodylic and methylphosphonic acids resemble that of phosphoric acid) and we see at first glance that the correlations are bad, some times very bad, for all the catalyts, except for the hydronium ion and water ! The "best" slopes of the plots are negative for H<sub>3</sub>O<sup>+</sup>,  $\rho \approx -0.5$ , increasingly positive for the weak acids and strongly positive,  $\rho \approx +2.8$ , for water. The same kind of "erratic" Hammett plot has been observed by Capon and Nimmo in their study of methyl substituted-phenyl benzaldehyde acetals (2, R = CH<sub>3</sub>) (Ref. 5). These "bad" Hammett plots cannot result from inaccurate measurements since in that event the Brønsted plots would have been bad also ; they probably reflect the particular character of the proton transfer process and it is this character that we have tried to find out and explain.

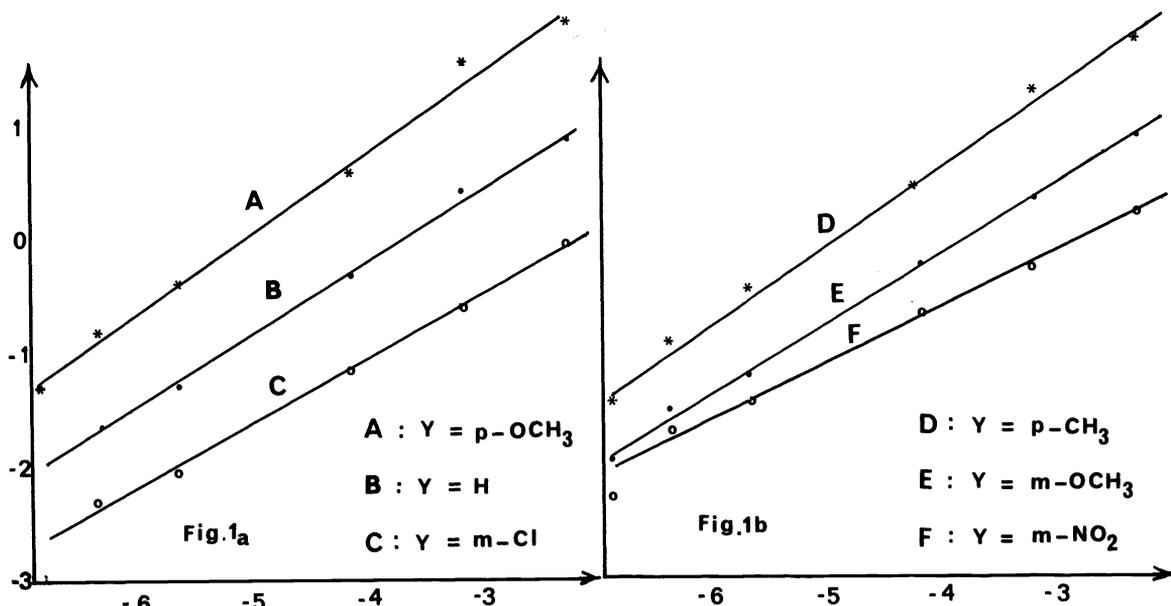


Fig. 1. Plots of  $\text{Log}(k_{\text{AH}}/p) = -(\rho K_a + \text{Log } p/q)$

Ordinates :  $\text{Log}(k_{\text{AH}}/p) + 2$  for lines A and D ;  $\text{Log}(k_{\text{AH}}/p) + 1$  for lines B and E ;  
 $\text{Log}(k_{\text{AH}}/p)$  for lines C and F .

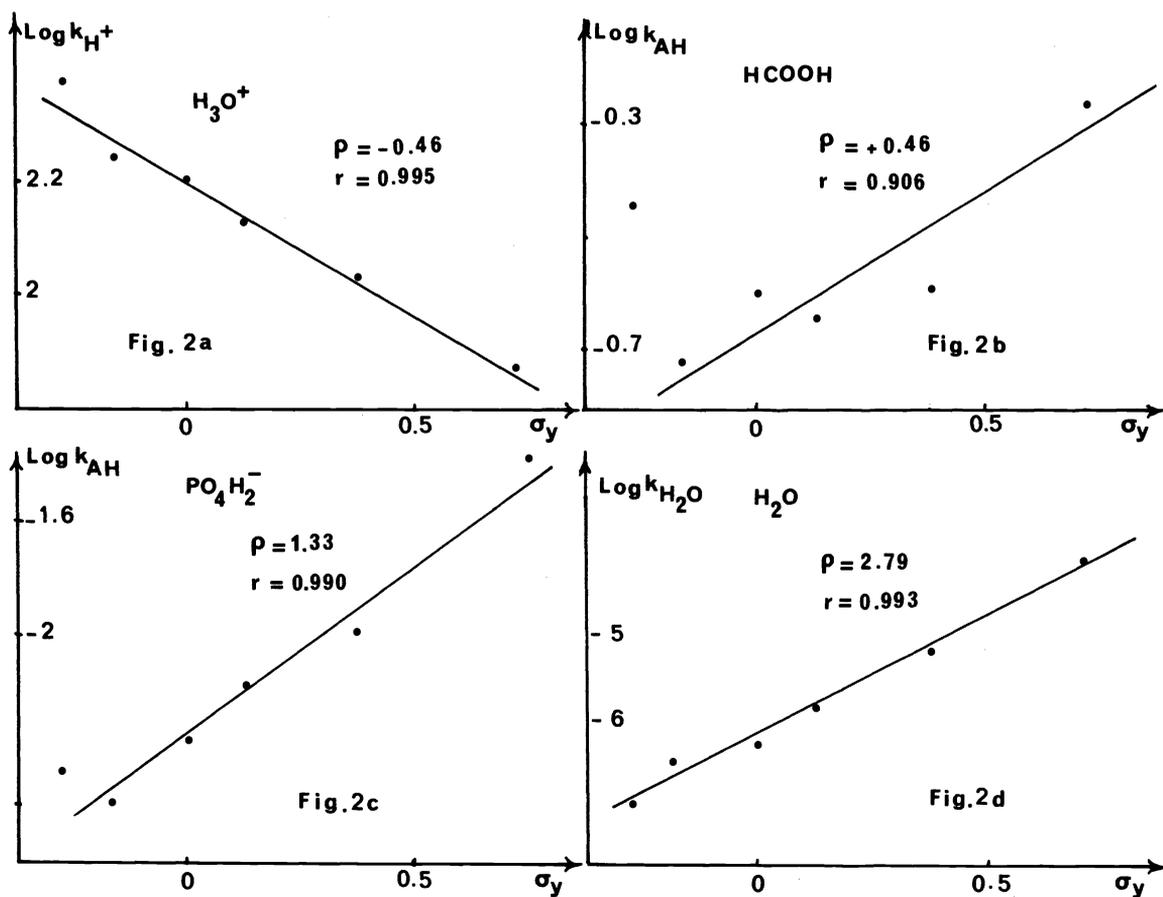
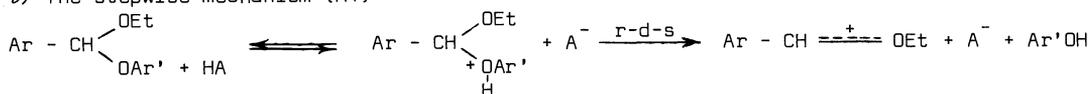


