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ION-EXCHANGE SEPARATION PROCESSES

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12.1 Introduction

Ion exchange involves the substitution of one ionic species for another without significant change in structure. In chromatographic systems in which the stationary phase is relatively rigid, the restriction against significant change in structure becomes important. Although "significant change" is sometimes difficult to define, it is apparent that substitutions at surfaces and in porous media often may be classified as ion-exchange phenomena. On the other hand, if potassium ion with a crystal radius of 1.33 Å were substituted for cesium ion, with a crystal radius of 1.67 Å, in a cesium chloride crystal, the structure would have significantly different crystallographic properties. Therefore this is not considered to be ion exchange. Most useful ion exchangers are porous materials containing ionogenic groups; that is, they have fixed ionic groups and potentially mobile counterions.

Utilization of ion exchange in separation schemes frequently involves techniques and instrumentation similar to those used in liquid-liquid chromatography (Chapter 10). However, the ion-exchange process is not limited to these applications and systems. It has been cited as an important process in the transport of ions in living cells and is significant in maintaining electrolyte balance. Cellular membranes apparently display some properties

that are formally equivalent to those of ion-exchanger membranes. Transmission of nerve impulses has been theorized as an exchange process. Similarly, the mechanism and the electrical potential of the glass electrode have been described in ion-exchange terms.

Each of these fields has benefited by the stimulation provided by the others. Some major advances in ion-exchange theory have resulted from the pursuit of biophysical principles, and phenomena discovered while studying ion exchange have been important in the aforementioned fields (1, 2).

Most applications of this versatile technique have been carried out with ion-exchanger particles in packed beds such as chromatographic columns (3). Other arrangements such as incorporation of ionogenic groups in membranes, are also important (Chapter 16), but the major direction of this chapter is the consideration of column systems, primarily those in which solutes to be separated are present in small quantities compared to the stationary phase. Although exchangers have been utilized for catalysis and the preparation of molecular species through oxidation or reduction of starting materials (utilizing redox ion exchangers), these applications are not considered in this chapter.

12.2 Structure

12.21 INORGANIC MATERIALS

Naturally occurring sands that desalt brackish waters were known in classical times, although characterization of these occurred only in the twentieth century. Such common materials as the zeolites, which include some sodium aluminum silicates, and clays, such as montmorillonite, have ion-exchange properties. Zirconium phosphate, $Zr(HPO_4)_2 \cdot H_2O$, and hydroxyapatite, $Ca_5(PO_4)_3OH$, are among the inorganic exchangers produced in the laboratory. The former has a layered structure with planar Zr atoms bridged by phosphate groups between the planes. Interlayer cavities about 8 Å in height provide the sites for cation exchange. Hydroxyapatite has found important application in the chromatography of proteins and nucleic acids such as DNA (4). The mechanism of separation is probably surface exchange, since these macromolecules are too large to penetrate the pores of the stationary phase. The relatively rigid frameworks of these materials and their fixed pore sizes restrict the penetration of molecular species into the framework. Thus separations have been carried out on the basis of molecular size as well as ion exchange (see Section 15.2).

Styrene–Divinylbenzene Copolymers

Resins based on these copolymers are the most widely used ion exchangers. They are commonly produced by suspension polymerization in which styrene and divinylbenzene are suspended in water as droplets. Addition of a catalyst such as benzoyl peroxide initiates polymerization. The resulting beads are porous, and swell but do not dissolve when placed in common hydrocarbon solvents. The degree of swelling depends on the amount of divinylbenzene cross-linking agent present. Typically, 8 to 12% of this compound is used. Much lower crosslinking results in soft materials, while higher quantities of divinylbenzene produce an excessively rigid structure. Treatment of the hydrocarbon-swollen beads with sulfuric or chlorosulfonic

