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## ION EXCHANGE RESINS IN MEDICINE AND BIOLOGICAL RESEARCH

BY

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\* This series of papers is the result of a Conference on *Ion Exchange Resins in Medicine and Biological Research* held by the Section of Biology and Section of Physics and Chemistry of The New York Academy of Sciences, November 14 and 15, 1952.

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## INTRODUCTION: ION EXCHANGE RESINS AND THEIR APPLICATION TO BIOLOGY AND MEDICINE

By Harry Sobotka and Harry P. Gregor

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When we planned the conference on Ion Exchange Resins in Medicine and Biological Research, on which this monograph is based, it soon became apparent that the biochemical and medical applications of the ion exchange substances could best be presented within a wider framework including the preparative and physical chemistry of these compounds. Thus, Doctor Gregor undertook to organize the first half of the program, while Doctor Sobotka arranged its second moiety. We wish to thank, at this juncture, those who contributed their services as Session Chairmen: Doctors H. F. Mark, Polytechnic Institute of Brooklyn; Th. Shedlovsky, Rockefeller Institute for Medical Research; and Wm. Dock, State University of New York, who was the first physician to use ion exchange resins in patients.

In discussing the synthesis of ion exchange resins, Craig points out that the matrix of the resin is synthesized by either condensation polymerization or addition polymerization, and that substitution of the acidic or basic groups, which are responsible for the cation or anion exchanging properties, is usually effected by a separate procedure. In addition to the phenol-formaldehyde and styrene-divinylbenzene matrices, resins prepared from cellulose (in the form of cloth or yarn) and proteins are described. Doctor Craig sets forth methods for preparing resins of high as well as low density, the latter being the so-called "popcorn" polymers. Synthetic procedures for preparing resins having a variety of different exchange groups are outlined, and the general problem of preparing specific exchange resins is discussed. It is these specific resins which are potentially of greatest importance to biologists.

The present status of the problem of the synthesis and characterization of electron exchange polymers is presented by Ezrin and Cassidy. These new resins are prepared from vinylhydroquinone, and are the polymeric analogues of the quinone-hydroquinone redox system. Potentiometric titrations of the polymer, its use in chromatography when dispersed on filter paper, and its column behavior are described. This new material, which will effect redox reactions without being soluble itself, will find many important biological uses.

The general thermodynamic properties of ion exchange resin systems (in particular, their swelling properties as related to their ion selectivities) are discussed by Gregor and Frederick. The Gibbs-Donnan theory which applies to these systems is described. Free energies of swelling as evaluated from water sorption data are discussed and the calculation of approximate thermodynamic osmotic pressures is given. Where interactions exist between the resin or its fixed exchange group on the one hand and the exchanging ions on the other hand, it is shown that free energies of swelling are not reliable indications of ionic selectivity, but that volume changes *per se* are reliable indices usually.

The use of Harned's Rule in evaluating activity coefficients of ions in ion exchange resin systems is described by Davidson and Argersinger. This method is applied to exchange equilibria between hydrogen, sodium and silver ions in a sulfonic acid cation exchange resin system.

Soldano treats the kinetics of ion exchange processes, and discusses the effect of several factors upon rate processes. These include: (a) crosslinking, which slows the diffusion processes; (b) the influence of ionic charge; (c) the exchange capacity; and (d) the effect of resin composition. The diffusion of the solvent systems is described.

The general characteristics of cation exchange processes are described by Bregman, starting from a consideration of the resin systems as being cross-linked polyelectrolytes. The effect of several variables upon the selectivity of the resin is taken up, including (1) the resin matrix, (2) the acidic exchange group, (3) the fraction of the exchange capacity occupied by each cation, (4) the exchange capacity of the resin, (5) the ionic strength, and (6) the temperature of the ambient solution. The properties of a new phosphonic acid resin are described in terms of these considerations.

Anion exchange processes are described by Peterson, who first takes up the many applications of these resins, and then presents tables of data on anion selectivity coefficients. The sorption and exchange of several organic acids, many of these of biological importance, by various resins, are described.

A new process, termed ion exclusion, which involves the separation of ionic and non-ionic substances, is described by Wheaton and Bauman. Here one makes use of the different sorption affinities of various neutral molecules, *e.g.* glucose and methanol, for ion exchange resins. Separations are effected in most cases by merely eluting a sorbed mixture from a column with water. Many biologists will find this process of great interest.

The entire field of ion selective or ion exchange membranes is reviewed by Sollner, who has pioneered in this new field. The basic physical chemistry is discussed, and considerable experimental data on new and vastly improved membranes are presented. The exciting new applications to which these membranes apply is described by Doctor Sollner as well as their importance as models of living systems.