Fig. 2. Hammett plots for hydrolysis of acetals catalyzed by  $\text{H}_3\text{O}^+$  (Fig. 2a),  
 $\text{HCOOH}$  (Fig. 2b),  $\text{PO}_4\text{H}_2^-$  (Fig. 2c) and for the "spontaneous" reaction (Fig. 2d) .

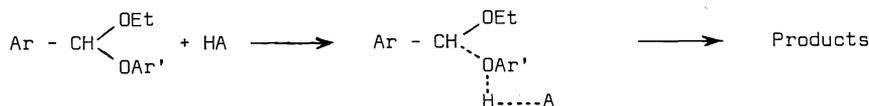
## MODELS FOR PROTON TRANSFER

As we have seen before there are two mechanisms leading from the acetal to the oxocarbenium ion :

i) The stepwise mechanism (A1)



ii) The concerted mechanism (A<sub>SE</sub>2)



The mechanisms of proton transfers and the reasons for a system to choose one way or the other have been extensively studied during the last twenty years, particularly by Jencks and his coworkers. Jencks has stated the necessary conditions a given system has to fulfill for the "concerted" mechanism to occur (Ref. 16) ; for this process involving the modification of 3 bonds during the rate-determining step of the reaction, - *i.e.* cleavage of the C - OAr' bond -, he has popularized the use of the More O'Ferrall contour diagram (Ref. 17) which consists in plotting along separate coordinate axes *x* and *y*, the proton transfer and the cleavage of the C - OAr' bond ; the energy is plotted along the *z* axis and the now so-called More O'Ferrall-Jencks diagrams are the plane projections of the intersection curves of a 3-dimensional surface by isoenergy (*z* = ct.) planes. Fig. 3 and 4 represent respectively the 3-dimensional potential energy surface (the "box") for acetal hydrolysis and the 2-dimensional contour diagram.

When the reaction proceeds the system moves from the front left corner of the "box" to its back right corner, that is from  $\text{Ar} - \text{CH} \begin{matrix} \text{OEt} \\ \text{OAr}' \end{matrix} + \text{HA}$  to  $\text{Ar} - \text{CH} \begin{matrix} \oplus \\ \text{OEt} \end{matrix} + \text{Ar}'\text{OH} + \text{A}^-$  with complete breaking of the C - OAr' bond and complete proton transfer from AH to Ar'O<sup>-</sup>. There are two ways of describing the motion of the system on the potential energy surface :

