

RECENT DEVELOPMENTS IN THE USE OF POLYMERS AS REACTANTS IN ORGANIC REACTIONS

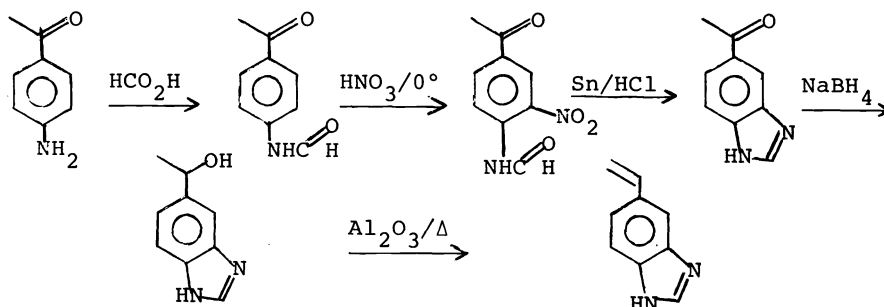
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Abstract--In a review article [*Accounts Chem. Res.*, 2, 217 (1969)] is a summation of our work up to 1968. In this review we summarized the activity of polyvinylimidazole and copolymers in esterolytic reactions. We explained the increased reactivity of these polymeric reactants in terms of cooperative effects and electrostatic factors. In 1967, we blundered into the extremely interesting discovery that long-chain esters provided us with enormous acceleration of rates at room temperature and we have attributed this in "general" terminology to apolar bonding as a third factor to understand the high reactivity of these synthetic macromolecules. Reference 1 describes our recent published work. We are heavily emphasizing the apolar bonding concept. Related work which conceptually can be regarded as similar to our own discovery was carried out by the group of Professor Irving M. Klotz at Northwestern(2), the group of Professor Kabanov at the University of Moscow(3), and the group of Professor Kunitake(4).

BACKGROUND TOPICS

- 1) Polymers Containing Imidazole Groups and Catalytic Imidazolium Iodide Groups. Two manuscripts have been published in this area(1a,1b). This work has culminated in our understanding that substituted apolar effects are possible in charged systems.
- 2) Polymers Containing Pendant Imidazole and Thiol Groups. One manuscript has been published on this problem(1c).
- 3) Catalysis by Oligo-4(5)-vinylimidazole. This work has culminated in a publication(1d). This is the first experimental demonstration of the molecular weight limits of a polymeric charged species to demonstrate electrostatic interactions.
- 4) Apolar Bonding with Poly-4(5)-vinylimidazole. Two manuscripts have been published(1e,1f). This latter paper is probably the most thorough kinetic treatment of the hydrophobic effect over an entire reaction profile published to date.
- 5) Benzimidazole-Containing Polymers and Their Catalytic Activity(1g,1h). A new synthetic procedure for the monomer, 5(6)-vinylbenzimidazole, has been developed. A brief description of the new synthesis is listed below(1i).



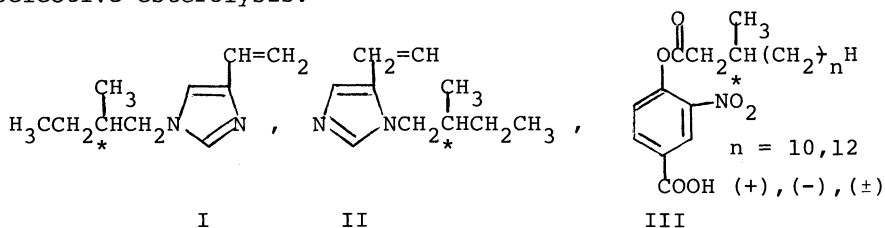
A study of polymer tacticity versus polymerization conditions was of interest because an earlier investigation of poly-5(6)-vinylbenzimidazole suggested the possibility of stereoregularity in the polymer obtained by free-radical initiation in methanol(lg, lh). Stereoregularity has been found for 2-vinylbenzimidazole under special conditions(5). For comparison, polymerizations were therefore carried out in glacial acetic acid, 10% aqueous hydrochloric acid and in methanol at 0°C. The initiation of the first two polymerizations was with AIBN at 70° and for the last one with UV light. NMR spectra of these polymers were obtained primarily in acetic acid-d₄ and also in methanol-d₄, DMSO-d₆. There was no evidence for appreciable stereoregularity changes in these polymers as a function of polymerization conditions; the spectra were essentially superimposable and exhibited only broadened resonances. We feel that atactic or perhaps slightly syndiotactic polymer is being produced under these conditions.

6) Poly-N-alkyl-4(5)-vinylimidazoles as Catalysts(lk, ll, lm).

NEW TOPICS:

1) Hydrolysis of Esters Catalyzed by L-Histidine Graft Copolymers(ln).