The application of ion exchange resins to biological and medical problems are manifold and may be classified as follows:

1. Chemical separations including uses in immunochemical problems;
2. Purification of pharmaceutical and biological preparations;
3. Therapeutic uses, primarily, the removal of sodium from the nutriment in conditions where a diet poor in sodium would be indicated;
4. Diagnostic applications.

In the field of the first two uses, Waldo Cohn gives a survey of biochemical separations on ion exchange columns. He reviews the work of Stone and Moore on amino acids and reports his own work and that of his collaborators on the separations of nucleotides and their smaller fragments. In the course of these experiments on the fractionation of chemical as well as enzymatic hydrolysates of nucleic acids, di-, tri-, and tetranucleotides were separated in addition to the known mononucleotides. The latter could be separated into



three types of isomers to which specific structures have been assigned. This work is rounding out a concept of nucleic acid structure which is in excellent agreement with the theories developed with different techniques by W. R. Todd and others. Throughout these experiments and also in the work on sugars and sugar phosphates, described later in his report, Doctor Cohn emphasizes that the sequence of adsorption of the individual compounds is not merely governed by their pK-values, but also by other less predictable features such as aromatic side-chains and other steric factors. Thus, we find a certain overlapping of ion exchange with the older adsorption chromatography.

This trend is also apparent in the next contribution by Isliker who deals with the purification of antibodies by means of antigens linked to ion exchange resins. Here the ion exchange resins function as a matrix to which the antigen of an immunochemical system is irreversibly linked by certain chemical operations. The fixed stroma of blood corpuscles, for instance, acting as an insoluble antigen, becomes adsorbed to an ion exchange resin. It then adsorbs, in its turn, the isoagglutinin (antibody) from serum with an exceedingly high degree of specificity. The conditions for the dissociation between antigen and antibody, the competition between various agents and their vicarious replacements, throw much new light on the nature of the link between antigen and antibody. Practical usefulness of this knowledge in the service of the patient when he is to be given a blood or serum transfusion is evident.

Doctor Segal leads us through the diagnostic field and exemplifies the utilization of ion exchange resins pretreated with quinine, methylene blue, serenium, and fluorescein in an ingenious method which demonstrates and gauges the degree of acidity in the gastrointestinal canal without intubation by a simple test on the patient's urine. The use of the quininium indicator exchange resin in particular has reached the stage of practical routine application.

The rest of the monograph is devoted to the consideration of the important therapeutic uses of ion exchange resins. Some of these compounds are administered in sizable quantities to man, in order to reduce the amount of sodium available in the gastrointestinal tract for absorption from the nutriment. As it is the sodium ion which one wishes to remove, the work reported deals primarily with the effects of cation exchange resins. But Kohlstaedt and his collaborators and Danowski also evaluate the use of mixtures of anion and cation exchange resins. Heming and his colleagues report on the relative effectiveness of carboxylic, sulfonic and phosphonic type of resins and alginic acid and conclude that much work remains to be done before an ion exchange resin will become available that answers all requirements for satisfactory medication. Doctor McChesney and his coworkers favor the sulfonic type of ion exchange resins on theoretical as well as practical grounds.

The effectiveness of ion exchange therapy depends obviously on the amounts and concentration of ions to be exchanged. Their effect will be less tangible when the patient is on a strictly sodium-free diet to begin with; but we must recognize that the gastrointestinal tract is neither a glass pipe nor a cellophane tube, but is subject to numerous physiological influences and their pathological modifications. There is the concomitant regulation of potassium metabolism which can be neither ignored nor avoided, since the selectivity of ion exchange

resins for sodium over potassium is limited. Doctors Danowski and Emerson, in their contributions, deal with the effect of the hormones of the adrenal cortex upon the transition of sodium and potassium through the intestinal wall from the blood into the lumen and *vice versa*. Doctor Levitt evaluates the effectiveness and indication of ion exchange resin therapy in its various cycles *i.e.* after pretreatment with the various ions. Doctor Visscher, a pioneer in this field, approaches the problem from the physiologist's angle with the most exact technique available. Using radioactive sodium from both sides, from the blood stream after injection or from the intestine after ingestion, he compares the rate of transition. His remarks throw much light on the reaction rate at various levels of the intestine and on the individual share of blood vessels and lymph vessels in the absorption process. The effect of ion exchange resins on organic cations, such as amines of physiological importance and on pharmaceuticals (*e.g.* digitalis) has not yet been considered. Dr. Levitt summarizes clinical experience in cardiac disease, acute renal insufficiency, and during cortisone and adrenocorticotrophic hormone therapy. Both he and Doctor Berger in his discussion remarks advise caution in the use of this powerful, but dangerous tool. Its use must be punctiliously followed by chemical analysis for the blood electrolytes and controlled by clear and intelligent reasoning on the part of the clinician.

