Substitution at a Saturated Carbon Atom. V. A Clarification of the Mechanism of Solvolyses of 2-Octyl Sulfonates. Kinetic Considerations[1]

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Ion pairs are identified as intermediates formed during solvolyses of 2-octyl sulfonates, and their intervention is shown to have both stereochemical and kinetic consequences. It is established that ion pairs, formed in the rate-determining step during solvolysis of 2-octyl mesylate in 25 vol. % aqueous dioxane, serve as asymmetric substrates for attack by nucleophiles, furnishing inverted products. In other solvent systems, 75 vol. % aqueous dioxane and 80 vol. % aqueous acetone, ion pairs have been shown to provide a pathway for racemization of 2-octyl sulfonates. Suggestive evidence is provided that a bimolecular, inverting displacement reaction, having all of the defining characteristics of an SN2 reaction, may have as its mechanism the rapid and reversible formation of an ion pair whose attack by nucleophile is rate-determining.

Substitution at a saturated carbon atom by mechanism SN1, as originally proposed by Ingold and his co-workers, has proved to be an accurate if incomplete description of the ionization process. Work dating from the 1950's has made it abundantly clear that ion-pair intermediates intervene between covalent starting material and the completely dissociated ions during this process.[6] Evidence for them has been gathered largely in solvent acetic acid[6] although they have also been recognized in better ionizing solvents.[7] Little attention has been paid to their importance in simple, unactivated secondary systems[8] and, in particular, to their involvement in simple, unactivated secondary systems in solvents of high ionizing power. We here report such an investigation.

Our results lead us to conclude that ion pairs are indeed important intermediates in solvolysis reactions of the 2-octyl sulfonates, affecting both the stereochemistry as well as the kinetics of these reactions. In fact we have found *no* evidence for free ions with these substrates, even in pure water; our data can be accounted for solely in terms of ion-pair intermediates (and solvent intervention). Our results further strongly suggest that an ion pair (in pre-equilibrium) may intervene as an intermediate in a bimolecular displacement reaction and that mechanisms SN1 and SN2 for this group of compounds may have a common ion-pair intermediate whose formation is rate-determining in the former case and whose destruction is rate-determining in the latter.

Results and Discussion

Kinetic data for solvolyses of 2-octyl sulfonates, which complement the stereochemical data reported in the accompanying paper,[9] were, in some cases, obtained both titrimetrically (k_t) and polarimetrically (k_α). The latter were obtained on a Rudolph, modified Model 200, photoelectric polarimeter at 365 mμ and the precision was comparable with that of the titrimetric rates. Typical runs are reproduced as Tables V, VI, and VII. The data are summarized in Tables I, II, and III.

It will be apparent (Table I) that, in 75% aqueous dioxane, sodium azide is influencing the rate of reaction and must therefore be included in the rate-determining step. Consistent with this kinetic conclusion is the fact that the 2-octyl azide formed under these conditions was highly inverted in configuration, its optical purity approaching 100% (Table I of ref. 9).

A different picture emerges, however, when the more aqueous 25% dioxane system is considered (Table II). Here the rate of reaction is unaffected by added sodium azide, even at 0.0462 *M* salt, where 31% of the starting ester ends up as alkyl azide. However, *the 2-octyl azide isolated from this run proved to be highly inverted* (Table I of ref. 9). The kinetic data make it clear that, in this system, azide ion is not involved in the rate-determining step, but the stereochemical fact of inversion requires that the intermediate, produced in the rate-determining step, be asymmetric, attack by azide on which gives rise to inverted 2-octyl azide. Such an intermediate is most reasonably formulated as an ion pair. Thus an ion pair is implicated as an intermediate in the solvolysis of 2-octyl mesylate in 25% aqueous dioxane.

Our evidence does not definitely preclude attack by solvent (dioxane and water) on covalent starting material although it does require that some solvolysis product (at least 31% in the absence of azide ion) must arise by solvent attack on the ion pair.[10] Accordingly

(1) Based on the Ph.D. Thesis of H. Weiner, Purdue University, 1963; parts I,[2] II,[3] and III[4] have appeared as preliminary communications.