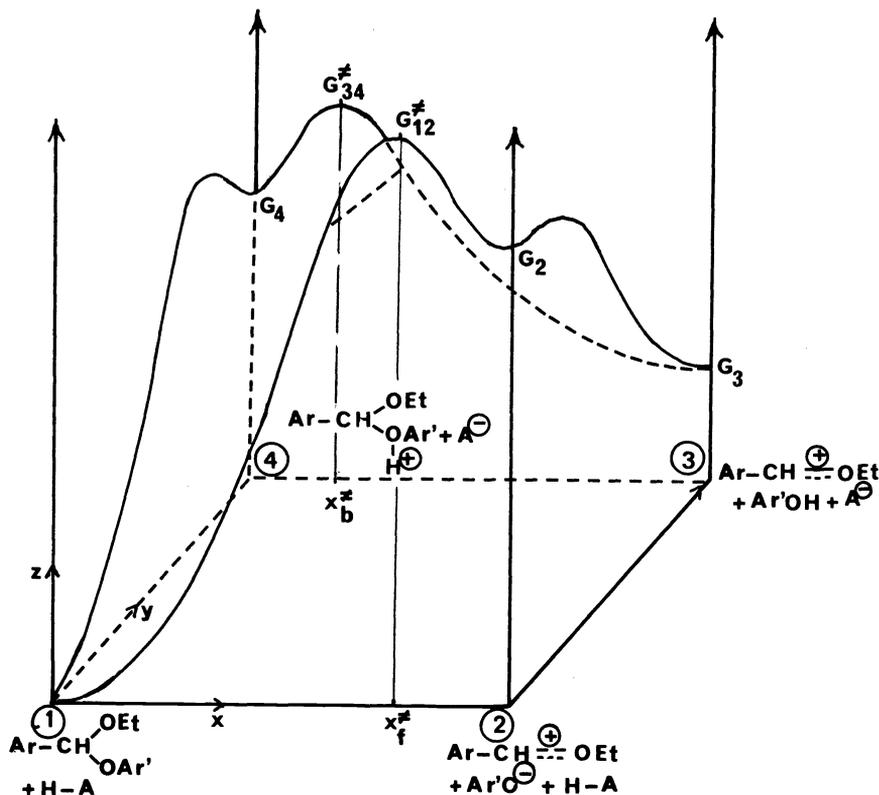


Fig. 3. 3-dimensional potential energy surface

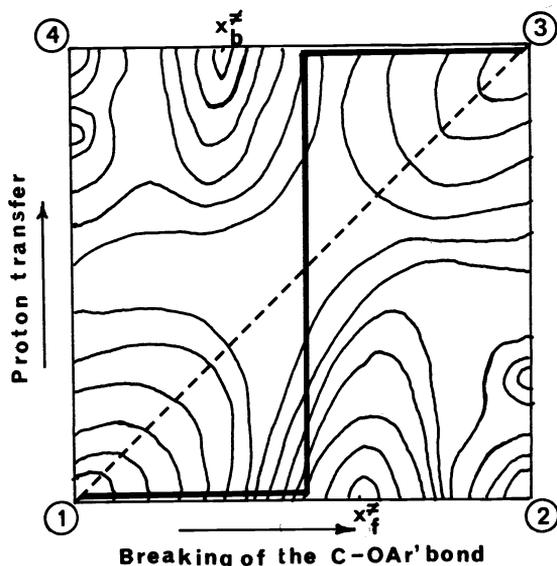


Fig. 4. Jencks-More O'Ferrall contour diagram

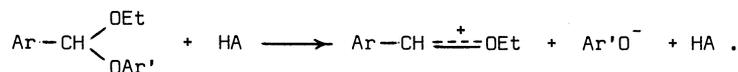
i) The first consists in treating symmetrically the two types of reactions which occur during the "crossing of the box"; if we do not make any difference between the two processes and assume that they can occur at "comparable" speeds, we can cross the box along a diagonal pathway (dashed line on Fig. 4). In that case we have a "partial proton transfer in the transition state" which is supposedly located somewhere around the middle of the "box"; this way of looking at the potential energy surface for concerted proton transfer is by far the most popular today.

ii) The second way to describe the motion of the system is to say that the two processes occurring during the "crossing of the box" cannot take place at the same speed: proton transfer between electronegative atoms are always extremely fast providing there is no thermodynamic adverse effect; when the basicities of the donor atom and of the acceptor atom are the same there is a very small kinetic barrier, if any, (Ref. 18) and the proton "jumps" at an almost immeasurable speed from the potential well of the donor to that of the acceptor. In the hydrolysis of acetals this fast proton "jump" is made possible because the basicity of the oxygen atom of the  $\text{Ar}'\text{-O}^-$  group increases tremendously when we move from the left to the right sides of the "box", that is during the C - OAr' bond cleavage. In the acetal the basicity is very low,  $\text{pK}_a \approx -8$ , in the phenol it is on the contrary rather high,  $\text{pK}_a \approx +10$ ;

there will thus exist a "degree of C-O bond breaking" for which the basicity of the phenoxyl oxygen will be the same as that of the acid catalyst; in consequence the proton will remain in the potential well of the catalyst as long as the basicity of the phenoxyl oxygen will not be roughly equal to that of the donor; when the two basicities will match the proton will pass from one potential well to the other, a motion corresponding to the crossing of the "box" from the front to the back sides. In this model the proton will be entirely transferred, or not at all, and it is irrelevant to talk about a "degree of proton transfer" since this degree can be only 0 or 1. With this model, we follow to cross the "box", an orthogonal pathway, first moving from left to right along the front side (stretching of the C-O bond), then crossing the "box" perpendicularly (proton jump) and finally moving again from left to right along the back-side (complete breaking of the C-O bond). This orthogonal pathway is indicated by a solid line on Fig. 4; it is much less in use than the diagonal one and has been very recently proposed by Eliason and Kreevoy (19) and modelised by Guthrie (20); we can't say now whether it offers a better representation of the reality than the diagonal one but it is much easier to build a mathematical model for it and it appears to have greater explanative and predictive values as I'll try to demonstrate.