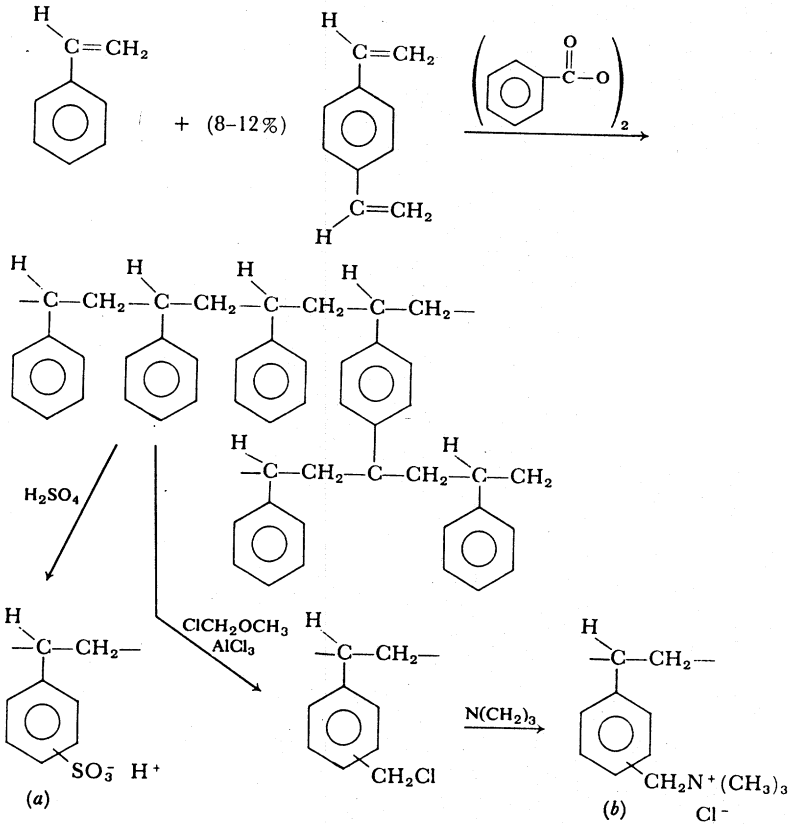


Figure 12.1. Preparation of styrene–divinylbenzene-based ion exchangers: (*a*) sulfonic acid cation exchanger, (*b*) quaternary ammonium chloride anion exchanger.

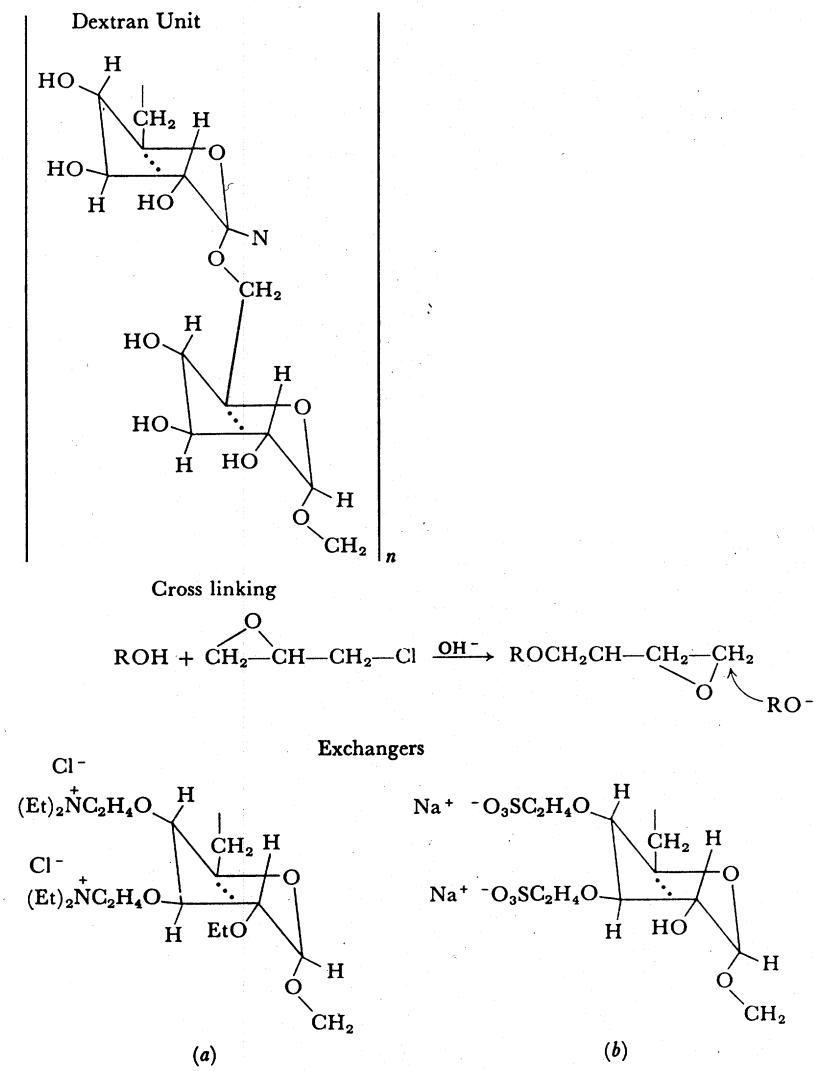


Figure 12.2. Preparation of dextran-based exchangers: (*a*) tertiary amine (weak base) anion exchanger, (*b*) Soudim-form cation exchanger.

acid results in a sulfonic acid cation exchanger. When the beads are treated with chloromethyl ether and then trimethylamine, the common quaternary ammonium chloride anion exchanger results (Fig. 12.1). The resins are treated to remove unpolymerized monomers, low polymers, and foreign counterions and are sold commercially. They swell slightly or not at all in organic solvents but markedly in aqueous solutions. The sulfonic acid

resin is referred to as a strong-acid type, whereas the quaternary-ammonium resin in the hydroxide form acts as a strong base. Resins thus produced have fairly good mechanical stability. Strong-acid resins, their salts, and strong-base resins in their salt forms are relatively stable chemically and are among the most commonly used ion exchangers. Many other functional groups have also been incorporated, such as tertiary amines, carboxylic acids, and iminodiacetic acid [$N(CH_2COOH)_2$] moieties, which result in weak-base, weak-acid, and chelating resins, respectively.

