mp 132–135° (lit.[26] 112.8–113.6°); **2-adamantyl benzenesulfonate,** mp 85–86.2° (lit.[26] 88.2–89.0°); **2-adamantyl *p*-toluenesulfonate,** mp 78.0–79.5° (lit.[26,27] 82.1–82.5°, 82.7–83.7°); **2-adamantyl *p*-methoxybenzenesulfonate,** mp 60.0–61.5° (lit.[26] 62.7–63.2°).

Benzhydryl Benzoates. These compounds were prepared by reacting a mixture of the benzoyl chloride (approximately 10% excess) (Aldrich), benzhydrol, and a minimum amount for solution of dry pyridine at 5° for 4 hr and then at −20° for 18 hr. The pyridine solution was poured into ice and water and extracted twice with ether, and this solution was dried. The usual[28] acid wash to remove pyridine was omitted. The esters were then recrystallized from pentane. All esters gave satisfactory nmr and ir spectra and the two of the series examined gave satisfactory analyses: **benzhydryl 3,5-dinitrobenzoate,** mp 137.5–141.0°; **benzhydryl *p*-nitrobenzoate,** mp 133–134° (lit.[29] 133.4–134.0°) (*Anal.* Calcd: C, 72.03; H, 4.54. Found: C, 72.00; H, 4.64); **benzhydryl *p*-trifluoromethylbenzoate,** mp 93.5–95.0°; **benzhydryl *p*-fluorobenzoate,** mp 80.5–82.5°; **benzhydryl *p*-chlorobenzoate,** mp 86.5–88.0°; **benzhydryl *p*-methoxybenzoate,** mp 96.0–98.0° (*Anal.* Calcd: C, 79.22; H, 5.70. Found: C, 79.12; H, 5.80).

Ethanol was distilled from magnesium ethoxide.

Pyridine was distilled and stored over potassium hydroxide pellets.

Kinetic Procedure. Rates were determined conductimetrically as previously described.[11]

Product Determination. Product ratios were determined by direct gas chromatographic analysis of reaction mixtures. A 6 ft × 1/8 in. column packed with SF96 on 60–70 mesh Anakrom ABS was used.

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Effect of Polyelectrolytes upon the Kinetics of Ionic Reactions. IV. The Decomposition of Aspirin in Aqueous Solutions Containing Polycations

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Abstract: The decomposition of aspirin in aqueous solutions of cationic polyelectrolytes has been studied over a considerable pH range (1.5–11.0). Poly(ethylenimine), a weak polyelectrolyte containing free amino groups which act as nucleophilic reagents upon the substrate, and the strong polyelectrolyte poly(vinylbenzyltrimethylammonium chloride), without such reactive groups in its molecule, were employed in the present study. Poly(vinylbenzyltrimethylammonium chloride) was found to modify only slightly the rate of hydrolysis of aspirin in the pH independent region (5–9), but it increases by a factor of 9 the rate of bimolecular saponification of the ester in alkaline solutions. This acceleration can be explained satisfactorily with an electrostatic model which predicts an enhanced local concentration of the substrate anion and OH^- near the chains due to the large charge density of the polymeric chains. On the other hand, in poly(ethylenimine) solutions the rate of decomposition of aspirin is substantially increased, passing through a maximum at pH 7.8, where the rate constant is 1275 times greater than in the absence of polyelectrolyte. A further increase in pH causes a decrease in rate constant until the value corresponding to solutions without polyelectrolyte is reached at pH ~11. The explanation of this behavior is given in terms of two competing effects. When the pH increases, the fraction of amino groups which are free increases also, thus enhancing the possibility of nucleophilic attack on the substrate; on the other hand, the concomitant decrease of charged groups on the macroion reduces the local concentration of the charged substrate near the polymeric chain.

It has been shown[2,3] that the rate of decomposition of *p*-nitrophenyl phosphate (NPP) is modified by the presence of polycations in the solution. The observed effect depends on the pH of the solution and on the nature of the polycations. When the polyelectrolyte was poly(ethylenimine) (PEI), which has groups capable of acting as nucleophilic reagents, the rate of decomposition was substantially increased. For polyions like poly(vinylbenzyltrimethylammonium chloride) (PVBA-Cl), having no reactive groups, the rate of hydrolysis at those pH values where the mechanism of hydrolysis is known to be unimolecular was found to be higher than in water. It was conclusively shown that these modifications of the rate of decomposition of NPP depend on the existence of a high charge density on the macroions; *i.e.*, it is a manifestation of the so-called polyelectrolyte effect.