## SYNTHESIS OF ION EXCHANGE RESINS

By Paul N. Craig

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Although ion exchange agents such as the zeolites have been used as water softeners for many years, the advent of "tailor-made" synthetic ion exchange resins has opened entirely new fields for their use. The physical and chemical properties of such resins can be modified to fit particular requirements by the proper choice of reagents and conditions used either in the polymerization reactions or in subsequent chemical alterations of preformed resins. Any cross-linked polymer will be termed a "resin" in this paper.

An ion exchange resin is a crosslinked polymer which contains either acidic or basic structural units and which can exchange either cations or anions on contact with a solution. Resins are insoluble in all solvents, due to their infinite molecular size which arises from the crosslinks. An excellent discussion of structure-property relationships in ion exchange resins is given by Bauman.<sup>1</sup>

The criterion of insolubility is an important one for most resin uses, and a resin which is crosslinked with 5 to 20 per cent of crosslinking agent (the range in commercial resins) is literally as soluble as a brick. Despite the enormous size of the resin molecules and their complete insolubility, such a polymeric acid or base will exhibit the chemical activity of a monomeric acid or base, subject to the restrictive conditions imposed by the insolubility and the immobility of the massive organic ion. These differences lead to complex thermodynamic relationships between the resin and a solution in contact with it. These relationships will be treated in succeeding papers of this monograph.

There are two general types of polymerization reactions, both of which can be used to synthesize ion exchange resins. These are known as condensation polymerization and addition polymerization. The formation of condensation polymers is accomplished by reacting polyfunctional molecules in such a manner that new carbon-carbon, carbon-nitrogen or carbon-oxygen bonds are formed. These act as the joining links which bind the starting molecules together into the polymeric network. Condensation reactions are always accompanied by the formation of one small molecule such as water, alcohol or ammonia, for each new carbon-carbon, carbon-nitrogen or carbon-oxygen bond created. Such polymers have a composition which differs from that of the monomers by the elements of the molecule which was split off in the polymerization. Some of the resins prepared in this fashion are not stable indefinitely over the entire pH range, as carbon-oxygen and carbon-nitrogen links are susceptible to hydrolytic cleavages.

In contrast, polymers prepared by addition polymerization of olefinic compounds contain only carbon-carbon bonds as the links which join the monomers. These polymers have the same empirical composition as the monomers used in their preparation. Such polymers are stable to heat and pH changes. An excellent bibliography of reported preparations of ion exchange resins up to 1950 is given by Kunin and Myers.<sup>2</sup>



FIGURE 1 shows the formation of a phenol-formaldehyde type resin by means of a condensation reaction between meta-phenolsulfonic acid and formaldehyde.<sup>3</sup> Each benzenoid ring in the product contains one sulfonic acid group which can exchange cations with a solution in contact with the resin. A high degree of crosslinkage, however, exists here, as each ring is joined (theoretically) to 3 other rings. This tight network creates a hard, brittle resin, and prevents the contacting solution from diffusing rapidly throughout the entire resin matrix. Indeed, the theoretical capacity is never reached, which is believed to be due to certain tightly enmeshed "pockets", inaccessible to the solvent. Such a resin will require a much longer time for exchange processes to reach equilibrium than for a soluble polymeric acid or monomeric acid. Simultaneously, the high degree of crosslinking will prevent extreme swelling or shrinkage of this type of resin with changing environment.

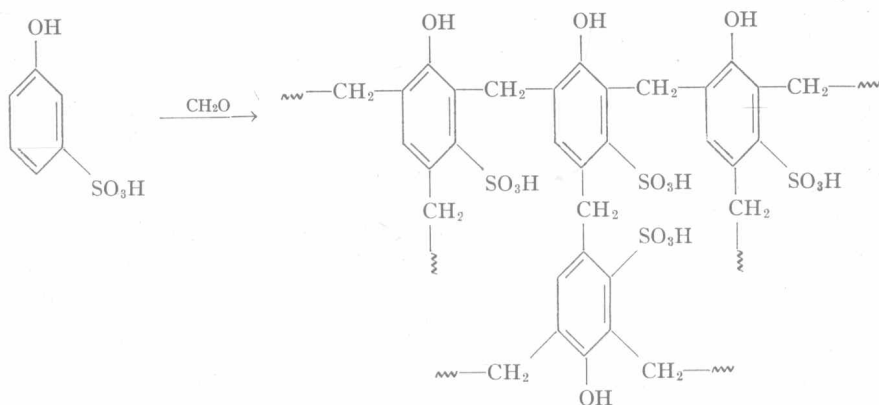


FIGURE 1

FIGURE 2 illustrates another phenol-formaldehyde type condensation polymer in which the sulfonic acid groups are attached to the alkyl side chains which link the rings together.<sup>4</sup> FIGURE 3 illustrates how a carboxylic acid resin and a sulfonic acid resin were prepared in Germany during World War II by condensation reactions.<sup>5</sup>