When copolymerization is carried out in the presence of an inert diluent that is a good solvent for the monomers, but not the polymer, resin beads with pools of diluent distributed throughout the matrix are obtained. When these are washed out, a macroporous structure results which is usually rigid because of the use of large amounts of cross-linking agent. Functionality is incorporated as described. The pores are much larger than in the usual exchangers, and these "macroreticular resins" have been finding increasing use in technological applications such as water purification.

Carbohydrate-Based Polymers

An important class of materials commonly used in biochemical and polymer studies is based on dextran gels prepared by the action of the microorganism *Leuconostoc mesenteroides* upon sucrose. The linear polymers are cross-linked with epichlorohydrin and converted to the commonly used diethylaminoethyl (DEAE) and sulfonic acid derivatives (Fig. 12.2). Similar materials have been prepared directly by treatment of cellulose, and ion-exchange celluloses have been packed into columns as powders, cast onto plates for use in thin-layer chromatography, or, in preformed sheets, utilized in paper chromatographic work.

12.3 Properties of Ion Exchangers

12.31 CAPACITY

The number of ionogenic groups per unit weight or volume of exchanger is easily determined. For anion exchangers, chloride ions are readily exchanged for nitrate and the desorbed halide is easily determined with silver ion. In the case of cation exchangers, hydrogen ions may similarly be displaced by sodium ion in a salt solution and the resulting acid titrated with base. Alternatively, the hydrogen-form resin may be titrated directly with base. A typical titration curve is depicted in Fig. 12.3. The apparently great buffer capacity at the start of the titration is deceptive, since addition of strong acid

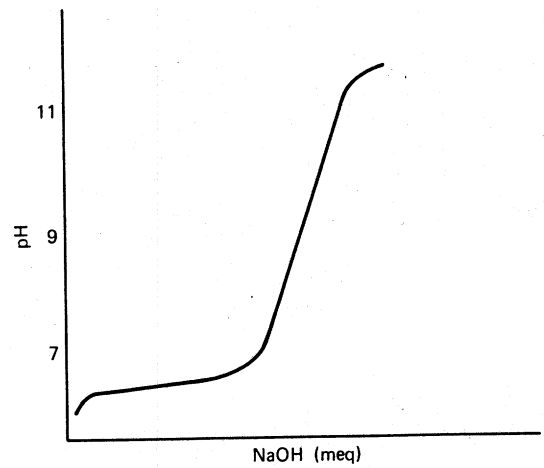


Figure 12.3. Direct titration of a cation exchanger with NaOH. The capacity of the exchanger can be calculated from the number of milliequivalents of base required to reach the equivalence point.

at this point would greatly decrease the pH of this system. The capacities of the usual polystyrene-based exchangers are on the order of 3 and 5 meq/g of resin (on a dry basis) for anion and cation exchangers, respectively.

12.32 SWELLING

Dry ion exchangers have a strong affinity for water. Use is made of this property, as molecular sieves are widely utilized for removing traces of water from organic solvents. Water diffuses into the porous exchangers, hydrating the fixed ions and counterions. In the early stages of water sorption, the volume of the system, water plus resin, is less than the sum of the volumes of the original materials. As subsequent water molecules penetrate the exchanger, the increase in volume is an additive function of the amount of water sorbed. Although linear polymers would eventually dissolve or form micelles, the presence of cross links limits the amount of water imbibed. The flexibility of these matrices allows swelling of the exchanger; however, swollen resins placed in contact with concentrated salt solutions shrink.

The amount of swelling depends on the degree of crosslinking and flexibility of the chains, and highly cross-linked resins swell least. Other important considerations are the concentration of the external solution and the ionic form of the resin. For example, the sequence of counter ions giving increasing resin volumes for most sulfonate type cation exchangers is $Cs^+ < Rb^+ < K^+ < Na^+ < Li^+$ and parallels the hydrated ionic volumes, that is, the hydrated ionic volume of lithium is greater than that of sodium. Swelling

is similarly favored by high capacity of resin, polar solvents, and complete dissociation of ionogenic groups within the resin. For example, carboxylic acid resins do not swell appreciably in acid solution.

12.33 EQUILIBRIA

Uncharged Species

Thermodynamic description of resin swelling and sorption of undissociated solutes is formally equivalent to a system with a semipermeable membrane separating a solution containing a polyelectrolyte from another solution containing undissociated solute. The polyelectrolyte is unable to pass through the membrane, whereas all other species may be transported through this semipermeable barrier. Van't Hoff's law of osmotic pressure applies to these cases. Solute may pass into the polyelectrolyte solution, but equilibrium will be attained only if pressure is applied to the chamber containing the polymer. The difference in pressure applied to the two chambers is π, the osmotic pressure. In a resin the fixed ions are equivalent to the polyelectrolyte described, and the cross links, due to copolymerization of divinylbenzene, are the source of pressure on the solution within the exchanger. As species such as water diffuse into the resin the matrix is expanded until the force exerted by the cross links results in an osmotic pressure sufficient for equilibrium to be reached.