2) Optically Active Polyvinylimidazoles and Asymmetric Substrates. In order to investigate the effects of optically active macromolecules on the solvolytic rates of asymmetric substrates, optically active polymers containing imidazole groups (I or II) and asymmetric substrates, 4-alkanoyloxy-3-nitrobenzoic acids (III), were prepared. An optically active monomer, 1-(2-methylbutyl)-4-vinylimidazole (I), was prepared by the reaction of sodium salt of 4(5)-vinylimidazole and optically active 1-bromo-2-methylbutane derived from primary active amyl alcohol. Another monomer, 1-(2-methylbutyl)-5-vinylimidazole (II) was obtained from the reaction of 1-trimethylsilyl-4-vinylimidazole and 1-bromo-2-methylbutane. Homopolymers of I and II and copolymers of I or II with acrylamide, 4(5)-vinylimidazole and 3-methyl-1-vinylimidazolium iodide were prepared in 1-methoxy-2-ethanol in the presence of α, α -azobisisobutyronitrile (AIBN) and were soluble in water-ethanol mixtures. The kinetics of the solvolysis of III are being investigated. Some of the preliminary kinetic results indicate that not only hydrophobic interaction between catalyst and substrate plays an important part in the stereoselective hydrolyses of esters, but also hydrogen bonding between them may participate in the stereoselective esterolyses. Structural rigidity around the active imidazole group due to hydrogen bonding or other directional forces between polymer catalyst and substrate may be one of the main control factors in stereoselective esterolysis.



3) Hydrophobic Interactions in Catalysis by Imidazole-Containing Polymers. The catalytic activity of imidazole-containing polymers for the hydrolyses of substrates with poor leaving groups has been examined. Hydrolyses of *p*-methoxyphenyl esters (S_n) catalyzed by poly[4(5)-vinylimidazole] (pvIm) relative to imidazole (Im) indicates that both cooperative and hydrophobic interactions are operative. Hydrolyses of 3-methoxy-4-acyloxybenzoic acid substrates (S_n^-) catalyzed by pvIm and a water-soluble copolymer, copoly-[1-methyl-4-vinylimidazole/4(5)-vinylimidazole] exhibits many characteristics of enzyme-catalyzed reactions like saturation kinetics, bell-shaped pH-rate profiles and nonproductive binding. The importance of general-base cooperative interactions for substrates with poor leaving groups and hydrophobic interactions in the formation of stable catalyst-substrate complex in the case of long-chain ester are demonstrated. The interesting similarity between the Michaelis constants, K_m , for the two polymer catalysts, pvIm and the copolymer, suggests that the common underlying principle involved in binding is hydrophobic interactions and the presence of N-CH₃ group in the copolymer does not increase the hydrophobicity significantly. The pH-rate profiles for the hydrolyses of S_n^- by pvIm show the optimum pH to be around neutrality indicating that the presence of both neutral Im units to serve as nucleophiles and protonated Im units to serve as electrostatic binding sites is essential for maximum catalytic efficiency. The rate enhancement as a

function of acyl chainlength at different pH leads to the conclusion that cooperative effect between electrostatic and hydrophobic interactions would reduce the nonspecificity of hydrophobic interactions leading to a better realization of the latter. An approximate calculation shows that the binding of S_{12}^- , relative to S_7^- , with the copolymer in aqueous solution corresponds to the additional interactions of two methylene units.

4) Esterolytic Activity of Water-Soluble, Hydrophobic Terpolymers of 4(5)-Vinylimidazole. Water soluble terpolymers with varied hydrophobic side chains were prepared under controlled conditions and tested for effectiveness as nucleophilic polymers in the hydrolyses of hydrophobic ester substrates. Terpolymers of 4(5)-vinylimidazole, acrylamide and either 3-buten-2-one, 1-penten-3-one, 1-undecen-3-one, or 1-hexadecen-3-one were synthesized. The esterolyses of 3-nitro-4-acyloxybenzoic acid substrates (S_n^-) with 2,7,12 and 18 carbons were examined in water and 30 volume per cent ethanol-water solutions. The terpolymers with the apolar side chains revealed high catalytic activity as shown by the faster rates for the 1-hexadecen-3-one and 1-undecen-3-one terpolymers. The data also revealed the effectiveness of the terpolymer side chains, in some instances greatly exceeding the enhancement of rate attributed to the hydrophobic nature of the terpolymer backbone. In addition, the presence of apolar hydrocarbons in fewer but longer terpolymer side chains was demonstrated to be superior to a similar amount of apolar hydrocarbon present in a larger number of shorter chain monomers. Kinetic determinations were carried out under conditions of excess catalyst and were second order. The advantage of water over 30 volume per cent ethanol-water solutions in demonstrating hydrophobic effects was delineated.

The various aspects of synthesis were discussed including syntheses of hydrophobic monomers, crosslinking of terpolymer, attainment of suitable terpolymer molecular weight, homogeneity of terpolymer, terpolymer ketone reduction, and purification of terpolymer. Terpolymers were prepared by free radical solution polymerization. Monomer mole per cent compositions of terpolymers were obtained from titration and elemental analytical data. The terpolymer ketone was reduced to prevent a possible reversible "pseudo-amide" equilibrium involving 4(5)-vinylimidazole and the ketone of the 1-alken-3-one monomeric residues on the terpolymer molecule.

Excess substrate concentrations were employed with the 1-hexadecen-3-one terpolymer to show an example of substrate inhibition of deacylation.