FIGURE 4 shows the preparation of a weak-base anion exchange resin by a condensation reaction.<sup>6</sup> A Mannich reaction is shown at the top. This reaction can occur at reactive positions in the phenolic rings of "Bis-Phenol-A", and competes with the usual formation of a methylene bridge between two rings. For simplicity the letter "R" is used to indicate the residue, enclosed in brackets, which arises from formaldehyde and tetraethylenepentamine. This particular resin was found to be effective as an antiacid agent<sup>7</sup> and either it or a related resin may be used in medicine for this purpose.

In FIGURE 5 is shown the preparation of a weak-base anion exchange resin by an amine-formaldehyde type condensation reaction.<sup>8</sup> Since there are so many possible ways in which the three reagents used can react, the structures shown are merely meant to represent possible structures which might exist in the resin. This is also true of all the formulas used to represent resins, as

no absolute proof of the exact structure of any crosslinked polymer has ever been made, due to the inherent difficulties of dealing with a heterogeneous and insoluble resin.

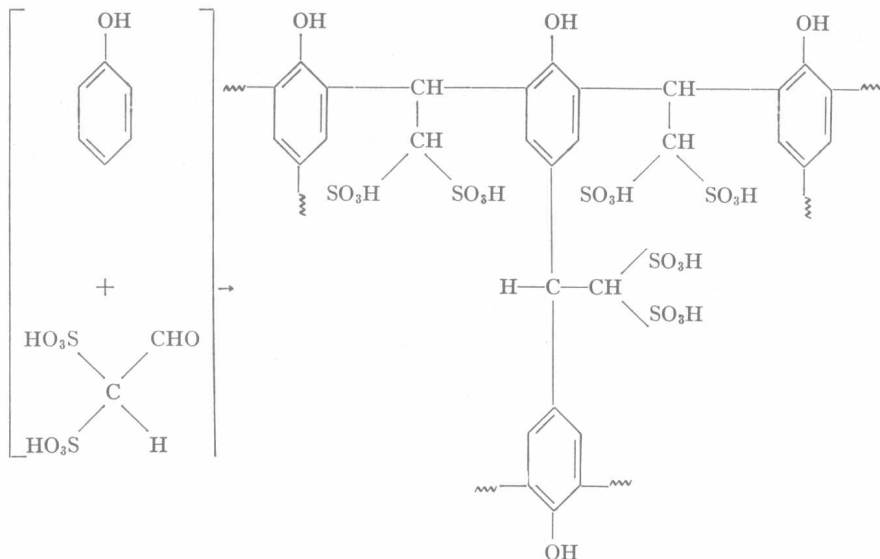


FIGURE 2

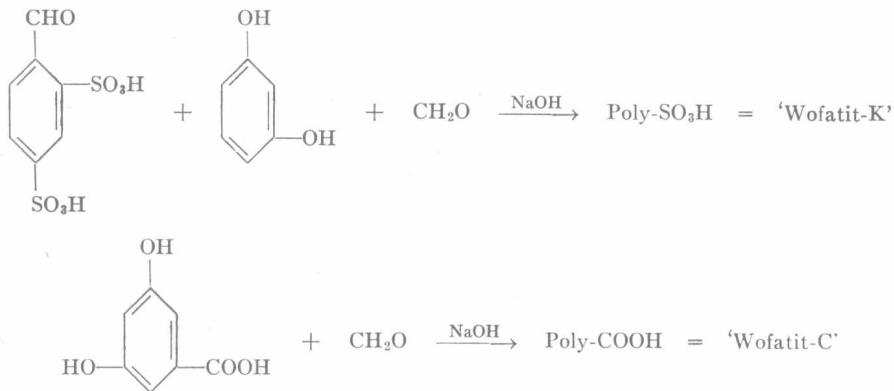


FIGURE 3

The structural features of several ion exchange materials which have been prepared from cellulose are shown in FIGURE 6.<sup>9</sup> The interesting feature of these exchangers is that some of them can be prepared from cellulose in bulk, yarn, or woven cloth without changing the physical form of the cellulose. Such materials are reported to exchange ions with great rapidity. Both weak and strong anion and cation exchangers have been made from cellulose.

Cation exchanging resins have been prepared from casein on treatment with

formaldehyde.<sup>10</sup> These resins are susceptible to hydrolytic breakdown due both to the peptide nature of the backbone structure of the resin and to the C—N—C crosslinks. Capacities of such resins are quite low.