(2) H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, 84, 3599 (1962).

(3) H. Weiner and R. A. Sneen, *ibid.*, **85**, 2181 (1963).

(4) H. Weiner and R. A. Sneen, *Tetrahedron Letters*, **No.** 20, 1309 (1963).

(5) Predoctoral Fellow of the National Institutes of Health, 1962–1963.

(6) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *J. Am. Chem. Soc.*, 78, 328 (1956), and later papers in this series; see also E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1265 (1957), and accompanying papers.

(7) For a general review and listing of pertinent references see C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, p. 135.

(8) See however A. Streitwieser, Jr., and T. D. Walsh, *Tetrahedron Letters*, **No.** 1, 27 (1963).

(9) H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, 87, 287 (1965).

(10) In theory a technique developed in a search for solvent attack on allylic ion pairs[11] can be applied to the data of Table II to provide a quantitative answer to this question. In practice the data are sufficiently imprecise that only a suggestive, although not definitive, answer can be obtained. A plot of the ratio, [ROS]/[RN_3], *vs.* 1/[N_3^-] for the four pertinent entries of Table II, when analyzed by the least-squares method, gives a best straight line with intercept = 0.16, within experimental error of zero but certainly less than unity. Since this intercept corresponds to

Table I. Kinetics of Solvolyses of 0.018 *M* 2-Octyl Brosylate in 75 Vol. % Aqueous Dioxane at 65.0°

Salt	[Salt] × 10², *M*	2-Octanol, %	k_t, sec.⁻¹ × 10⁵	k_α, sec.⁻¹ × 10⁵	k_α/k_t
...	...	99.4[a]	9.18 ± 0.08[a]	...	..
...	...	99.6	23.2 ± 0.5	...	..
...	...	99.1	23.8 ± 0.2	24.7 ± 0.6	1.04
NaN_3	0.633	91.2	23.2 ± 1.0	27.3[b]	1.17
NaN_3	1.25	71.1	23.7 ± 0.6[c]	...	..
NaN_3	2.50	42.8	51.7 ± 1.2	64[d]	..
NaN_3	6.20	22.3	121 ± 7.0[d]	110 ± 3.0[d]	..
NaN_3	11.96	13.9	182 ± 4.0[d]	174 ± 5.0[d]	..
NaN_3 / HOTs	1.26 / 0.688	95.3	23.7 ± 0.3	25.3[b]	1.08
NaN_3 / HOTs	1.26 / 1.38	100.5	23.6 ± 0.6	27.2 ± 0.8	1.15
LiOTs	8.67	100[e]	22.3 ± 0.2	...	...

[a] Temperature, 55.1°. [b] Rate constant calculated after all of the azide ion was utilized. [c] Initial rate constant, 32.5 × 10⁻⁵ sec.⁻¹. [d] Approximate rate constants. [e] Infinity titer at 10 half-lives was only 98% of theory; at 20 half-lives titer had increased to 100%.

Table II. Kinetics of Solvolyses of 2-Octyl Methanesulfonate in 25 Vol. % Aqueous Dioxane

[Ester] × 10², *M*	Salt	[Salt] × 10², *M*	Temp., °C.	2-Octanol, %	k_t, sec.⁻¹ × 10⁵
1.10	...	...	35.0	...	21.1 ± 0.9
1.11	NaN_3	3.35	35.0	79	18.9 ± 0.4
1.03	$LiClO_4$	3.50	35.0	100	20.0 ± 0.6
1.06	NaOAc	2.80	35.0	100	20.3 ± 1.0
0.434	...	...	38.6	...	38.7 ± 0.6
0.618	NaN_3	2.90	38.6	80	35.0 ± 0.8
0.642	NaN_3	4.62	38.6	69	37.6 ± 0.6
0.644	NaN_3 / $LiClO_4$	6.10 / 3.00	38.6	69	37.2 ± 0.8