Klotz and coworkers[4] and Overberger and coworkers[5] have studied a large number of reactions in solution in the presence of added polymeric solutes; in general their macromolecules had groups capable of reacting with the substrates, and with a proper selection of these groups the effect of polymers on the reactions can be very large. In polyionic solutions the reactions between the reactive groups on the macroions and oppositely charged substrates may be considered affected by two

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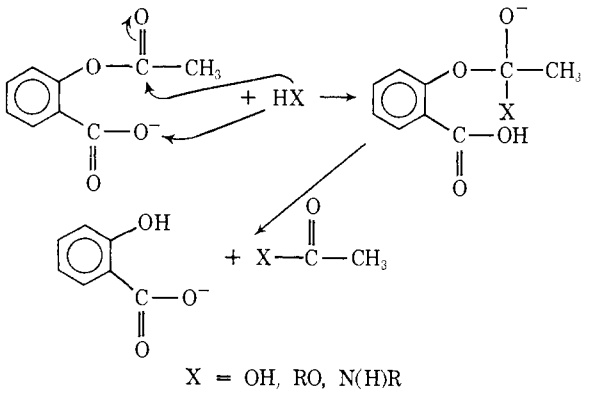
factors: the nature of the reactive groups and the high charge density on the chains.[5] Furthermore, the effect of charged polymers with reactive groups upon substrate decomposition is much larger than that of their low molecular weight analogs.[3,5] This concerted action in which the high electric field of the polyions concentrates the substrate near the reactive groups on the polymer chains may be deemed related to the mechanisms of enzymatic reactions.

In the present paper, the effect of PEI and PVBA-Cl upon the decomposition of aspirin is reported. In the pH range 5–8.5 the first-order rate constant for the hydrolysis of aspirin is pH independent.[6,7] The pseudounimolecular hydrolysis is attributed to intramolecular general base catalysis involving water. When other suitable nucleophilic species like amines or alcohols exist in solution, the same mechanism is responsible for the decomposition of aspirin with the nucleophile molecule replacing that of water.[8,9] The reaction scheme (Scheme I) is that proposed by St. Pierre and Jencks[9] for the decomposition of aspirin.

Scheme I



The rates of hydrolysis of aspirin and NPP in water show a pH-independent region where only a single charged reactant species is involved in each case, but the mechanisms of hydrolysis are different. Moreover, the aspirin anion is monovalent while that of NPP is divalent. Thus it was interesting to compare the polyelectrolyte effect[10] on the rate of hydrolysis of NPP with that of aspirin, as well as the rate of substrate decomposition in solutions containing polycations with free amino groups which act as nucleophilic reagents toward the substrates.

PVBA-Cl modifies only slightly the rate of hydrolysis of aspirin in the pH-independent region, while it accelerates the bimolecular saponification of the ester in alkaline solutions. In PEI solutions, there is a marked increase in the rate of decomposition of aspirin having a maximum at pH 7.8; specific nucleophilic attack of the substrate by the free amino groups of PEI takes place in this region. In alkaline solutions, on the other hand, PEI does not affect the rate of hydrolysis of aspirin.

Experimental Section

PEI was Polymine P from B.D.H.; it has an average molecular weight of 40,000. The molecular weight per ionogenic group was obtained by careful titration of PEI samples with HCl and determination of counterion concentration in the samples; its value is 62 g. PVBA-Cl was obtained from Dow Chemical Co.; the product has an average molecular weight of 300,000 and a monomer molecular weight of 222 g.

The hydrolysis of aspirin was followed measuring the optical absorption due to salicylic acid at its isosbestic point, which corresponded to 299 nm in the Perkin-Elmer 139 spectrophotometer employed. The optical absorption of salicylic acid at 299 nm was the same in solutions containing PEI or PVBA-Cl and without them at all pH's and agreed within experimental error with the concentration obtained from the weight of salicylic acid (ϵ_{299} 3500 cm^{-1} mol^{-1} l.[6]).