Some resins, which are prepared by addition polymerization methods and may be used directly as obtained, are illustrated in FIGURE 7. An advantage of addition polymerization over condensation methods in resin preparation is that the addition methods can be adapted to the preparation of the polymer in bulk, powdered or bead forms of various sizes. The condensation reactions usually give a bulk product which must be broken to desired sizes. Bulk polymers of acrylic or methacrylic acid, together with from 0 to 24 per cent of

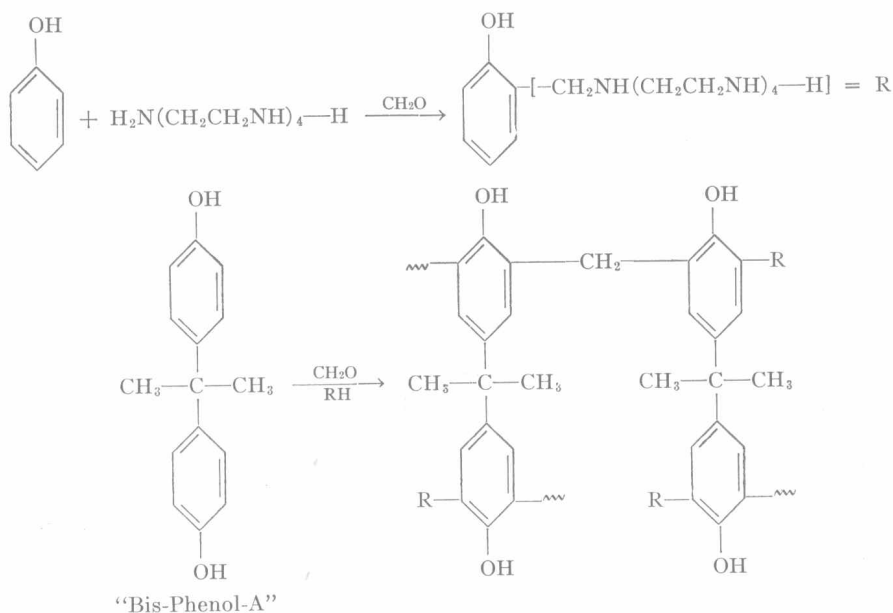


FIGURE 4

divinylbenzene as crosslinking agent, were studied by Bernstein and Gregor.<sup>11</sup> The total capacities were slightly reduced and the ability to swell was greatly reduced with increasing degree of crosslinking. The time required for establishment of equilibrium between a resin and the contacting solution varied directly with the degree of crosslinking.

Similar polymers prepared using either divinylbenzene, butadiene or isoprene as crosslinking agents for methacrylic and acrylic acids were described by Bodamer.<sup>12</sup> The polymerization conditions used by Bodamer lead to the so-called "popcorn" resins, which are much less dense and more porous than the copolymers prepared by Bernstein. These resins exchange ions more rapidly than the bulk polymers. Even when the same ratio of starting materials is used, the "popcorn" resins are less dense than the bulk resins. Carboxylic acid cation exchange resins similar to those shown in FIGURE 7 have high total