5) The Esterolytic Activity of Imidazole-Containing Polymers. Synthesis and Characterization of Copoly[1-alkyl-4- or 5-Vinylimidazole/4(5)-vinylimidazole] and Its Catalytic Activity in the Hydrolysis of *p*-Nitrophenyl Acetate. The water-soluble monomers, 1-methyl-4-vinylimidazole, 1-methyl-5-vinylimidazole, 1-ethyl-5-vinylimidazole, and 1-propyl-5-vinylimidazole have been synthesized, polymerized, and copolymerized with 4(5)-vinylimidazole. The copolymers were characterized by ^{14}C -labelling, NMR, pK_a determination and viscosity measurements. The monomer reactivity ratios determined by ^{14}C counting are $r_1 = 1.04$; $r_2 = 0.94$ [M_1 :4(5)-vinylimidazole, M_2 :1-methyl-4-vinylimidazole] and $r_1 = 1.01$; $r_2 = 0.86$ [M_1 :4(5)-vinylimidazole, M_2 :1-methyl-5-vinylimidazole]. The esterolytic activity of the copolymers for the hydrolysis of *p*-nitrophenyl acetate (PNPA) at pH 7-8 in 28.5% ethanol-water was higher than that of the mixtures of homopolymers. At pH 5-6 the esterolytic activities of the copolymers and the mixtures were similar. The most efficient esterolytic activity for PNPA hydrolysis at pH 7.11 in 28.5% ethanol-water occurred for copolymers containing 75 mole percent 4(5)-vinylimidazole and for copolymers containing 1-methyl-4-vinylimidazole rather than 1-methyl-5-vinylimidazole.

6) The Esterolytic Activity of Imidazole-Containing Polymers. Hydrophobic Influences in Copoly[1-alkyl-4- or 5-Vinylimidazole/4(5)-vinylimidazole] Catalyzed Hydrolysis of 3-Nitro-4-acyloxybenzoic Acids. Water soluble copolymers containing imidazole and N-alkylated imidazole pendant groups have been synthesized in order to investigate the hydrophobic interactions between polymeric catalysts and long alkyl chain ester substrates. Copoly[1-methyl-4-vinylimidazole/4(5)-vinylimidazole], copoly[1-methyl-5-vinylimidazole/4(5)-vinylimidazole], copoly[1-ethyl-5-vinylimidazole/4(5)-vinylimidazole] and copoly[1-propyl-5-vinylimidazole/4(5)-vinylimidazole] were synthesized and their catalytic activity toward 3-nitro-4-acyloxybenzoic acid substrates (S_n^-) was determined in 28.5% ethanol-water and in water and compared with that of the mixtures of homopolymers. Hydrophobic interactions were important for rate enhancement of the hydrolysis of long-chain ester substrates compared to that of short-chain ester substrates. The copolymers catalyzed the

hydrolysis of 3-nitro-4-dodecanoyloxybenzoic acid (S_{12}^-) about two times faster than the mixtures at pH 7.11 in 28.5% ethanol-water. The hydrolysis of S_{12}^- by the copolymers was about five times faster in water than in 28.5% ethanol-water.

There has been considerable interest in utilizing hydrophobic interactions to enhance the rate of hydrolysis of esters by synthetic macromolecules. Klotz has studied the effect of partially lauroylated poly(ethylenimine) on the hydrolysis of long chain neutral esters. Kunitake has been active in the study of water-soluble copolymers containing imidazole residues. We have shown that long-chain anionic esters (S_n^-) are hydrolyzed very efficiently in the presence of poly[4(5)-vinylimidazole](PVI). In some cases accelerative kinetics were observed. These rate enhancements have been attributed to the accumulation of more hydrophobic acylated-PVI esterolytic intermediates caused by a slow rate-determining deacylation step. On the other hand, water soluble poly[1-methyl-5-vinylimidazole] p(1-Me-5VI) efficiently catalyzed the hydrolysis of S_n^- because of the hydrophobic nature of the polymer itself rather than due to the accumulation of a more hydrophobic intermediate. The esterolytic intermediate is a positively charged acylonium ion, which is very reactive and decomposes upon formation to regenerate catalytically active imidazole residues.

This difference in ester hydrolysis mechanisms has led us to synthesize and investigate the catalytic activity of copolymers containing 4(5)-vinylimidazole (VI) and 1-alkyl-4- or 5-vinylimidazole for the hydrolysis of S_n^- . Rate enhancements due to electrostatic effects, cooperative effects and hydrophobic effects are expected for these copolymers. The increased water solubility of the copolymers makes it possible to study the increased hydrophobic interactions between the polymers and substrates and therefore achieve very large hydrolysis rates. The previous paper in this series contains the synthesis of the copolymers containing 4(5)-vinylimidazole and 1-alkyl-4- or 5-vinylimidazole and their effect on the hydrolysis of the neutral ester, p-nitrophenyl acetate. The paper contains the results for the catalytic activity of these copolymers toward long-chain anionic ester substrates such as 3-nitro-4-acyloxybenzoic acid, S_n , where n denotes the acyl chain length.

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