The kinetic runs were carried out at 35.0 ± 0.1° using a concentration of acetylsalicylic acid ranging from 2 to 7 × 10^{-4} *M*. Aliquots were withdrawn from the reaction vessels at appropriate times and were diluted in an equal volume of HCl of such concentration that the final pH was in the region of 2–3, where the decomposition of aspirin is very slow. The runs were always followed until 1.5 half-lives had passed, in some cases aspirin decomposition was followed up to 3 half-lives. In general, the data corresponded to first-order rates in aspirin, in some instances the plots of logarithm (salicylic acid) against time deviated somewhat from linearity, this could be explained on account of the inherent uncertainty of the method employed, estimated as 3% for slow reactions and amounting to 6% for the fastest reactions. The absorbance at infinite time, necessary to determine the initial concentration of aspirin, was obtained by two procedures. For fast reactions (half-lives ≤30 min), the reaction was allowed to proceed for a sufficient time to ensure that all the substrate had decomposed; the optical density of the final solutions was then measured as described above. In the case of slow reactions, an aliquot was withdrawn from the reaction vessel and was mixed with an equal volume of 0.2 *M* NaOH; in these alkaline solutions the reaction is very fast, allowing the determination of the final concentration of salicylic acid in about 30 min. The first-order rate constants reported here were obtained from the slope of the straight line corresponding to the plot of logarithm (salicylic acid) against time.

In order to fix the pH of the solutions without polyelectrolyte and those containing PVBA-Cl, appropriate buffers were employed; their ionic strengths were in general ten times greater than the substrate concentration. In PVBA-Cl solutions the concentration of polyelectrolyte (in monomoles) was at least twice as large as that of the buffer. PEI solutions, on the other hand, have buffer capacity and the pH was adjusted by adding appropriate amounts of HCl, the degree of ionization of the polyelectrolyte was determined from the titration curve.[3]

In order to verify the nature of the products of aspirin decomposition in PEI solutions, where there is specific attack of the substrate by PEI, their properties were compared with those of a solution of PEI and salicylic acid of the same concentration. NaCl was added to both solutions after complete decomposition of the aspirin. The solutions were then thoroughly dialyzed until no salicylic acid was detected in the dialysate. The dialyzed solutions had no salicylic acid, indicating that this product is not bound by PEI. The uv spectra of both solutions were identical and corresponded to pure PEI, except in the region from 210 to 250 nm, where the absorption of the solution which originally had aspirin was somewhat higher. This is the spectral region where *N*-methylacetamide absorbs, suggesting therefore that the acetyl groups of aspirin remain attached to PEI after the reaction. This is confirmed with the ninhydrine test, which allows the determination of primary amino groups. The test applied to the solutions of PEI which originally had aspirin showed that 50% of the original primary amino groups were blocked. This value corresponds to acetylation of nearly all the primary amino groups of PEI which were free at the pH of the solution. These evidences agree with the mechanism for decomposition of aspirin proposed by St. Pierre and Jencks.[9]

Results

The values obtained for the rate of hydrolysis of aspirin in water at 35° agree generally with those of Garrett,[7] but are slightly larger. The results of the kinetic runs are illustrated in Figure 1 and summarized in Table I.

For PVBA-Cl solutions a small acceleration of the

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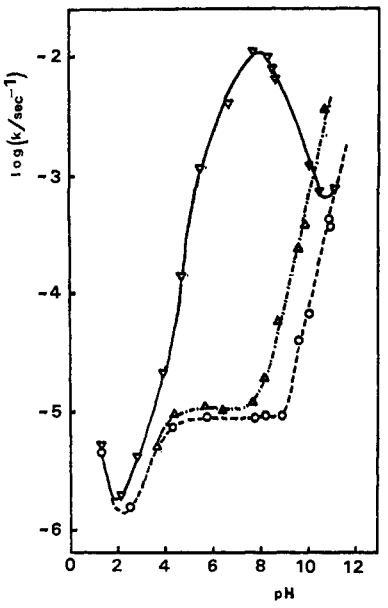

Figure 1. Rate of decomposition of aspirin at 35°: (○) in water, (△) in PVBA-Cl solutions, (▽) in PEI solutions; [PVBA-Cl] 7.5×10^{-3} monomoles/l.; [PEI] 2.35×10^{-2} monomoles/l.