The chemical potentials of species in solutions corresponding to the one external to the resin were considered in Chapter 2, as in Eq. 2.3:

$$\mu_i^{aq} = \mu_i^{0,aq} + \mathrm{RT} \ln a_i^{aq} \tag{2.3}$$

and succeeding expressions. In many studies the external solution is essentially incompressible and is generally near 1 atm in pressure; the effect of pressure on its chemical potential is thus usually neglected. Pressure, however, must be considered within the resin phase. The chemical potential of species within the resin, μ_i^r, is a function of the internal pressure P and the molar concentration of the solute C:

$$d\mu_i^r = \left(\frac{\partial \mu_i^r}{\partial C}\right)_{T,P} dC + \left(\frac{\partial \mu_i^r}{\partial P}\right)_{T,C} dP \tag{12.1a}$$

$$\mu_i = v_i \, dP - s_i \, dT \tag{12.1b}$$

$$\mu_i^r = \mu_i^{0,r} + RT \ln a_i^r + v_i(P^r - P^{aq}) \tag{12.2}$$

and

$$\mu_i^r = \mu_i^{0,r} + RT \ln a_i^r + v_i \pi \tag{12.3}$$

All terms have their usual significance, while s_i and v_i are the partial molar entropy and the volume of species i. Expression 12.3 is useful for study of the equilibrium of an electrically neutral solute such as water or ethanol between the resin and an external solution.

Charged Species

Consider a resin with a typically univalent fixed functional group R and a counterion A of charge Z_A. When in equilibrium with a totally dissociated salt, $Y_{Z_A}A_{Z_Y}$, electroneutrality requires that the total concentration of positive charges within the resin equals the total concentration of negative charges within the resin:

$$[R] + |Z_Y|\,[Y^r] = |Z_A|\,[A^r] \tag{12.4}$$

The presence within the resin of small amounts of ion with the same charge sign as the fixed groups on the resin is termed *Donnan penetration.* In general, it is favored by high concentration of ions in the external solution, low cross-linking, and low capacity of resin. Donnan equilibrium also has been used to give a thermodynamic representation of ion exchange for electrolytes.

When charged species are to be considered, the electrochemical potentials, η of the species in each phase are equal at equilibrium, for example,

$$(\eta_i)^r = (\eta_i)^{aq} \tag{12.5}$$

The electrochemical potential is related to the chemical potential by

$$\eta_i = \mu_i + Z_i\mathscr{F}\phi \tag{12.6}$$

where $\mathscr{F}$ is the Faraday constant, and ϕ is the electrical potential acting on species i. The Donnan potential is the difference in electric potential between the ion exchanger ϕ^r and the solution ϕ^{aq}, and the chemical potential may be determined as in Eqs. 2.3 and 12.3. Reference states for ionic species in both resin and solution are taken usually as the infinitely dilute aqueous species. Thus

$$E_{\text{Donnan}} \equiv \phi^r - \phi^{aq} = \frac{1}{Z_i\mathscr{F}}\left(RT\ln\frac{a_i^{aq}}{a_i^r} - \pi v_i\right) \tag{12.7}$$

The partial molar volume of species i is assumed to be the same in aqueous or resin phase.

Consider the exchange of ion B, which is initially in the resin, by ion A:

$$|Z_B|A^{Z_A} + |Z_A|(|Z_B|R^{\pm 1} + B^{Z_B}) \rightleftharpoons |Z_B|(|Z_A R^{\pm 1} + A^{Z_A}) + |Z_A|B^{Z_B}$$

The exchange reaction may be described in terms of a thermodynamic equilibrium constant:

$$K_B^{0,A} = \frac{(a_A^r)^{|Z_B|}(a_B^{aq})^{|Z_A|}}{(a_A^{aq})^{|Z_B|}(a_B^r)^{|Z_A|}} \tag{12.8}$$

a classical equilibrium constant where the molar concentrations of solute in both phases are used:

$$K_B{}^A = \frac{[A^r]^{|Z_B|}[B^{aq}]^{|Z_A|}}{[A^{aq}]^{|Z_B|}[B^r]^{|Z_A|}} \tag{12.9}$$

and the Donnan potential:

$$E_{\text{Donnan}} = \frac{1}{|Z_A|\mathscr{F}}\left(RT\ln\frac{(a_A{}^{aq})}{(a_A{}^r)} - \pi v_A\right) = \frac{1}{|Z_B|\mathscr{F}}\left(RT\ln\frac{(a_B{}^{aq})}{(a_B{}^r)} - \pi v_B\right) \tag{12.10}$$

The value of this potential is independent of whether ion A or B is chosen for consideration and is a measure of the relative abundance of the ions in the two phases. Thus

$$\ln\left[\left(\frac{a_B{}^{aq}}{a_B{}^r}\right)^{|Z_A|}\left(\frac{a_A{}^r}{a_A{}^{aq}}\right)^{|Z_B|}\right] = \ln K_B{}^{0,A} = \frac{\pi}{RT}(|Z_A|v_B - |Z_B|v_A) \tag{12.11}$$

Selectivity of the resin for A over B is reflected in a positive value of $\ln K_B{}^{0,A}$. Equation 12.11 indicates that species of higher (absolute value) charge are favored by the resin over those of lower charge. Conversely, species of low partial molar volumes sorb preferentially, but it should be stressed that "partial molar volume" here refers to the hydrated species. Selectivity should be favored by large values of π, which occur when a high degree of cross linking is present. Examination of Section 12.32 indicates that swelling of cation exchangers increases when counterions are in the order from cesium to lithium. A related order prevails for selectivity, that is, cesium ion is favored. Similarly, barium ion is favored over strontium, and so on through beryllium ion. Typical selectivity for strong-acid cation exchangers is as follows: $Li^+ < H^+ < Na^+ < NH_4^+ < K^+ < Rb^+ < Cs^+ < Ag^+$ and $Mg^{2+} < Zn^{2+} < Co^{2+} < Cu^{2+} < Cd^{2+} < Ni^{2+} < Ca^{2+} < Sr^{2+} < Pb^{2+} < Ba^{2+}$.