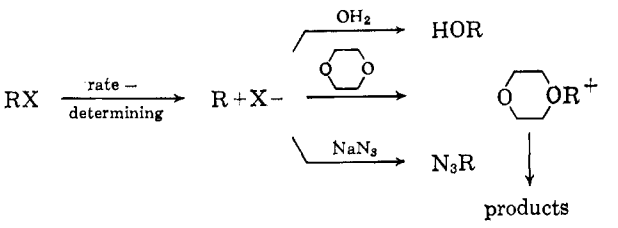
Table III. Kinetics of Solvolyses of 0.018 *M* 2-Octyl Brosylate in 80 Vol. % Aqueous Acetone at 65.0°

Salt	[Salt] × 10², *M*	k_t, sec.⁻¹ × 10⁵	k_α, sec.⁻¹ × 10⁵	k_α/k_t
...	...	20.7 ± 0.6	21.7 ± 0.9[a]	1.05
$LiClO_4$	4.99	21.3 ± 0.2	23.7 ± 0.6	1.11
LiOBs	1.52	21.0 ± 0.3	22.7 ± 0.3	1.08

[a] Concentration of ester in polarimetric run was 0.0098 *M*.

only this mode of formation of solvolysis product is included in Scheme I.

Scheme I. Solvolysis of 2-Octyl Mesylate in 25 Vol. % Aqueous Dioxane



It is of more than passing interest that these results establish the stereochemical course of nucleophilic displacement on an ion pair to be inversion.

Two additional techniques for the detection of ion-pair intermediates, used to advantage in the investigations of the Winstein school,[6] have also been applied for the successful identification of ion-pair intermediates in solvolyses of 2-octyl sulfonates in other solvent systems. The first of these involves a comparison of the measured polarimetric rate constant, k_α, with the titrimetric rate constant, k_t. The constant k_α, of course, measures the rates of all processes for the change in optical activity, including racemization of starting material; the latter measures only the rate of formation of products. In the present study, where comparisons are possible, the polarimetric rate constant, k_α, proved always to be somewhat greater than the titrimetric rate constant, k_t (Tables I and III). Thus for solvolysis of 2-octyl brosylate in 75% aqueous dioxane the ratio, k_α/k_t, varied from 1.04 in the absence of added salt to 1.15 in the presence of 0.0126 *M* sodium tosylate, while for solvolyses in 80% aqueous acetone this ratio varied from 1.05 in the absence of salt to 1.11 with added 0.05 *M* lithium perchlorate. Clearly a mechanism must exist for the racemization of starting material, competitive with the product-forming reactions, a mechanism which involves catalysis by salts. Although alternative mechanisms can be imagined, evidence against these will be presented below and the mechanism most reasonably involves racemization at the ion-pair stage.

A stereochemical consequence of this scheme should be the decreased optical purity of the solvolysis products and indeed such has been found to be the case (Table IV). Thus the optical purity of isolated alcohol from the solvolysis of 2-octyl brosylate in 75% aqueous dioxane was decreased from 77% in the absence of salt

Table IV. Optical Purity of 2-Octanol from the Solvolyses of 2-Octyl Brosylate in the Presence of Added Salts at 65.0°

Solvent[a]	Salt	[Salt] × 10², *M*	Optical purity of 2-octanol, %
D:W[b]	...	...	77[b]
D:W	LiOBs	2.58	68.4
D:W	HOTs	2.02	69.8
D:W	LiBr	17.90	71.9
A:W[b]	...	...	98.7[b]
A:W	$LiClO_4$	4.99	93.2

[a] 0.018 *M* ester in 75 vol. % aqueous dioxane (D:W). 0.018 *M* ester in 80 vol. % aqueous acetone (A:W). [b] Ref. 9.

the ratio of the rate of solvent attack on covalent starting material to the rate of unassisted ionization[11] it indicates that, at best, the former mode of reaction is relatively unimportant if, indeed, existent.