Table I. Experimental Conditions and First-Order Rate Constants for the Decomposition of Aspirin at 35.0°

Water		7.5×10^{-3} monomolar PVBA-Cl		0.0235 monomolar PEI	
$10^6 k$, sec^{-1}	pH	$10^6 k$, sec^{-1}	pH	$10^6 k$, sec^{-1}	pH
5.0	(1.10)	5.12	3.65[h]	5.23	1.38[j]
4.6	1.33[a]	9.7	4.34[i,c]	1.98	2.18
1.31	(2.50)	10.7	5.6[d]	4.2	2.83[j]
1.61	2.60[b]	10.4	6.33[d]	21.9	3.90
7.60	4.45[c]	12.1	7.65[e,i]	142	4.70
8.03	(5.05)	20.0	8.20[e]	729	5.45
9.2	5.8[d]	60.0	8.75[f]	5,100	6.73
9.02	7.85[e]	242	9.55[f]	11,500	7.70
9.65	8.25[e]	390	9.90[f]	10,300	8.27[k]
9.42	8.97[f]	3840	10.7[g]	7,820	8.5
41.0	9.70[f]			6,670	8.66
70.5	10.1[f]			1,242	10.05
440	11.00[g]			720	10.5
414	(11.3)			801	11.15

[a] 0.088 *M* HCl. [b] 0.5 *M* acetic acid. [c] CH_3COO^- + CH_3COOH. [d] $H_2PO_4^-$ + OH^-. [e] Tris. [f] Borax + OH^-. [g] OH^-. [h] $KHC_4H_4O_6$. [i] 3.8×10^{-3} monomolar PVBA-Cl. [j] 9.4×10^{-3} monomolar PEI. [k] 0.056 monomolar PEI. Values in parentheses are from ref 7: solvent contained 0.5% ethanol, buffers and ionic strength were different from those in the present work.

reaction rate is observed in the pH-independent region. In alkaline solutions, where the rate-determining step is the bimolecular reaction between OH^- and acetylsalicylate anion, the polycation increases substantially the rate of hydrolysis.

In PEI solutions the rate of decomposition of aspirin increases with pH passing through a maximum at pH 7.8, where the ratio of first-order rate constants with and without PEI is 1275. In more alkaline solutions the rate of decomposition of aspirin in PEI solutions decreases becoming equal to the rate of hydrolysis in water at pH ~11. For those solutions having a pH smaller than 3, the effect of PEI is small (*cf.* Figure 1) and tends to disappear in very acid solutions, because the substrate exists in the neutral acid form.

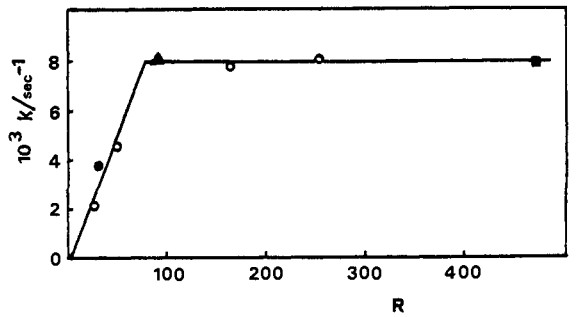

Figure 2. Rate of decomposition of aspirin against R = [PEI]/[aspirin] at 35° (pH 8.5). [aspirin] (mol dm^{-3}): (■) 1.16×10^{-4}; (○) 1.55×10^{-4}; (▲) 4.4×10^{-4}; (●) 5.6×10^{-4}.

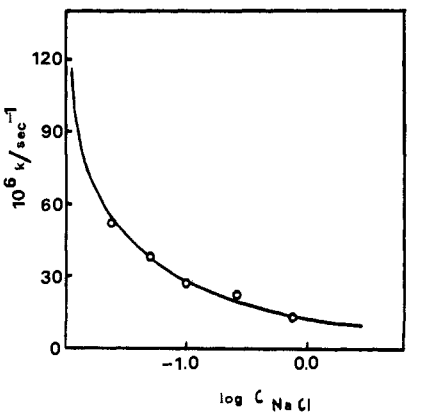

Figure 3. Effect of added NaCl on the rate of decomposition of aspirin at 35° (pH 4.7).