#### MATHEMATICAL DESCRIPTION OF THE MODEL

To build a mathematical representation of the orthogonal pathway we should have first at our disposal a mathematical description of the free energy curves drawn on each side of the "box". It has been suggested recently (Ref. 21, 22) that the free energy along the reaction path on a two dimensional surface could be approximately represented by a mathematical function of the form:  $g(x) = ax^4 + bx^3 + cx^2$ ,  $x$  being the reaction coordinate. Let's take as an example the calculation of the free energy curve drawn on the front side of the "box", corresponding to the pH-independent cleavage of the C - O bond:



The reaction coordinate,  $x$ , varies arbitrarily from 0, corner 1, to 1, corner 2; the free energy goes from 0 to  $G_2$  and passes <sup>through</sup> a maximum  $G_{12}^\ddagger$  for a value of the reaction coordinate  $x_f^\ddagger$  corresponding to the abscissa of the transition state (Fig. 5). Le Noble (Ref. 22) has shown that  $c = -(4a + 3b)/2$  and that the other two coefficients  $a$  and  $b$  can be calculated (see Note a) as soon as we know  $G_2$  and  $G_{12}^\ddagger$ ; thus all we need to determine completely the quartic function for any reaction are the free energy of the reaction,  $\Delta G_0$ , and the free energy of activation,  $\Delta G^\ddagger$ . In our system the only curves of real interest are those drawn on the front side and on the back side of the "box"; those drawn on the left and right sides represent protolytic equilibria and cannot be the slow steps of the reaction. To construct the front and the back quartics we have to know  $G_2$ ,  $G_{12}^\ddagger$ ,  $G_3$ ,  $G_4$  and  $G_{34}^\ddagger$ . Let's see how we have evaluated these energies for the benzaldehyde acetals.

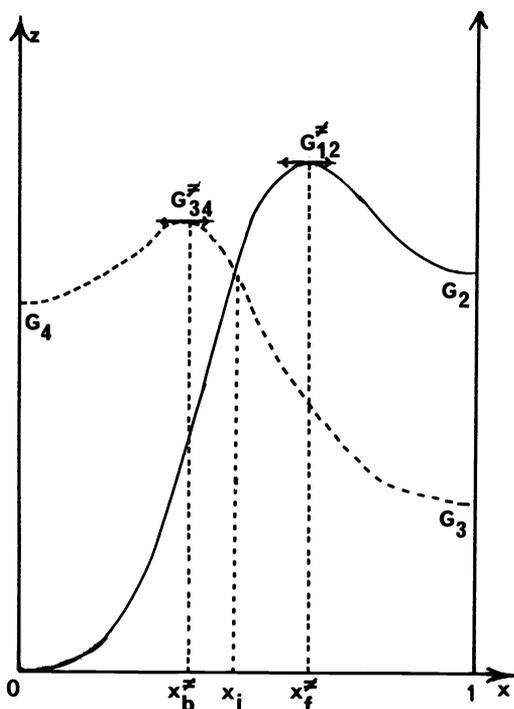


Fig. 5. Front projection of the free energy curves drawn on the front side (solid line) and on the back side (dashed line) of the "box". For the meaning of the symbols see text.

-  $G_{12}^\ddagger$  is the free energy of activation for the "spontaneous" cleavage of the C - OAr' bond; it corresponds to the "water reaction" and can be calculated from  $k_{H_2O}$  by the classical equation:  $G_{12}^\ddagger = -2.3 RT \text{ Log}(hk_{H_2O}/kT)$ .

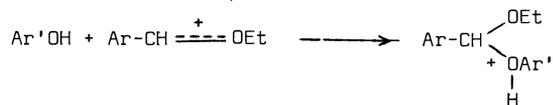
-  $G_2$  is more difficult to estimate; the reverse reaction, from corner 2 to corner 1, is the nucleophilic addition of a phenoxide anion  $\text{Ar}'\text{O}^-$  to an oxocarbenium ion. Jencks has shown (Ref. 14) that the addition of thiophenoxide anion  $\text{ArS}^-$  to the same oxocarbenium ion was a diffusion-controlled reaction with a rate constant of about  $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ; he has also shown that the rate of attack of the thiophenol  $\text{ArSH}$  on the same ion was 40 times smaller than that of the thiophenoxide anion; since the nucleophilic constants  $n$  (Ref. 23) of the phenoxide anion and of thiophenol are about the same we can take the same constant for the addition of  $\text{Ar}'\text{O}^-$  to  $\text{Ar} - \text{CH}^+ - \text{OEt}$ ; for the substituted-phenoxide ions we have to change slightly the  $n$  values, to take into account the influence of the substituent on the nucleophilicity of the ion, using a Hammett  $\rho$  coefficient of -1.25 (Ref. 24).

Note a. It is out of the scope of this paper to describe in detail the mathematical manipulations required to construct the quartic; these manipulations have been called "cumbersome" by Le Noble. However proper change of variables can alleviate greatly the mathematical chore and the authors can send, on request, to every interested chemist the "recipe" to calculate  $a$ ,  $b$  and  $x_f^\ddagger$  from  $G_2$  and  $G_{12}^\ddagger$  with the minimum of trouble.

-  $G_3$  is easy to calculate from  $G_2$ . The reaction on the right side of the box is the protonation of the phenoxide ion :  $\text{Ar}'\text{O}^- + \text{H-A} \rightleftharpoons \text{Ar}'\text{OH} + \text{A}^-$

$G_3 - G_2$  is the free energy of this reaction. If  $\text{pK}_{\text{AH}}$  and  $\text{pK}_{\text{Ar}'\text{OH}}$  are the respective pKs of the acid catalyst and of the phenol,  $G_3 - G_2 = -2.3 \text{ RT} (\text{pK}_{\text{AH}} - \text{pK}_{\text{Ar}'\text{OH}})$ .

-  $G_{34}^\ddagger$  can be calculated from  $G_3$ . The reaction from right to left on the back side is the nucleophilic attack of the phenol on the oxocarbenium ion :



$G_{34}^\ddagger - G_3$  being the activation energy of this reaction.