The order for anion exchange is somewhat more complex, although iodide ion is the most strongly held of the halides. A typical order for anion-exchange resins of the strong-base type is: $F^- \simeq OH^- < CH_3COO^- < HCOO^- < H_2PO_4^- < HCO_3^- < Cl^- < NO_2^- < HSO_3^- < CN^- < Br^- < NO_3^- < HSO_4^- < I^-$. Some of the complexity is due to formation of ion pairs in the resin phase or association, as in the case of acetate ion interacting with hydrogen ion to form dimerized undissociated acetic acid. The presence of tertiary and secondary amines as fixed groups in anion exchangers further complicates the picture. These sites can be protonated during washing of the resin and can act as a source of hydrogen ion, as well as a site for hydrogen bonding.

to the convention that discussions of selectivity should be referred to a resin that contains 50 equivalent per cent of the two ions being considered. When this is the case and the resin is in equilibrium with an extremely dilute solution of two counterions of the same charge, the thermodynamic and classical equilibrium constants are equal by convention. As the equivalent fraction of an ion in the resin approaches 1, the selectivity, on the concentration scale, for that ion decreases. If we assume for the present that $\ln K_B{}^A$ is proportional to $\pi(|Z_A|v_B - |Z_B|v_A)$, it is easy to understand why highly cross-linked resins display high selectivity. Furthermore, as the resin is converted to the ionic form of lower partial molar volume, π decreases, leading to a decrease in $\ln K_B{}^A$. This apparently is most important for resins with a high degree of cross linking.

Selectivity reversals are difficult to understand on the basis of this theory. It has been suggested that in a group such as the alkali-metal ions the most highly hydrated species tend to be stripped of some or all of their exterior water of hydration when the resin is under the stress of a large osmotic pressure. This should be most important for highly cross-linked resins. It has been proposed that the partial molar volumes of the unhydrated ions are the important parameters in such cases. Although transport and activity coefficient measurements tend to support the concept of hydrated ionic radii, there is no direct method for measuring these quantities, nor have "partially hydrated" species been determined in ion-exchange resins. The difficulties encountered in rationalizing some of the aforementioned phenomena with thermodynamic and classical equilibrium expressions have led to searches for other interpretations of ion-exchange selectivity.

One of the most interesting of these was developed for glass electrodes, which show specificity (ion-exchange selectivity) for alkali-metal ions (7). In this approach it was assumed that ionic species interacting with fixed groups on the exchanger matrix are stripped of water of hydration and the energy of attraction is purely Coulombic. When an ionic species is replaced by another, the "desorbed" ion gains water of hydration after the exchange and gives up free energy of hydration. The change in free energy for the conversion of a resin, initially the A form to the B form, is

$$\Delta G_A^{0,B} = -RT \ln K_A^{0,B} = (\Delta G_{B,r}^{0,\text{Coulombic}} - \Delta G_{A,r}^{0,\text{Coulombic}}) + (\Delta G_A^{0,\text{hydration}} - \Delta G_B^{0,\text{hydration}}) \quad (12.12)$$

and

$$\Delta G_{B,r}^{0,\text{Coulombic}} \approx \frac{-332}{\rho_+ + \rho_-} \quad (12.13)$$

The terms have their usual significance, and $\rho_+ + \rho_-$ is the internuclear distance between the oppositely charged species in the absence of hydrating water molecules.

The free energy of hydration is roughly inversely proportional to the crystal radius of the exchanged ion. Eisenman (7) has made a careful study of the selectivity of glass electrodes for alkali-metal cations. When the anionic exchange site is large and dispersed, the difference in hydration energy between the two exchanging cations controls the overall free energy and thus the equilibrium constant. Conversely, small electrically dense exchange sites result in Coulombic control. Extrapolating this approach to porous exchangers, Eisenman and others have described sulfonate-ion groups as large exchange sites (8). For species of the same charge, if the crystal radius of ion A is smaller than that of ion B, the term $(\Delta G_A^{0,\text{hydration}} - \Delta G_B^{0,\text{hydration}})$ is negative, since the exothermic energy of hydration of species A is a larger negative number than that of B. In this type of case, the hydration energy controls the equilibrium. Thus the exchange of a resin initially in the A form for a larger (when unhydrated) B ion is a spontaneous process with a favorable free energy and equilibrium constant. This agrees with the observations that the resin favors the species of larger crystal radius, but the explanation differs from that presented before. In the interpretation of Gregor's work, selectivity was attributed to an affinity of the resin for the smallest hydrated species. In the interpretation of Eisenman's work, however, the affinity of the resin for the species of larger crystal radius is due to the relatively great (negative) energy of hydration of the species of smaller crystal