(11) R. A. Sneen and A. M. Rosenberg, *J. Am. Chem. Soc.*, 83, 900 (1961).

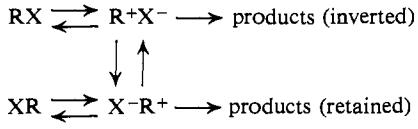
Table V. Solvolysis of 0.0178 *M* 2-Octyl Brosylate in 75 Vol. % Aqueous Dioxane at 65.0°[a]

Time, sec.	Titrant, ml.	k_t, sec.$^{-1}$ × 10^5
0	0.142	...
800	0.740	24.0
1260	1.032	24.4
1700	1.271	23.8
2220	1.530	23.9
2800	1.770	23.3
3450	2.050	23.9
4170	2.269	23.6
5000	2.502	23.7
5850	2.681	23.5
6850	2.892	24.1
17 half-lives	3.520	...
34 half-lives	3.542	...
		Av. 23.8 ± 0.2

[a] [NaOH] = 0.0250 *M*; blank = 0.015 ml.; theoretical infinity titer = 3.560 + 0.015 = 3.575 ml. Per cent of theory (3.531 − 0.015)/3.560 = 98.8%.

to 70% in the presence of 0.020 *M* lithium brosylate, and the optical purity of isolated alcohol from the solvolysis of this compound in 80% aqueous acetone was decreased from 99% in the absence of salt to 93% in the presence of 0.0499 *M* lithium perchlorate (see Scheme II).

Scheme II. Solvolysis of 2-Octyl Brosylate in 75 Vol. % Aqueous Dioxane and in 80 Vol. % Aqueous Acetone



Alternative mechanisms for racemization can be ruled out. That it is not the result of return from dissociated ions follows from the absence of any observable common ion depression.[12] That it is not the result of a direct attack by anion on covalent starting material is certain in view of the extremely low nucleophilicity of sulfonate and perchlorate anions.[13]

Perhaps the most convincing evidence for the involvement of ions pairs as intermediates in the solvolysis of 2-octyl brosylate in 75% aqueous dioxane is again provided by an experiment similar to one developed by Winstein for the detection of ion-pair intermediates.[6] Since brosylate esters in general react about three times faster than the corresponding tosylates,[14] an exchange reaction, competitive with solvolysis, could reveal itself in a drifting rate constant. Accordingly an experiment was undertaken in which 2-octyl brosylate was solvolyzed in 75% aqueous dioxane in the presence of 0.122 *M* lithium tosylate. Although the rate (titrimetric) appeared to be fairly constant over the measured extent of reaction[15] the amount of acid formed after 8.0 half-lives of reaction (99.6% reaction) of 2-octyl brosylate was only 95.8% of theory. After

(12) That the ratio, $k\alpha/k_t$, is invariably greater than unity while at the same time the rate constant, k_t, is independent of salt concentration at low concentrations of added salts (Tables I and III) argues against return from dissociated ions.

(13) In acetic acid solvolyses Streitwieser[8] had detected similar phenomena and has argued convincingly that reaction must take place at the ion-pair stage.

(14) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 654 (1956).

(15) Small amounts of exchange would not be expected to be distinguishable from experimental error by this relatively insensitive technique.

Table VI. Solvolysis of 0.0181 *M* Optically Active 2-Octyl Brosylate in 75 Vol. % Aqueous Dioxane at 65.0°

Time, sec.	Rotation, degrees[a]	k_α, sec.$^{-1}$ × 10^5
0	−0.329	...
500	−0.282	24.9
1100	−0.239	24.2
1800	−0.187	24.4
2600	−0.135	25.6
3425	−0.093	26.0
4425	−0.070	23.6
5350	−0.036	24.6
6700	−0.009	24.0
10710	+0.043	24.8
7 half-lives	+0.064	
30 half-lives	+0.071	Av. 24.7 ± 0.6

[a] Rotations obtained at 365 mμ in a 2-dm. polarimeter tube.