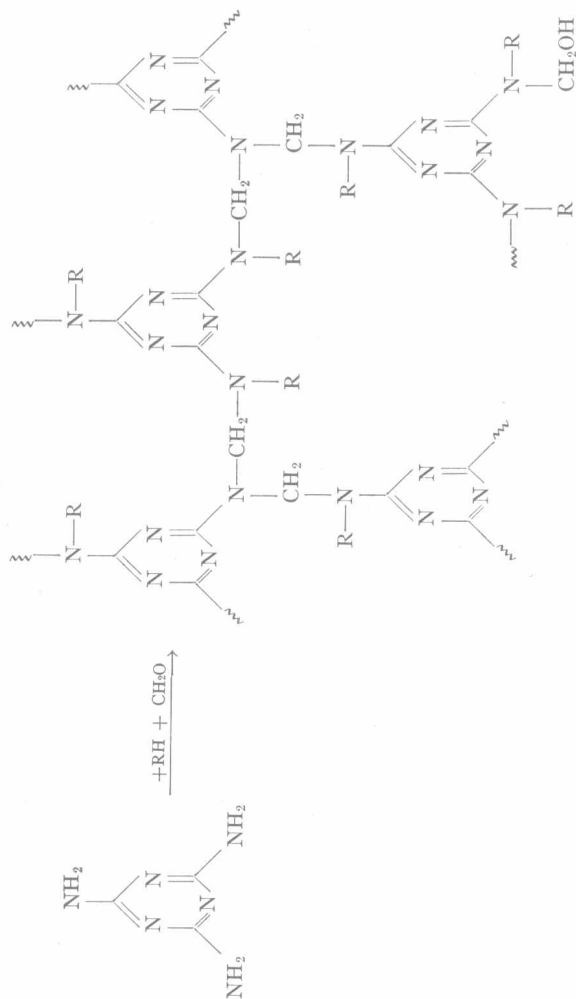


FIGURE 5

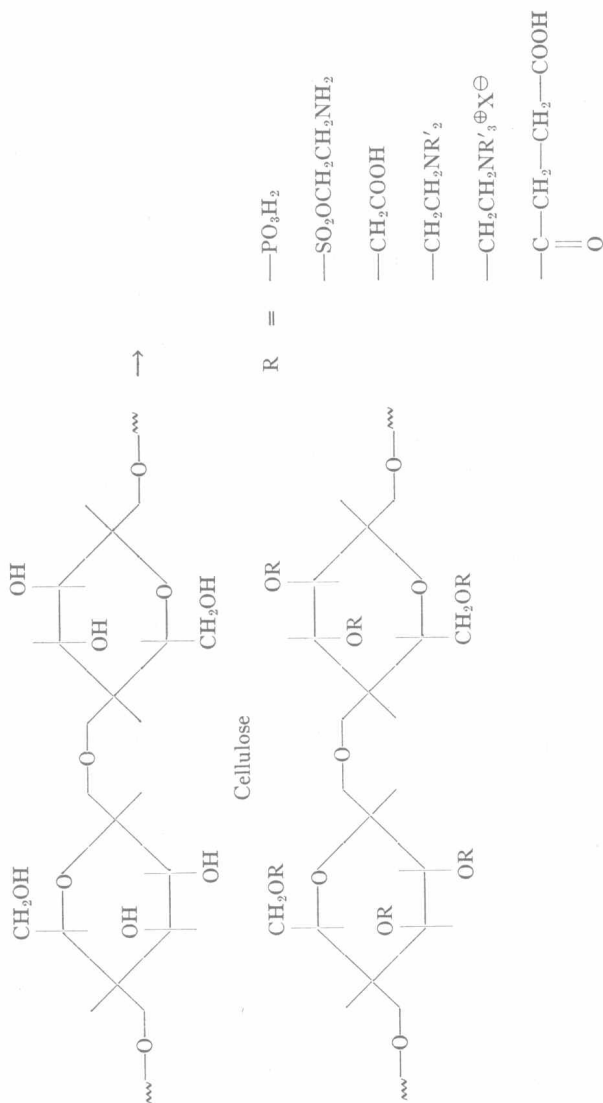
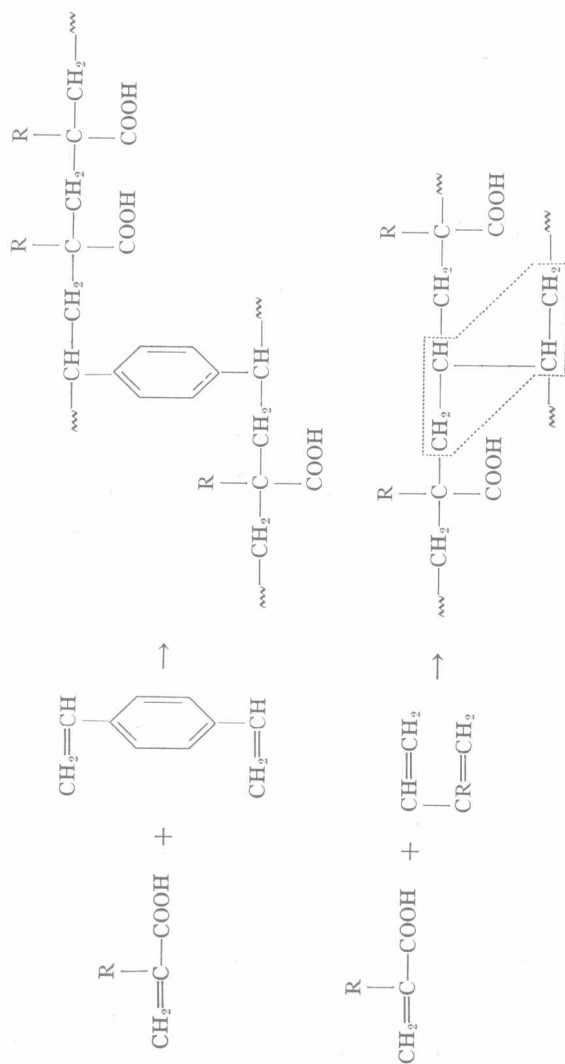


FIGURE 6



"Popcorn" Type Resins

FIGURE 7



capacities for cations, and are now being used in medicine to remove sodium ions from the human body upon ingestion.<sup>13</sup>

In FIGURE 8 is shown the basic structure of a styrene-divinylbenzene copolymer. Although the commercial divinylbenzene contains almost equal amounts of ethyl-vinylbenzene and divinylbenzene, we shall consider the basic structural unit to be that which is illustrated at the bottom of FIGURE 8. It is helpful to consider this basic structure to be analogous with that of benzene as a chemical intermediate.