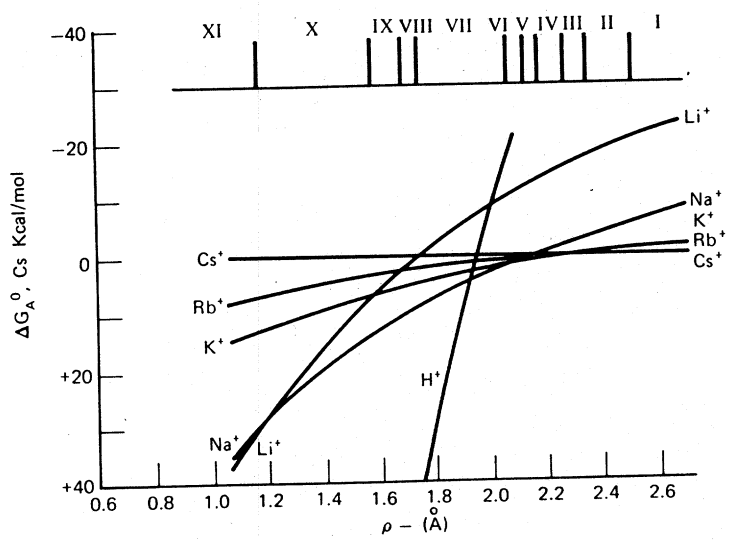


Figure 12.5. ΔG° for the production of a Cs^+-form resin from a resin initially in the A form (A = Li^+, Na^+, etc.) plotted against radius of the exchange site. The Roman numerals indicate 11 distinct selectivity orders at differing values of ρ^-, more than half of these orders have been experimentally observed (7).

radius. In the former case the explanation claims that the resin favors the species with the smaller hydrated radius, whereas in the latter case the solution favors the species with the smaller crystal radius, which might have a larger hydrated radius. Eisenman's approach has had an interesting degree of success.

In Fig. 12.5 a plot of ΔG° calculated as a function of the size of the unhydrated exchange site is depicted for alkali-metal cations, based on their crystal radii. For large exchange sites the predicted selectivity order is the same as that observed for sulfonic acid type resins. For small, electrically dense exchange sites, however, the selectivity order is reversed, that is, Li^+ is apparently favored over Na^+. This is the observed selectivity order for carboxylic acid resins, which in Eisenman's approach would be defined as small exchange sites. Phenomena observed for highly cross-linked resins have been explained on the basis of overlapping electron clouds of the fixed sites, yet no fully acceptable rationalization of selectivity reversals, which occur as the fraction of a counterion in the resin is changed, has been advanced. Although a number of other theories of selectivity have been published, the explanation of these phenomena awaits further investigation.

12.35 KINETICS

In ion exchange, as in the other forms of chromatography, kinetic processes are extremely important (Chapter 3). In addition to longitudinal transport of solute-containing eluent through the column, a number of other processes are also significant: (1) transport of species in the void volume between the resin particles, (2) diffusion of species through the relatively stationary film around the resin particles, (3) diffusion within the resin particles, and (4) exchange of ions at the fixed groups within the resin. Steps 2 and 3, called *film* and *particle diffusion*, are the slowest processes in ion exchange.

Ion-exchange kinetics is complex, and rigorous solutions have been made in only a few cases. Most attention has been paid to spherical beads and planar membranes, and much of the knowledge in this field is due to the work of Helfferich (1). He has shown for particle diffusion control that the half time for complete conversion may be given by

$$t_{1/2} = 0.0075 \frac{dp^2}{D^r} \tag{12.14}$$

Here dp is the bead diameter, and D^r is the diffusion coefficient within the resin. In this case the beads were in contact with a large excess of solution, in which the system was agitated so that they did not clump together. Since half time is inversely proportional to the rate of exchange, this rate is then

proportional to the diffusion coefficient and inversely proportional to the square of the bead radius. In the case of film diffusion control, for a system similar to that previously described, half time for conversion of a resin initially in the A form to the B form may be calculated by

$$t_{1/2} = (0.17 + 0.064K_B{}^A)\frac{dp\delta q}{2D^{aq}[B]} \tag{12.15}$$

Here the concentration of B in the external solution remains constant throughout the experiment. Film thickness is denoted by δ, the diffusion coefficient within this stationary layer of solution is D^{aq}, and q is the capacity of the resin in milliequivalents per milliliter of resin.