Table VII. Solvolysis of 0.00642 *M* 2-Octyl Methanesulfonate in 25 Vol. % Aqueous Dioxane Containing 0.0462 *M* Sodium Azide at 38.6°[a]

Time, sec.	Titrant, ml.	k_t, sec.$^{-1}$ × 10^5
0	0.360	...
195	0.557	39.9
409	0.810	34.2
857	1.250	36.1
1065	1.450	37.8
1334	1.710	37.8
1595	1.900	37.2
2020	2.160	37.4
2375	2.360	37.4
2662	2.510	37.6
3082	2.660	36.6
3582	2.880	37.7
4306	3.150	39.8
6 half-lives	3.730	...
10 half-lives	3.840	...
		Av.[b] 37.5 ± 1.0

[a] [NaOH] = 0.00600 *M*; blank = 0.070 ml.; theoretical infinity titer = 5.350 + 0.070 = 5.420 ml. Per cent of theory (3.760 − 0.070)/5.350 = 69%. [b] Based on an infinity titer of 3.760 ml.

10.5 half-lives the acid titer had increased to 98.4% and after 12.5 half-lives to 99.0%.[16] Thus an exchange reaction is evident, the slower-solvolyzing 2-octyl tosylate accumulating as reaction progresses.[17]

The Mechanism of the SN2 *Reaction.* The mechanism by which 2-octyl brosylate, in 75 vol. % aqueous dioxane containing sodium azide, interacts with azide ion to form inverted 2-octyl azide is a matter of some interest. The reaction has been seen to take place at a rate dependent on azide ion concentration and as such has all of the characteristics of a typical SN2 reaction—bimolecular, backside attack by azide ion on covalent 2-octyl brosylate.

$$RX + N_3^- \xrightarrow[\text{determining}]{\text{rate-}} N_3R$$

The intriguing possibility exists however that the reaction in question proceeds *via* an alternative mechanism—bimolecular, backside attack by azide ion on the preformed ion pair, a reaction which also would show "SN2" characteristics.

(16) That these differences are significant will become apparent from the precision indicated by a typical run summarized in Table V.

(17) Arguments similar to those presented above make it improbable that this exchange take place other than at an ion-pair stage.

$$RX \rightleftharpoons R^+X^- \xrightarrow[\text{rate-determining}]{N_3^-} N_3R$$

Consider the evidence. (1) In the more aqueous solvent system (25 vol. % aqueous dioxane) asymmetric intermediates derived from 2-octyl mesylate, formulated as ion pairs, have been detected. These intermediates, formed in the rate-determining step, subsequently undergo fast reactions with azide ion and solvent, furnishing inverted 2-octyl azide and 2-octanol. Thus evidence for nucleophilic attack on 2-octyl sulfonate ion pairs has been uncovered and its stereochemical course is inversion. (2) Ion pairs have been implicated as intermediates, if not precursors of product, during the solvolyses of 2-octyl brosylate in 75 vol. % aqueous dioxane.

Certainly rate-determining attack by nucleophile on the preformed ion pair must be considered a possibility as the mechanism of this "SN2" reaction. As a matter of fact the available facts are highly suggestive, if not definitive, that this is the operative mechanism. And it becomes increasingly attractive when one considers that it allows for a gradual and smooth mixing of SN1 and SN2 processes; the ion pair is seen to be a common intermediate by this interpretation, its formation being rate-determining in the former case and its destruction being rate-determining in the latter. Experiments are in progress to define more clearly the mechanism of these "SN2" reactions of 2-octyl sulfonates.