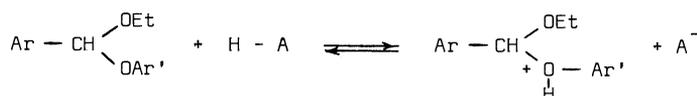
Jencks (14) has demonstrated that the ratio of the rate constants for the attack of phenol and phenoxide ion on the oxocarbenium ion was given by the relation :

$$\text{Log}(k_{\text{Ar}'\text{O}^-}/k_{\text{Ar}'\text{OH}}) = \text{pK}_{\text{Ar}'\text{OH}} + \text{Log } k_{\text{H}_2\text{O}}/k_{\text{H}^+}$$

in which  $k_{\text{H}_2\text{O}}$  and  $k_{\text{H}^+}$  are the catalytic constants of water and hydronium ion ;  $k_{\text{Ar}'\text{OH}}$  and

therefore  $G_{34}^\ddagger - G_3$  are easily deduced from this relation.

-  $G_4$  : its evaluation is less accurate since it rests upon the estimation of the basicity of the acetal. The reaction on the left side of the "box" is the formation of the conjugate acid of the starting material :



$G_4$  is the free energy of this process and is equal to  $-2.3\text{RT}(\text{pK}_{\text{AH}} - \text{pK}_{\text{acetal}})$ ,  $K_{\text{acetal}}$  being the dissociation constant of the conjugate acid of the acetal. pKs of weak bases can be found in the literature : from the data of Kankaanperä (25) a value of -8.4 can be estimated for the pK of the unsubstituted acetal ; the pKs of the substituted compounds can be deduced from this value using  $\sigma_Y$  parameters and the reasonable value of  $\rho = -2.5$  for the reaction constant (average of the  $\rho$  values for dissociation of phenols and protonation of anilines).

We have all we need now to construct the two quartics drawn on the front and the back sides of the "box". On Fig. 5 these two quartics have been drawn together, front curve in solid line, back curve in dashed line. It is important to notice that the front curve represents an endergonic process,  $G_2$  is always  $> 0$ , when the back curve represents an exergonic process,  $G_3$  is always  $< G_4$  ; as a consequence  $x_f^\ddagger$  will be  $> 0.5$ , which means that the transition state of the "water reaction" will always be reached later than the transition state of the hydronium ion catalysed reaction.

It should be mentioned, at that point, that there is one "box" for every acetal and every acid, that is 36 "boxes" altogether ; however we found convenient to show on the same picture all the "back curves" corresponding to the same acetal (Fig. 6. dashed lines, one for each acid) ; these curves have the same general shape and can be deduced from one another by a mere vertical translation ; the vertical distance between the curves corresponding to two acids, -AH and A'H for example -, is equal to the difference between the energies  $G_4$  and  $G_4'$  of the corner 4 ; as we could expect, the weakest the acid the higher the value of  $G_4$  since it is more difficult for it to protonate the acetal ; but once the acetal has been protonated the breaking of the C - OAr'H bond occurs with the same facility and the activation energy  $G_{34}^\ddagger - G_4$  is the same for all acids.

Let's see now how we can explain general-acid or specific-acid catalysis with this diagram ; starting from corner 1 the system has the choice between two pathways to reach corner 3.

i) the stepwise pathway, first along the left side from corner 1 to corner 4, then along the back side from corner 4 to corner 3. The total activation energy for this process is  $G_{34}^\ddagger$ , which is the energy of the activated complex situated between the conjugate acid of the acetal and the oxocarbenium ion ; in the case, for example of the m-chloro compound this

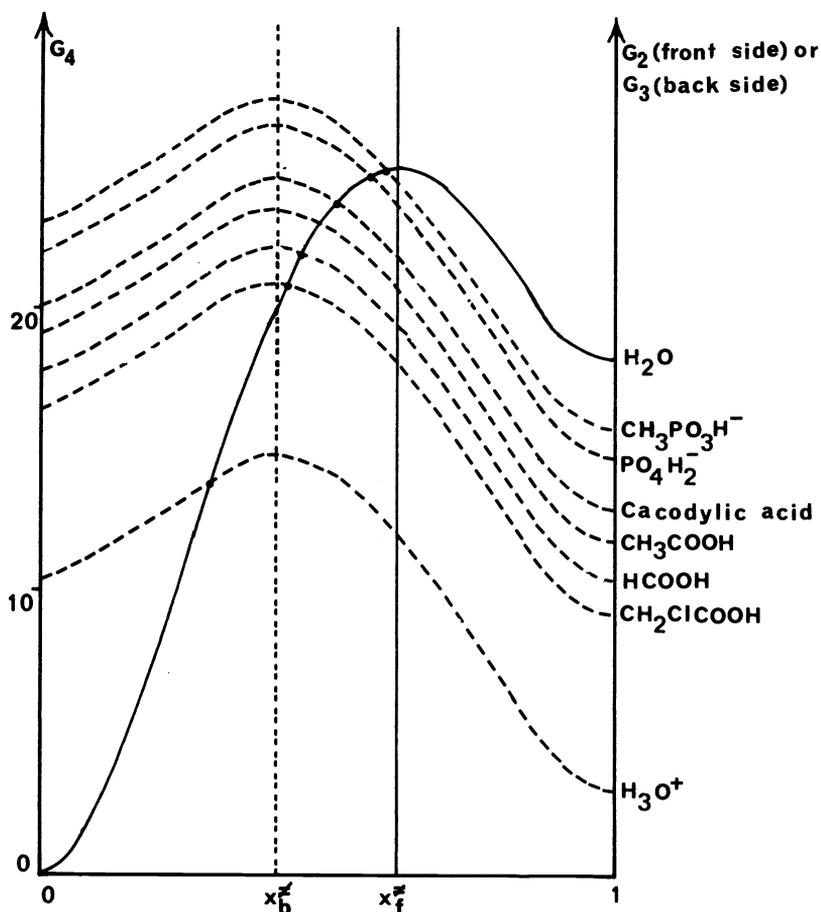


Fig. 6. Front (solid line) and back (dashed lines) curves for the hydrolysis of ethyl *m*-chlorophenyl benzaldehyde acetal.

activation energy will correspond, on Fig. 6, to the maxima of the "dashed" curves ; it depends upon the catalyst and increases when the acid strength of the catalyst decreases. For the acids that we have studied it runs from 14.8 Kc/mole for the hydronium ion to 27.4Kc/mole for the sodium methylphosphonate ; in this mechanism there are two well-separated steps, the conjugate acid of the acetal being a real intermediate with definite lifetime.