Figure 2 shows the change of the first-order rate constant in PEI solutions at pH 8.5 as a function of the ratio R, which expresses the number of monomoles of polyelectrolyte per mole of aspirin. The rate constant is seen to increase until $R_{max} = 77$, thereon the rate of decomposition of aspirin is constant. The slight dispersion of the data from the lines in Figure 2 must be attributed to the fact that in such pH region small pH fluctuations produce a marked change in the rate constant.

Figure 3 illustrates the effect of NaCl on the rate of decomposition of aspirin in PEI solutions. The first-order rate constant of aspirin decomposition decreases from 1.42×10^{-4} sec^{-1} (pH 4.7), when no NaCl is present, to a value close to that in pure water when the solution is 0.7 *M* NaCl. The rate constant of aspirin decomposition in 0.0235 monomolar PEI solution is reduced to half its value when the concentration of NaCl is about 0.014 *M*.

Discussion

Hydrolysis of Aspirin. The first thorough kinetic study of the hydrolysis of aspirin was that of Edwards.[6] The pH–rate profile in the range 0.53–12.77 (*cf.* Figure 1 and ref 6 and 7) was interpreted by Edwards in terms of the contributions of all possible species in solution, namely acetylsalicylic acid and its anion, H_2O, OH^-, and H_3O^+. In very acid solutions the reaction between the acid form of the substrate and the H_3O^+ ion predominates; near the minimum there is an appreciable contribution of the bimolecular reaction between substrate anion and H_3O^+ ion. For the pH-

independent region, Edwards suggested that the rate-determining step was the attack of the aspirin anion by a water molecule; finally, in alkaline solutions the reaction is between the anion and the hydroxide ion.

The point requiring further elucidation was the detailed mechanism of hydrolysis in the pH-independent region. The careful work of Fersht and Kirby[8] and of St. Pierre and Jencks[6] seems to have settled finally the issue. The hydrolysis in the pH-independent region would be due to an intramolecular general base catalysis by the carboxylate group, involving a water molecule, as depicted in Scheme I. The rate-determining step is thus bimolecular.

It is interesting to analyze the different effect of PVBA-Cl on the hydrolysis of NPP and of aspirin in the pH-independent region. The hydrolysis of NPP involves the unimolecular splitting of the substrate dianion,[3] while that of aspirin requires an intramolecular rearrangement. It is not surprising then that in the first instance PVBA-Cl increases the rate of hydrolysis by a factor of about 6.4,[3] while in the latter case the increase is at most 1.3. The highly charged polymeric chain is capable of increasing the rate at which two groups in the substrate are torn apart by unimolecular bond cleavage, especially when both groups are of a strong dipolar character or bear charges opposite to the polyelectrolyte, thus facilitating strong interactions of each of the groups with different points of the chain.[3] In the case of aspirin hydrolysis, the activated complex involving H_2O is more compact and it is less likely that its energy is affected in a very different way from that of the reactants by the presence of the macroion in the solution. Moreover, in the case of aspirin, only the carboxylate group will interact strongly with the charged polymeric backbone.

In alkaline PVBA-Cl solutions there is a very notable increase in the rate of hydrolysis of aspirin (*cf.* Figure 1). The ratio k/k_0 between first-order rate constants with and without polyelectrolyte in the solution is constant in this range and equal to 9.1. Thus k varies linearly with concentration of OH^- ions in water or in PVBA-Cl solutions. This is the behavior expected when the macroion's influence is essentially electrostatic, *i.e.*, it increases the local concentration of reactants by electrostatic attraction between the charges on the chain and the oppositely charged reacting ions.

Finally, it may be interesting to compare the present kinetic results to those obtained in micellar solutions. The aspirin hydrolysis reaction has been studied in the pH range 1–7 in the presence of nonionic micelles,[11–13] anionic micelles,[13] and cationic micelles.[13,14] The case which is more relevant to our work is that corresponding to cationic micelles, where a decrease in the rate of hydrolysis was observed in the whole pH range studied, a behavior which differs from that observed in the present study.

This discrepancy may be attributed to the fact that electrostatic forces are only one contributing factor to micellar catalysis (and usually not the biggest one), while this is the only effect in the polyelectrolyte solutions employed in the present study.