The question of whether film or particle diffusion is the rate-controlling step is readily answered in these nonchromatographic systems by setting the half times equal and rearranging. Remembering that the rate-determining step is the slowest process, that with the longest half time, we can express the control criterion as

$$\begin{pmatrix}\text{Particle}\\ \text{diffusion}\end{pmatrix} 1 \gg (6 + 2K_B{}^A)\frac{D^r\delta q}{dpD^{aq}[B]} \gg 1 \begin{pmatrix}\text{Film}\\ \text{diffusion}\end{pmatrix} \tag{12.16}$$

A typical value for D^r/D^{aq} is about 0.1, q is often 3 meq/ml, and δ is about 0.001 cm in well-stirred solutions. In a system where $K_B{}^A = 1$, the product of dp and $[B]$ would have to be 2×10^{-3} for the system to lie in the intermediate range between clear-cut film and particle diffusion. A common bead size is 200 mesh, which reflects a diameter of 8×10^{-3} cm. In this system when $[B]$, with a charge of ± 1, is less than 0.1 M, film diffusion would occur. It should be remembered that these situations are related to, but are not equivalent to, columnar processes. Only rarely are large quantities of resin beads of identical diameter available. Even if such a condition were met, packing these into columns under the ideal condition of closest packing would result in each bead touching twelve others. Film diffusion through the complex figure would have somewhat different properties than that through a system with radial symmetry. In a similar manner the boundary conditions stated for particle diffusion, although useful in separation processes such as countercurrent ion exchange, are not often equivalent to those in chromatography. The overall pictures, however, show great similarity.

Diffusion of ions in the mobile phase was considered in Eq. 3.46. In this case the coupled movement of cations and anions results in an interdiffusion coefficient. Diffusion within the resin is at first sight more complex, since the counterions are mobile whereas the fixed ions are stationary and exclude mobile coions. Under this condition

$$|Z_A|[A^r] + |Z_B|[B^r] = q \tag{12.17}$$

and

$$Z_A J_A = -Z_B J_B \tag{12.18}$$

Equation 12.18 indicates that, when ion A moves in one direction, an equivalent amount of ion B moves in the opposite direction. This coupled diffusion reflects an absence of electrical current. The driving force for transport, as described in Chapter 3, is the gradient in chemical potential or, in the case of charged species, the gradient in electrochemical potential. Equation 3.1 described diffusion in the absence of an electrical potential. The existence of the Donnan potential, however, requires consideration of electrical transport. The flux of a species within a resin bead may be described by

$$J_A = -D_A{}^r \left(\text{grad } [A^r] + |Z_A|[A^r] \frac{\mathscr{F}}{RT} \text{ grad } \phi \right) \tag{12.19}$$

Combination of Eqs. 12.17 through 12.19 results in

$$J_A = -\left[\frac{D_A{}^r D_B{}^r (Z_A{}^2[A^r] + Z_B{}^2[B^r])}{Z_A{}^2[A^r] D_A{}^r + Z_B{}^2[B^r] D_B{}^r} \right] \text{grad } [A^r] \tag{12.20}$$

The term in brackets, the so-called interdiffusion constant, depends on the concentrations of A and B. Diffusion coefficients are of the same magnitude for most species within the resin phase. For ions of similar charge magnitude, it becomes apparent that the term in brackets reduces to $D_B{}^r$ when $[B^r] \ll [A^r]$. This means that the effective diffusion coefficient is that for the less concentrated species within the resin phase! This consideration is important in chromatographic systems where the eluent counter ion A, is in great excess to the ion being chromatographed, B. The diffusion coefficient is dependent on the latter. Furthermore, in the conversion of resin in the A form to the B form and, after completion, the reconversion of the latter to the A form, the initial rates are quite different.

12.4 Applications

12.41 REMOVAL OF SPECIFIC IONS

Use of many techniques is restricted by the presence of interfering counterions. Ion exchange becomes a valuable tool in the removal of these species. Sodium ion may be substituted for other cations in a solution by passing the solution through a bed containing cation exchanger in the sodium form. Similarly, nitrate ions may be substituted for interfering anions by passing the solution through an anion exchanger in the nitrate form.

One example of a frequently carried out technique is the preparation of tetramethylammonium hydroxide from tetramethylammonium chloride. This quaternary ammonium ion is desired in many potentiometric studies in which the effects of the complexing of a supporting electrolyte are to be minimized. It is desirable to convert the solution used as titrant to tetramethylammonium hydroxide, which is expensive and not always available at high purity. The procedure requires converting the bed of cation exchanger to the tetramethylammonium form by passing a solution of tetramethylammonium chloride through the bed. The bed is washed with water, and sodium hydroxide solution is passed through the bed. Sodium ions exchange with the quaternary ammonium ions, and tetramethylammonium hydroxide appears in the effluent ready for use. Because of the instability of anion exchangers in the hydroxide form, this procedure is far superior to utilizing an anion exchanger, converting it to the hydroxide form, and then passing the quaternary amine chloride through the anion exchanger. Furthermore, the low selectivity of resins for hydroxide ion results in a requirement for large quantities of base in order to prepare a resin that is totally in the hydroxide form.

12.42 DETERMINATION OF TOTAL SALT

Determination of the total number of equivalents in a salt solution is often a difficult task but is readily carried out by passing the solution through a cation exchanger in the hydrogen form. The acid that evolves is determined. Anion exchangers may be utilized, but their use in the hydroxide form involves a number of difficulties. Besides the aforementioned instability and difficulty of regeneration, they have lower capacities per unit volume than cation exchangers. Alkaline effluents have to be protected against atmospheric carbon dioxide, and insoluble hydroxides precipitate on the exchanger and clog it. The alternative is to use anion exchangers in the chloride form, but in utilizing this technique it is necessary to make sure that undissociated complexes do not cause errors.