*ii*) the "concerted" pathway : starting from the same corner 1, the system moves on the front side following the left leg of the "water" reaction ; the catalyst and the substrate have probably formed an "encounter complex", the proton which



is to be transferred being hydrogen-bonded to the phenoxyl oxygen atom ; during this movement the length of the C - O bond and the basicity of the oxygen atom increase together ; when the system reaches the intersection point,  $x_1$ , of the two curves (Fig. 5) the proton crosses the "box" and jumps from the acid onto the phenoxyl oxygen atom ; after that the system goes down along the right leg of the specific-acid catalysed reaction until it reaches the corner 3.

Which pathway will be actually chosen by the system ? Of course that of least energy expense. Three cases can arise depending on the position of  $x_1$ .

*i*) If  $x_1 < x_b^\ddagger$ , which is the case on Fig. 6 for the hydronium ion, the system cannot avoid the back side maximum and we will observe a specific-acid catalysed reaction.

*ii*) If  $x_1$  is between  $x_b^\ddagger$  and  $x_f^\ddagger$ , which is the case for all the other acids, the system has a strong interest in choosing the "concerted" pathway since the crossing of the "box" at the intersection point allows it to avoid both maxima. We will observe a general-acid catalysed reaction .

iii) If  $x_1 > x_f^\ddagger$ , we observe only the "water" reaction and there will be no catalysis by acids except, may be, a kind of "spectator" catalysis by stabilization of the incipient phenoxyl anion by the weak acid. The rate will not be very different from that of the "spontaneous" hydrolysis and the reaction will be merely a  $SN_1$  reaction.

We see with this model that the type of catalysis actually observed is not a characteristic of the substrate alone but depends upon both the substrate and the catalyst ; in the cases we have studied we observed a general-acid catalysed reaction for the six buffer acids, a specific-acid catalysed reaction for the hydronium ion and the  $SN_1$  reaction for  $H_2O$ .

The Brønsted  $\alpha$  coefficient can easily be visualised with this model ; the actual energy of activation for the general-acid catalysed process is the energy of the intersection point of the two curves ; for two acids  $A_1H$  and  $A_2H$  whose energies of the intersection points are  $E_i^1$  and  $E_i^2$ ,  $\alpha$  is equal to  $E_i^2 - E_i^1 / \Delta pK$ , that is to  $E_i^2 - E_i^1 / (G_4^2 - G_4^1)$  as shown on Fig. 7.  $\alpha$  is then directly related to the steepness of the front curve and decreases when this steepness

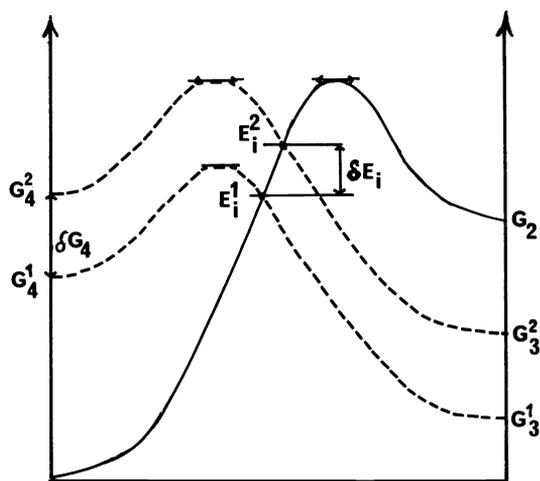


Fig. 7. Front and back curves showing the calculation of the  $\alpha$  Brønsted exponent.  
 $\alpha = \delta E_i / \delta G_4$

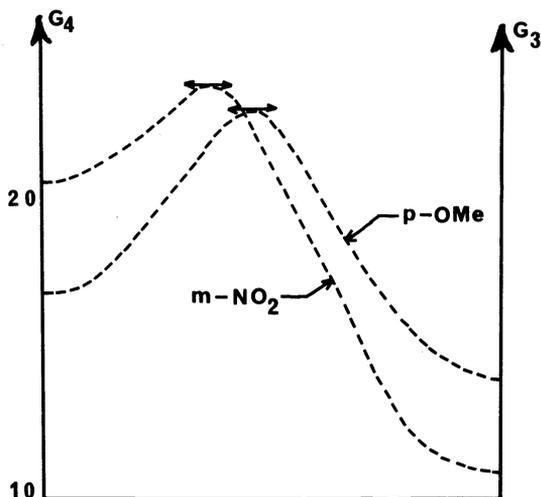


Fig. 8. Back curves representing the specific-acid catalysed hydrolysis of m-nitro and p-methoxy acetals.

decreases. The front curve reflects the case of spontaneous breaking of the C - OAr' bond : the better the leaving group, the easier this cleavage, the smaller the value of  $\alpha$ . It is exactly what we have found.