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Decomposition of Aspirin in PEI Solutions. St. Pierre and Jencks[9] have studied the reaction of aspirin with organic bases; the reaction with methylamine, which is particularly relevant for the present study, was shown to be quite fast. In view of the results reported here and the fact that primary amino groups of PEI appear acetylated after decomposition of aspirin has taken place, it is concluded that a reaction similar to that with monomeric amines occurs in PEI solutions.

In acid solutions (pH ≤ 2), PEI does not alter the kinetic behavior of aspirin because the substrate is in the uncharged acid form. As the pH and consequently the fraction of substrate anion increases, the rate of decomposition of aspirin is enhanced because the anion hydrolysis is faster than that of the uncharged species.[6,7] This point is about pH 2.5 in PEI solutions, a pH value which is, however, substantially smaller than the pK_a of acetylsalicylic acid ($pK_a' = 3.62$[7]). This enhancement of substrate dissociation is due to the high charge density of the polymeric chain, which has been shown[15] to be responsible for an increase in the extent of dissociation of the weak neutral acid at a given pH. The increase in rate constant is moderate because PEI has a very small fraction of free amino groups at such pH values and the reaction that occurs is essentially the hydrolysis. As the pH increases, all aspirin is in the form of anion, which is then drawn close to the chain where there is now a larger fraction of free primary amino groups that may attack the substrate. As the pH increases further, the charge on the polymer becomes smaller, the substrate will be less attracted to the macroion and its decomposition rate will decrease. The maximum rate of decomposition is observed to occur at pH 7.8 where the degree of ionization of the macroion is 0.50.[3] As seen in Figure 1, when all the amino groups in PEI are in the form of free bases (pH ≥ 11), PEI does not modify the rate of aspirin decomposition. This is a clear evidence of the importance of electrostatic interactions to produce the observed effects in PEI solutions.

Further support to the idea that the electrostatic interactions are the causative factor of the enhanced rate of decomposition of aspirin is afforded by the results illustrated in Figures 2 and 3. The dependence of the rate constant on the ratio R, rather than on the concentration of PEI, is a consequence of the applicability of the domain model to polyelectrolyte solutions, as discussed elsewhere.[3] On the other hand, the fact that k increases with R until a maximum value is reached ($R_{max} = 77$ at pH 8.5 and $i = 0.36$ in the present case) and thereon remains constant, reflects the involvement of a single mobile ion, apart from H_3O^+ or OH^- ions, in the rate-determining step. This is the case for the decomposition of NPP as well as that of aspirin in PEI solutions.

The electrostatic nature of the phenomenon is corroborated by the fact that R_{max} for the aspirin monoanion is much larger than that found for the NPP dianion, which is more strongly attracted to the macromolecule. It was found[3] that for PEI–NPP R_{max} ($i = 1.0$) = 10, while for PEI–aspirin R_{max} ($i = 1.0$) = 28.

The decrease of rate constant in PEI solutions when NaCl is added, illustrated in Figure 3, also agrees with

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the electrostatic nature of the phenomenon. The added salt shields partially the charges on the chain and its ions will compete with the substrate ion for positions close to the macroion. A solution 0.014 *M* NaCl and 0.0235 monomolar PEI presents half the rate of decomposition observed in a solution at the same polyionic concentration and with no added NaCl. Furthermore, there is a dramatic change of the effect of added NaCl when passing from the univalent to the divalent substrate. For the reaction of the NPP dianion with PEI 0.048 monomolar, the same decrease to half the rate of decomposition is observed only when the NaCl has a concentration of 0.32 *M*.[3] This is further accentuated by the fact that the values quoted above correspond to pH 4.7 (i = 0.80) for the aspirin–PEI system, while for the NPP–PEI system they refer to pH 7.8 (i = 0.50), and it would be expected more NaCl must be added to reduce the polyelectrolyte effect of those macroions having a larger charge density.

The Electrostatic Model. All the observations reported in this paper as those in ref 3 agree qualitatively with the fact that the causative factor of the observed changes in rates of reaction is electrostatic. One of the simplest, albeit successful, electrostatic models for polyelectrolyte solutions is that proposed by Manning.[10,16] This theory explains quite well the observed thermodynamic and transport properties of PEI and PVBA-Cl solutions, which are summarized now.