Some reactions which can be applied to a crosslinked styrene polymer are shown in FIGURE 9. The sulfonation reaction leads to a polystyrene sulfonic

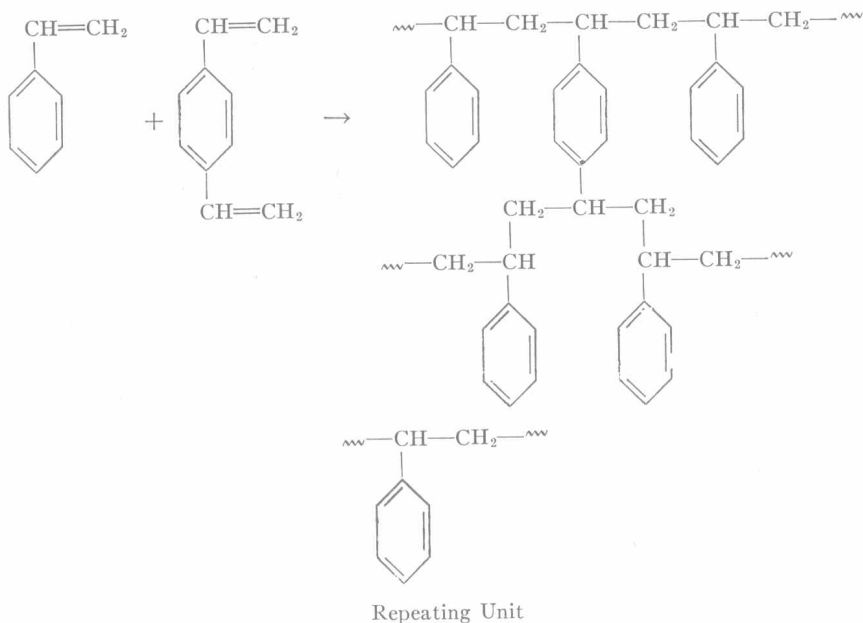


FIGURE 8

acid in which it appears, from capacity determinations, that every benzene ring in the polymer contains one sulfonic acid group.<sup>14</sup> The resulting resin is a strong acid, and several commercial cation exchange resins have this general composition with about 10 per cent of crosslinking agent. Recently a series of such polysulfonic acid resins with various degrees of crosslinking has been made commercially available (Dow Chemical Company).

The chloromethylation of crosslinked polystyrene gives the intermediate resin, which is a polymeric benzylchloride. This can be reacted with secondary or tertiary amines to form either "weakly" or "strongly" basic anion exchange resins.<sup>15</sup> Analogous resins are commercially available at present. The chloromethylation of linear polystyrene is complicated by crosslinking reactions, and, unless the reaction is stopped before or at the introduction of chloromethyl groups into 65 per cent of the polymer, an insoluble product will form.<sup>16</sup> These

results probably mean that in a crosslinked polymer, chloromethylation leads to further crosslinking. The anion exchange resins prepared by this route probably have an unknown degree of crosslinking in excess of that of the starting polymer. This factor has no bearing on practical uses of the resins.

The resulting quaternary ammonium resins have considerable industrial significance, as they can be used to remove weak acids, such as silicic and carbonic, from water. Weak amine resins can be prepared from the chloromethylated resin as illustrated.

In carrying out reactions upon these crosslinked resins, it is essential that the reactants can diffuse readily throughout the polymer matrix. The resulting polymer must be swelled by the reaction mixture to allow this diffusion, but it is not necessary that the initial resin be swelled by the reagents. For example, the crosslinked polystyrene resins are not swollen in sulfuric acid, but