The Hammett correlation is more difficult to represent but, nevertheless, we can at least explain why the correlation observed is bad. We have to correlate the activation energies for different acetals with the same acid. The complication comes from the fact that the back curves corresponding to two different acetals intersect ; this is illustrated on Fig. 8 where we have drawn the back curves of the m-nitro and p-methoxy acetals with acetic acid as the catalyst ; the p-methoxy acetal is more basic than the m-nitro acetal, so the energy  $G_4$  of its conjugate acid is lower, 17.3 Kc/mole instead of 20.8 Kc/mole ; but the energy  $G_3$ , at the end of the reaction, is lower for the m-nitro (11.1 Kc/mole) than for the p-methoxy (14.2) compound. The representative back curves intersect some where around their maximum and this intersection complicates somewhat the picture (and the prediction). Fig. 9 is an enlarged view of the intersection area of all the curves ; we have joined together the intersection points corresponding to each weak acid ; we get an array of points more or less regularly arranged and we see that anything can happen (and, in fact, happened). On the contrary the maxima of the back curves are arranged regularly (Fig. 9. insert) and we can expect a good Hammett plot, with a negative slope, for the hydronium ion-catalysed reaction.

#### VALIDITY OF THE MODEL AND GENERALISATION

The model I talked about so far seems to give a simple and fair picture of what happens in acid-catalysed reactions. I must say that if the predictions we can make are qualitatively correct they are not quantitatively satisfactory. If we calculate the theoretical activation energies, - equal to the energies of the intersection points -, and if we compare them to the experimental activation energies we find that these latter energies are systematically lower

by 3 to 4 Kc/mole. Furthermore the mathematical treatment of the reaction path predicts a specific-acid catalysis for the p-methoxy compound in the presence of chloroacetic acid and an absence of catalysis ( $S_N1$  reaction) for the m-nitro compound in the presence of sodium

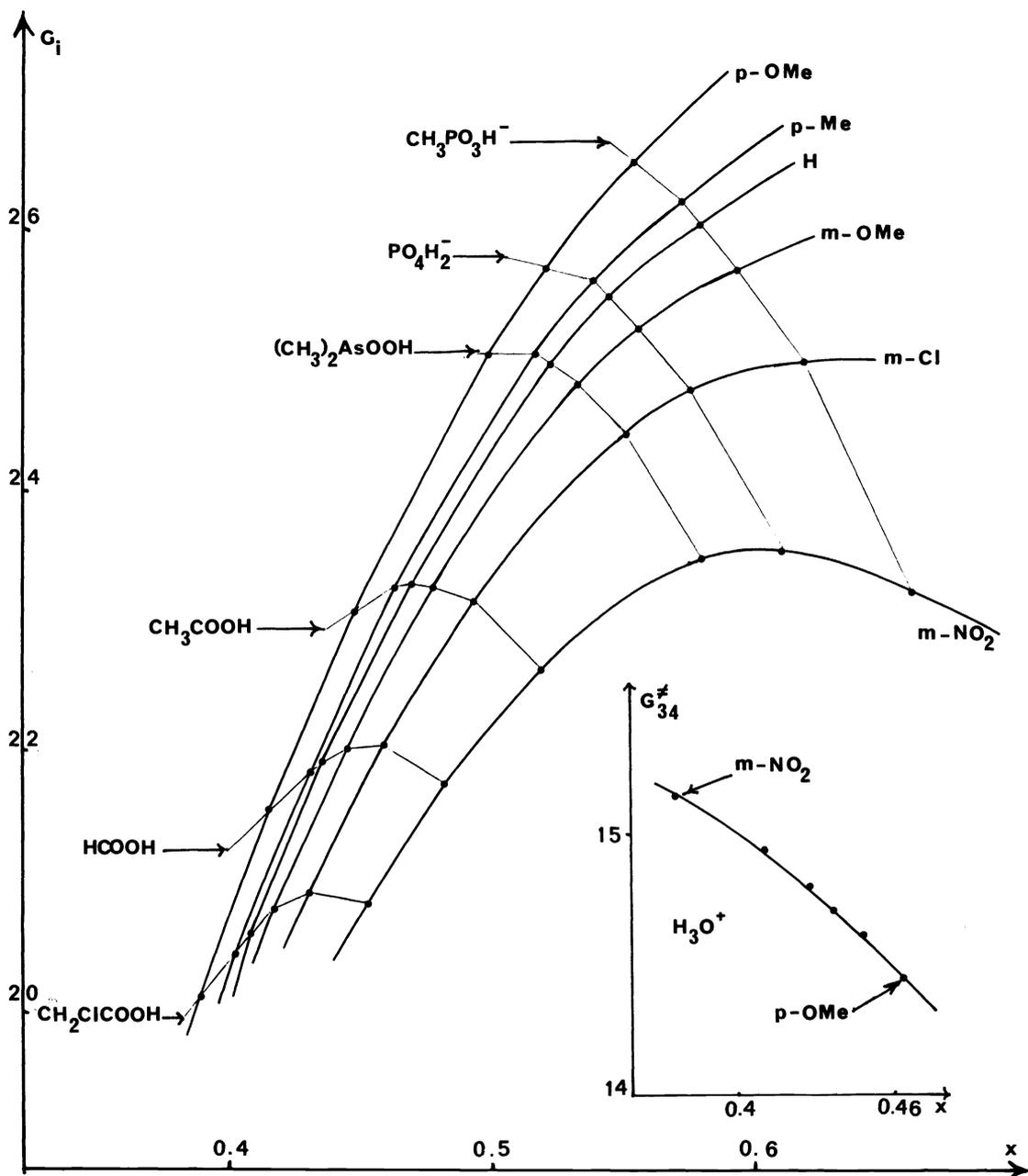


Fig. 9. Enlarged view of the intersection area. Insert : energy of activation of the hydronium ion catalysed hydrolysis.

phosphate and methylphosphonate ; in both cases a significant general-acid catalysed reaction is observed. This lack of quantitative agreement stems probably from the fact that a quartic function is a poor approximation of a potential energy curve ; as long as we have no better mathematical description of the potential energy we should be very cautious about validity of the conclusions we can draw from this model.