The measured activity coefficient of chloride counterion in salt free PEI solutions (i = 1.0)[17] is between 0.30 and 0.39 in the concentration range 0.02–1.0 *M*; the value predicted by Manning's theory is γ_{Cl^-} = 0.315. Self-diffusion measurements for the chloride counterion in the same solutions give D/D_0 = 0.46[17] and the calculated value is 0.45. The value observed for γ_{Cl^-} which was 0.02 monomolar PEI (i = 1.0) and 0.01 *M* NaCl is 0.56;[18] the value calculated is 0.52.

Darskus, *et al.*,[19] measured conductimetrically in PVBA-Cl solutions the value of f, the quantity which relates the conductivity observed in the polyelectrolyte solution to the contributions of the counterion and polyion according to $\Lambda = f(\lambda_c^\circ + \lambda_p)$.[10] For 1.6×10^{-3} monomolar PVBA-Cl f turned out to be 0.28; Manning's theory gives a value of 0.30 for f.

The theoretical calculation of the above properties of the polyelectrolyte solutions requires the value of the charge parameter[16] $\xi = e^2/DkTb = 7.25/b$ for water at 35° (b is the distance between two adjacent charges on the polymeric chain). For PVBA-Cl, as well as for other polyvinylic polymers, the distance between two ionogenic groups is b = 2.55 Å and ξ = 2.85. PEI, being a weak polyelectrolyte with a degree of ionization i, will have $b = b_{str}/i$, where b_{str} = 3.75 Å takes into account the average distance between nitrogen atoms in the chain[17,20] and the fact that 20–25% of the nitrogens are not titratable (cannot be ionized), thus ξ = 1.93 i. These ξ values were employed to calculate the properties of the polyionic solutions.

Thus Manning's model of counterion condensation reproduces fairly well the thermodynamic and transport properties of the polyelectrolyte solutions. Analysis of the values of R_{max} for aspirin and NPP shows qualitative agreement with the theoretical predictions of this model. Divalent anions such as NPP will condense on the polycation chain in preference to any monovalent counterion. The singly charged acetylsalicylate anion, on the other hand, will have the same tendency to condense on the macroion as the Cl^- counterions do; hence both ions will compete for positions near the chain. The consequence being that R_{max}(NPP) < R_{max}(aspirin), which agrees with the values of 10 and 28 found, respectively, in PEI solutions. The theory of counterion condensation can be employed to predict the value of R_{max} in the case of polyvalent substrate ions, because these ions will condense preferentially to Cl^- counterion until the value of the charge parameter ξ is reduced below its critical value of $^1/_2$. The theory predicts R_{max} (i = 1.0) = 2.7 for NPP in PEI solution, compared to the experimental value of 10. The possible contribution of nonelectrostatic interactions could be invoked to explain this difference, but they do not seem very significant in this case, due to the fact that identical results were found for NPP in both polyelectrolyte solutions and the effect of salt considered above. Moreover, the NaCl concentration necessary to reduce the polyelectrolyte effect on the kinetics of aspirin decomposition in PEI solutions is remarkably similar to that required to reduce the polyelectrolyte effect on the activity coefficient of the monovalent Cl^- counterion in PEI solutions of the same concentration.[18]

There seems to be a case for expecting a poor performance of the Manning model in the prediction of some properties of the polyelectrolyte solutions which depend on the detailed ionic distribution near the polymeric chain. This is the case for the reactions in PEI solutions, where the substrate decomposition only proceeds when a substrate counterion is able to reach the chain itself. This limitation is also manifest in the very recent work of Manning and Holtzer[21] on the titration of weak polyions, where the theoretical predictions show a more pronounced discrepancy with the experimental results when the titration has proceeded to a point where the charge parameter ξ has exceeded the critical value corresponding to counterion condensation. From thereon every charge created on the chain by the titration procedure requires the condensation of a counterion. Thus the whole change in the observed pK in this region depends on the detailed description of counterion distribution in the close vicinity of the chain.

MacGillivray[22] has demonstrated that the integration of Poisson–Boltzmann equation for the rod-like domain model of the polyelectrolyte solutions leads to Manning's concept of counterion condensation, as the solution is diluted, if the central cylinder is observed from a distance $1/\kappa$, or for that matter R ($1/\kappa$ = Debye's length, R = radius of the cylindrical polyionic domain). This average microscopic description does not apply to the cases where titration or direct reaction with groups attached to the chain are studied.