Conclusions

Evidence for ion pairs as intermediates in solvolyses of 2-octyl sulfonates has been presented and they, together with the phenomenon of "inert" solvent intervention discussed in the preceding paper,[9] have been seen to account adequately for the features of these reactions which had led both to the suggestion that their behavior is "borderline"[18] as well as to the suggestion that the stereochemistry of the reactions is determined by "partial shielding by the leaving group."[19]

The recognition of ion pairs as intermediates in solvolysis reactions, even in highly ionizing solvents, has many interesting and exciting implications. Thus it is interesting to speculate: (1) as to what extent ion pairs may be responsible for the frequently observed product spreads on solvolysis of allylic and homoallylic systems,[20] (2) as to whether ion pairs may serve as intermediates in certain SN2′ displacements and (3) as to whether ion pairs may serve as common intermediates in some competing SN2–E2 reactions. Experiments designed to provide answers to these questions are currently under active investigation.

Experimental

Lithium p-Bromobenzenesulfonate. To produce the acid, *p*-bromobenzenesulfonyl chloride (24.3 g.) was allowed to reflux with 25 ml. of water overnight. The water was removed under vacuum at steam bath temperatures. The residue was redissolved in 25 ml. of water, and the water was again removed under vacuum. This was repeated three more times to remove all of the hydrogen chloride. The crude acid was allowed to react with an excess of lithium carbonate in water. The excess carbonate was removed by filtration. The water was again removed and the salt was dried. The dry salt was dissolved in a minimum of hot ethanol. Sufficient acetone was added to cause the salt to precipitate. Recovery was low so the process was repeated many times.

Anal. Calcd. for $C_6H_4BrLiO_3S$: C, 29.65; H, 1.66; Br, 32.89. Found: C, 29.66; H, 1.82; Br, 33.10.

Lithium p-Toluenesulfonate. *p*-Toluenesulfonic acid was treated with an excess of lithium carbonate. The work-up was the same as described above for the brosylate salt. Lithium tosylate was recrystallized from cold ethanol.

Anal. Calcd. for $C_7H_7LiO_3S$: C, 47.19; H, 3.96. Found: C, 47.57; H, 4.04.

Other chemicals, solvents, and reagents have been described in the accompanying paper.[9]

Kinetic Runs. All glass equipment used for the kinetic runs, except the ampoules, was steeped in hot dichromate–sulfuric acid cleaning solution before use. It was then rinsed with copious amounts of distilled water and dried overnight at 100°. The ampoules were prepared by heating unused, 6-in. test tubes overnight in soapy, distilled water. They were then rinsed, dried, and constricted to facilitate sealing.

Solutions were first prepared by pipetting the required volume of each solvent into an erlenmeyer flask; *e.g.*, 75% aqueous dioxane was prepared from 3 vol. of dioxane and 1 vol. of water. The ester was weighed into a volumetric flask to which solvent was then added. If salts were present, the reaction mixture was initially prepared either from the organic solvent and a standard aqueous solution of the salt or by adding the salt to the volumetric flask together with the ester. Pure solvents were then added to give the proper volume.

Titrimetric rates were followed by placing the flask into a thermostatically heated oil bath and removing 5 ml. of the solution at various time intervals. These aliquots were added to 10 ml. of acetone which served as a quenching system. The time was noted and the quenched solution was titrated with standard aqueous sodium hydroxide. This procedure was repeated with time in order to obtain the change of acid titer as a function of time. For reactions which were relatively slow or were susceptible to evaporation, a sealed ampoule technique was employed. The solution was prepared in the manner described above and then 6-ml. portions of it were pipetted into precooled ampoules. After all the ampoules had been charged they were separately flushed with dry nitrogen for 10–15 sec. and sealed. When all the ampoules had been sealed they were placed in the rate bath. As each was removed from the hot bath it was placed in ice–water to quench the reaction thermally. After cooling, 5 ml. of solution was pipetted into a flask containing 10 ml. of acetone and was titrated.