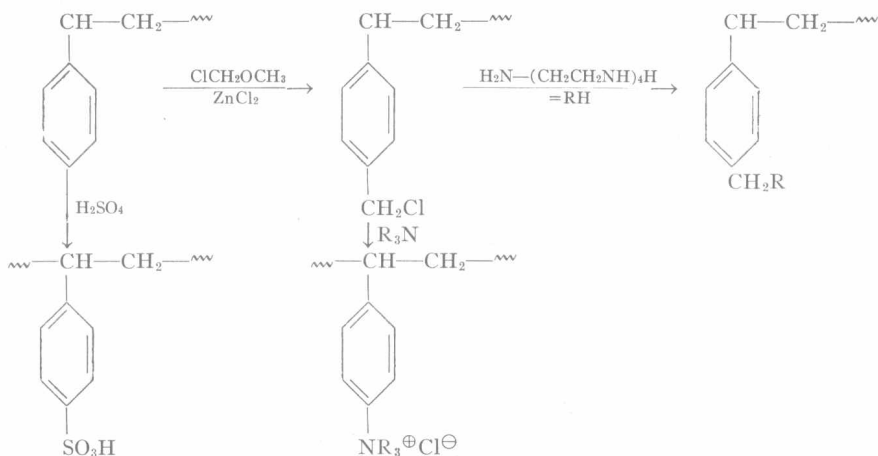


FIGURE 9

on heating the mixture with a catalyst the surface of the resin is sulfonated. The surface then consists of polystyrene sulfonic acid groups, which are swollen by sulfuric acid and allow it to diffuse into the interior until the entire resin particle is completely sulfonated and therefore has swelled to the limit allowed by the degree of crosslinking. Although it is not necessary for the polystyrene resin to be swollen before the sulfonation, it is advantageous to use an inert swelling agent such as trichlorethylene when bead particles are used.

Another example of the importance of the swelling factor is found when carrying out reactions with the chloromethylated resins. These are structurally analogous to benzyl chloride, and should readily hydrolyze to the polymeric benzyl alcohol. The chloromethylated resin, however, is not swollen in water or alcohol, and beads of the chloromethylated resin which are pre-swollen by tetrahydrofuran shrink on addition of these solvents. Therefore, essentially no reaction occurs on heating beads of the chloromethyl resin with alcoholic potassium hydroxide solutions. This swelling factor is so important

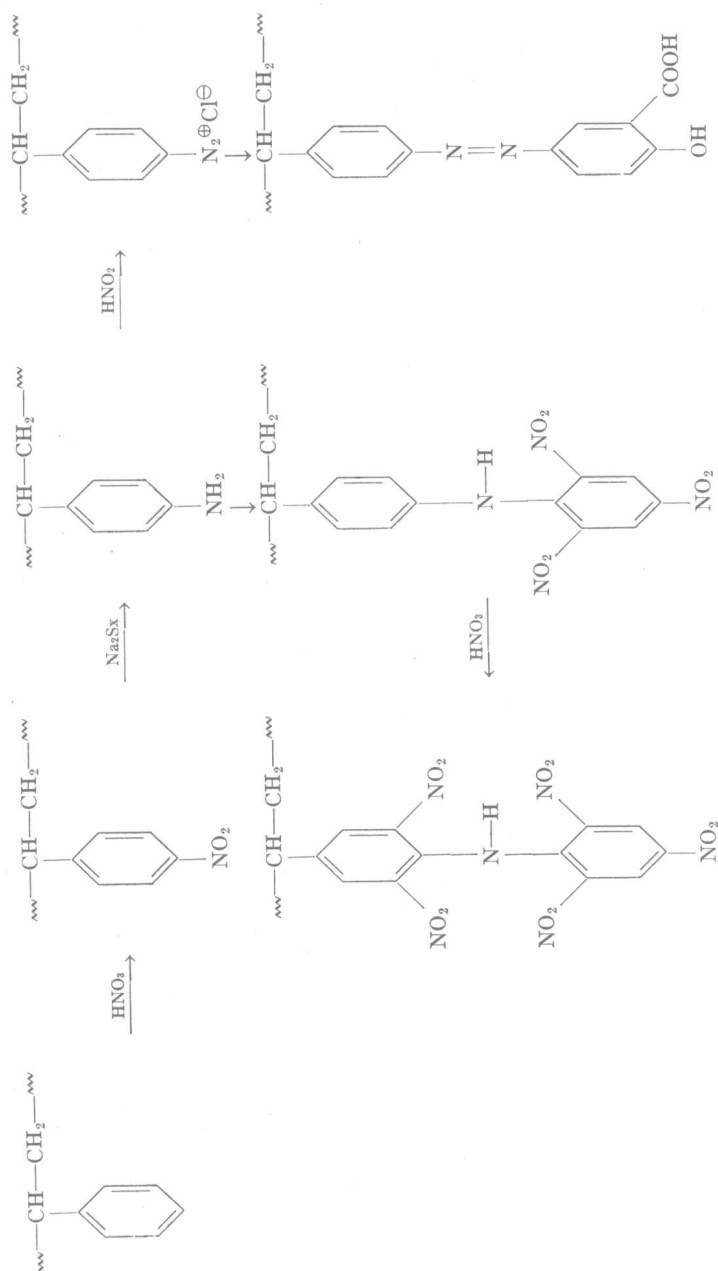


FIGURE 10