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Employing the uniformly charged-sheet model[23] as described elsewhere,[3] the qualitative features of the pH–rate profile for aspirin decomposition in PEI solutions are correctly reproduced and the maximum k for the aspirin–PEI reaction is predicted to occur at pH 8.1. However, the model predicts a very flat maximum in discrepancy with the sharp maximum observed experimentally (Figure 1); the rate is predicted to be reduced by a factor 10 at pH 3.5 compared to the value at the maximum, instead of the observed value of 1000. A similar result was obtained from preliminary calculations employing the more realistic cylindrical model for PEI.[24] On the other hand, the cylindrical model for PVBA-Cl solutions predicts satisfactorily the magnitude of the increase of rate constant observed in alkaline solution for the bimolecular reaction between aspirin anion and OH^-.

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Effect of Phenyl Substitution on Ortho Ester Hydrolysis[1]

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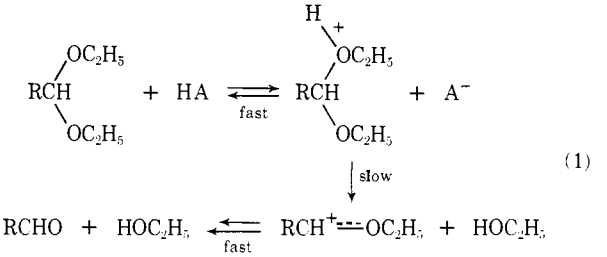
Abstract: Phenyl substitution at the pro-acyl carbon atom of the cyclic ortho ester 2-methoxy-1,3-dioxolane increases its rate of hydrolysis by a factor of 40. This stands in marked contrast to the retardation normally found for corresponding phenyl substitution in the hydrolysis of acyclic ortho esters and offers strong support for steric inhibition of resonance in the acyclic case. The hydrolysis of these cyclic substrates shows general acid catalysis, which, coupled with the fact that phenyl does accelerate, requires either (1) a concerted mechanism with proton transfer and C–O bond breaking in the same transition state, (2) a stepwise mechanism with proton transfer and C–O bond breaking in separate steps occurring at comparable rates, or (3) spectator catalysis.

The hydrolysis of acetals, ketals, and ortho esters has figured prominently in studies into the nature of acid–base catalysis, and these reactions have also received considerable attention in connection with investigations of the mechanism of lysozyme action. As a result of this large body of work, the broad features of these hydrolyses are now well understood.[2] Certain disturbing details, however, still remain, one of which is the effect of phenyl substitution at the pro-acyl carbon atom.[3]

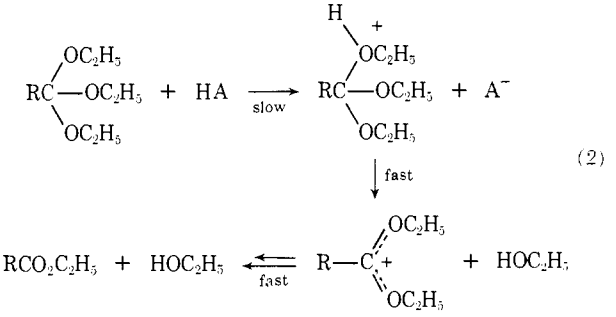
Introduction of a phenyl group at the pro-acyl carbon atom of an acetal greatly facilitates reaction, as it should for a process whose rate-determining step puts positive charge at this position (eq 1); for example, $C_6H_5CH(OC_2H_5)_2$ is 2×10^5 times more reactive than $HCH(OC_2H_5)_2$.[4] Similar substitution in ortho esters, on the other hand, has no accelerating effect, and $C_6H_5C(OC_2H_5)_3$ is actually 40% *less* reactive toward hydrolysis than $HC(OC_2H_5)_3$.[5]

This striking difference in behavior may be attributed



(1)

to a shift in rate-determining step. Conversion of an acetal into an ortho ester through introduction of another alkoxyl group lowers the oxygen basicity of the substrate, which slows the initial protonation step of the hydrolysis reaction. The additional alkoxyl group also raises the stability of the alkoxy carbonium ion intermediate, and that speeds up the C–O bond-breaking step. These changes combine to make protonation slower than C–O bond breaking, and proton transfer becomes the rate-determining step in the hydrolysis of simple orthobenzoate esters (eq 2, R = C_6H_5).



(2)

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