Polarimetric rates were followed using the sealed ampoule technique. At the required time the ampoules were removed from the rate bath and quenched in ice

(18) M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 634 (1954).
(19) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 381.
(20) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 794 (1956).

water. These ampoules were stored at *ca.* 5° until all the ampoules had been collected. Because the polarimeter tube held less than 3 ml., each ampoule was charged with only 4 ml. of solution. Usually 12 points were used for a kinetic determination. All optical measurements were made using the technique described in the accompanying paper.[9]

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The Enhanced Esterolytic Catalysis of Poly-4(5)-vinylimidazole and Poly-5(6)-vinylbenzimidazole[1]

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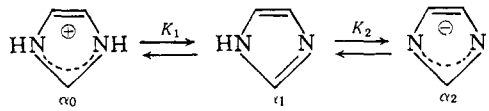
The homopolymers of 4(5)-vinylimidazole and 5(6)-vinylbenzimidazole were found to be better catalysts than imidazole and benzimidazole, respectively, for the solvolysis of p-nitrophenyl acetate at high pH values. The polymeric effect is pH dependent and is a result of enhanced contributions of the anionic fractions of the polymers. With the negatively charged substrate 4-acetoxy-3-nitrobenzoic acid and poly-4(5)-vinylimidazole a bell-shaped pH–rate profile was observed as a result of electrostatic attraction to the protonated sites of the polymer. This effect was not operating with poly-5(6)-vinylbenzimidazole at low pH values. On the other hand, the anionic sites of poly-5(6)-vinylbenzimidazole were found to be very reactive toward the negatively charged substrate at high pH values, which was in contrast to the inertness of the anions of the monomer. The possible mechanisms for the high reactivity of the polymeric anions are discussed.

Introduction

Imidazole has been implicated in the active site of several esterolytic enzymes by chemical and kinetic studies. Imidazole is an ampholyte having two pK_a values. In chymotrypsin imidazole probably participates in the acylation and deacylation steps, either as a



nucleophile or as a general base.[2] In chymotrypsin it reacts as the free base (α_1), though some indications point to contributions of the anionic form (α_2) as well.[3] In acetylcholinesterase[4] and β-galactosidase[5] the basic group may be supplied by the imidazole function. However, in α-amylase imidazole is probably furnishing the general acid part of the active site.[6] Ribonuclease may be utilizing two imidazole functions, one in the acidic (α_0) and one in the free-base form (α_1).[7]

The important role of imidazole in enzymatic reactions has prompted an extensive study of the esterolytic catalysis of monomeric imidazoles by Bruice,[8,9] Jencks,[10] and Bender.[11] No catalytic action of [IMH$^+$] in the monomers has yet been observed. So far the following contributions were noted.

$$\text{rate} = k_1[\text{IM}][\text{substrate}] + k_2[\text{IM}]^2[\text{substrate}] + k_3[\text{IM}][\text{OH}^-][\text{substrate}]^{10} \quad (1)$$

If the interaction between the imidazole group and the hydroxyl group occurs in a pre-equilibrium step, the contribution of the imidazole anion can be described as

$$k_{\text{anionic}}[\text{IM}^-][\text{substrate}] \quad (2)$$

or the total second-order contribution will be[8]

$$k_1 = k_{\text{neutral}}\alpha_1 + k_{\text{anionic}}\alpha_2 \quad (3)$$

k_3 and k_{anionic} are related by the equation

$$k_3 = k_{\text{anionic}}K_2/K_w \quad (4)$$

Since enzymatic reactions show different imidazole contributions than monomeric imidazoles, we thought that incorporation of imidazole groups on inert polyvinyl chain would provide additional interactions to those available for the monomers, and that cooperative effects may enhance the over-all catalytic rate. Low and high molecular weight polymers and copolymers of histidine employing the polypeptide backbone have been studied.[12-14] While the high molecular weight

(1) For a previous report see C. G. Overberger, T. St. Pierre, N. Vorchheimer, and S. Yaroslavsky, *J. Am. Chem. Soc.*, **85**, 3513 (1963). This paper comprises a portion of a dissertation submitted by T. St. Pierre in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

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