Nevertheless a few generalizations can be made about the type of catalysis we can expect to find in a given system. To be able to do that we have first to see how the shapes of the front and back curves are changed by a modification of the oxocarbenium and of the leaving group moieties of the substrate.

ii) Given a substrate,  $R-CH(OR')_2$ , and keeping  $R'$  constant, we can modify the stability of the oxocarbenium ion,  $-$  and at the same time the stability of the activated complex leading to it  $-$ , by changing the ability of the group  $R$  to stabilize a positive charge. When this ability increases the changes of the free energies along the different sides and corners of the "box" are as follows :  $G_2$  and  $G_3$  decrease strongly,  $G_{12}^\ddagger$  decreases less and  $G_{34}^\ddagger$  still less,  $G_4$  remaining probably unaffected or *decreasing* slightly ; as a consequence  $x_b^\ddagger$  and  $x_f^\ddagger$  will have lower values,  $x_b^\ddagger$  diminishing more than  $x_f^\ddagger$  ; these displacements are represented on Fig. 10. As a result the ratio  $k_H^+/k_O$  will decrease and the domain of occurrence of the general-acid catalysis will be enlarged and displaced towards the strongest buffer acids.

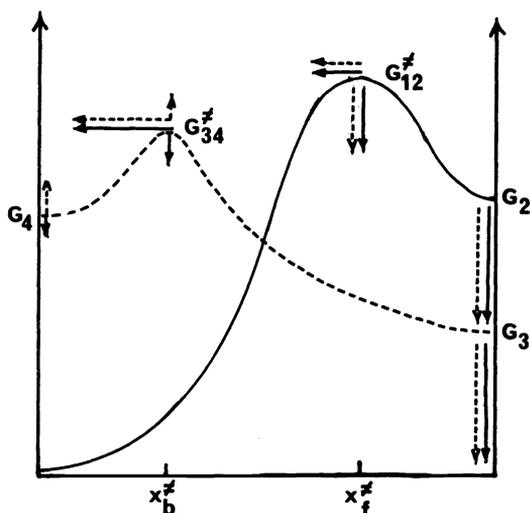


Fig. 10. Modifications brought to the front and back curves by increasing the stability of the oxocarbenium ion (plain arrows) or the nucleofugacity of the leaving group (dotted arrows). The lengths of the arrows are proportional to the intensity of the change.

ii) Let's see now what happens if we keep the oxocarbenium ion constant and change the leaving group ; it is the kind of situation we have examined since in the system we have studied we had always the same oxocarbenium ion,  $-Ar-CH^+=OEt-$ , and changed the substituent in the leaving group from  $p-OCH_3$  to  $m-NO_2$ . This change provokes, qualitatively, the same kind of energetic modifications as before :  $G_2$  and  $G_3$  decrease strongly,  $G_{12}^\ddagger$  a little bit less,  $G_4$  increases slightly since the leaving group is more difficult to protonate and  $G_{34}^\ddagger$  is more or less unaffected. As a consequence both  $x_b^\ddagger$  and  $x_f^\ddagger$  move towards the left of the diagram (Fig. 10.),  $x_b^\ddagger$  more than  $x_f^\ddagger$ , and the ratio  $k_H^+/k_O$  decreases again. It is what we have experimentally found : in going from the  $p$ -methoxy to the  $m$ -nitro acetal  $x_b^\ddagger$  decreases from 0.462 to 0.377,  $x_f^\ddagger$  from 0.644 to 0.607 and  $k_H^+/k_O$  from  $4.2 \times 10^7$  to  $2 \times 10^4$ . Here again the domain of general-acid catalysed reactions is enlarged and displaced towards the strongest acids : the strongest acid for which it is possible to observe a general-acid catalysis has a  $pK$  of 5 for the  $p$ -methoxy acetal and a  $pK$  of 0.1 for the  $m$ -nitro acetal.

A fact which strengthens our confidence in the soundness of this analysis is the study of the  $p$ -nitro acetal which we have prepared along with the above-mentioned compounds. We found for it a completely different behaviour in the sense that the rate-determining step, above  $pH$  4, is the decomposition of the hemi-acetal ; nevertheless the specific catalytic constant of the hydronium ion for step 1 can be determined in hydrogen chloride solutions and was found to be higher than expected, by a factor of 3, on the basis of the Hammett correlation for  $H_3O^+$ . The construction of the "box" for the  $p$ -nitro acetal shows that the intersection of the front and back curves occurs after the maximum of the back curve,  $x_b^\ddagger < x_1 < x_f^\ddagger$ , and that we are in the domain of the general-acid catalysis even for the hydronium ion catalysed reaction.

Of course, it is impossible here to draw general rules applying to all types of reactions ; each compound constitutes a particular case and should be the object of a particular study ;

however it seems that we can predict what kind of catalysis a given compound will be submitted to as soon as we know the value of the ratio  $k_{\text{H}^+}/k_{\text{O}}$  of the two rate constants for the hydro-ion catalysed reaction and for the "spontaneous" reaction. At the present time we can say that it is hopeless to search for a general-acid catalysis in any reaction with usual buffer acids if this ratio is not below  $10^9$  to  $10^{10}$

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