An interesting alternative procedure useful for obtaining salt samples from remote areas involves passing a measured amount of fluid, such as ground waters, through small columns of exchanger contained in plastic. The sealed columns are readily transported back to the laboratory for study of individual components after they have been eluted from the resins.

12.43 DEIONIZATION

Among the most common uses for ion exchangers is the preparation of deionized water. Solutions to be treated are passed successively through a

cation exchanger in the hydrogen form and an anion exchanger, usually a weak-base type, in the hydroxide form. The eluted solutions generally have low conductivity and may be useful for conductivity water, but they may contain traces of unremoved organic solutes. Similarly, decomposition of resins leaves traces of resin-breakdown products in the solutions. These solutions often have some surface activity, so that the deionized water, although useful in many applications, should not be employed for surface chemical studies without further treatment.

12.44 REMOVAL OF ORGANIC SPECIES

Ion-exchange resins tend to sorb some organic species and have some use for the removal of these materials. The removal of aldehydes may be carried out by converting anion exchangers to the bisulfite form. Solutions of aldehydes in ethanol may be purified by the formation of a bisulfite adduct of the aldehydes, leaving the ethanol unchanged. Weak acids may be removed by passage through weak-base anion exchangers in the hydroxide form. Use can be made of the sorption of organic (particularly benzenoid) species by the organic matrix of exchangers. Relatively large molecules are efficiently removed by macroreticular resins, which are used when the solvent is not sufficiently polar to swell ordinary exchange resins. The macroporous structure permits rapid mass transfer and facilitates sorption in continuous processes.

12.45 MICROSTANDARDS

Cation-exchange beads with rather homogeneous properties can be obtained in a wide range of particle sizes down to 0.001 mm in diameter. Since the size of individual beads can be measured with a calibrated microscope, one can make use of a single bead containing 10^{-12} equivalents of a cation such as sodium or calcium. Such beads, suspended in water and transferred by pipet, have been used as microstandards in mass regions where as yet there are no other reliable materials. For example, resin heterogeneity resulted in a 5% relative standard deviation in sodium-ion content at the 3-pg level (9).

12.5 Chromatography

12.51 SELECTIVITY AND ELUENT CONCENTRATION

Whenever a separation is to be attempted, a primary consideration is the relative selectivity of the separating tool for the solutes in question. In

chromatographic systems the solutes are usually present in low concentrations. In ion exchange the resin is initially in equilibrium with an eluent that is relatively concentrated, and the resin counterion is one of the ions present in the eluent. Consider the exchange of ion A^{Z_A} for the eluent ion $El^{\pm 1}$ and the subsequent separation of ion A^{Z_A} from B^{Z_B} (let $Z_A = Z_B$ for simplicity), that is,

$$|Z_A|(R^{\pm 1} + El^{\pm 1}) + A^{Z_A} \rightleftharpoons (|Z_A|R^{\pm 1} + A^{Z_A}) + |Z_A|El^{\pm 1}$$

Then

$$K_{El}{}^{0,A} = \frac{(a_{El}{}^{aq})^{|Z_A|}(a_A{}^r)}{(a_{El}{}^r)^{|Z_A|}(a_A{}^{aq})}; \qquad K_{El}{}^{0,B} = \frac{(a_{El}{}^{aq})^{|Z_B|}(a_B{}^r)}{(a_{El}{}^r)^{|Z_B|}(a_B{}^{aq})} \tag{12.21}$$

The thermodynamic separation factor α^0 (see Eq. 2.22) is identical to the selectivity coefficient, since

$$\alpha^0 = \frac{K_{El}{}^{0,A}}{K_{El}{}^{0,B}} = K_B{}^{0,A} = \frac{(a_A{}^r)(a_B{}^{aq})}{(a_A{}^{aq})(a_B{}^r)} \qquad (Z_A = Z_B)$$

In chromatographic systems the pertinent terms are concentration-based equilibrium constants. For example, the retention equation utilizes a classical equilibrium term K^A (Chapter 5):

$$V_R{}^A = V_M + V_S K^A \tag{5.6}$$

In the systems under question, this term may be related to the selectivity coefficient, $K_{El}{}^A$, since

$$K^A = \frac{[A^r]}{[A^M]} \tag{2.1b}$$

and

$$K^A = K_{El}{}^A \frac{[El^r]^{|Z_A|}}{[El^{aq}]^{|Z_A|}} \tag{12.22}$$

Under the conditions of chromatography, virtually all the sites on the resin have $El^{\pm 1}$ as counterions; thus $[El^r]^{|Z_A|}$ depends on the capacity of the resin and is essentially constant. Similarly, under these conditions, $K_{El}{}^A$ is invariant. Let the product of these two terms be $J_{El}{}^A$. Then

$$K^A = \frac{J_{El}{}^A}{[El^{aq}]^{|Z_A|}} \tag{12.23}$$

and

$$\alpha = \frac{K^A}{K^B} = \frac{J_{El}{}^A}{J_{El}{}^B} = K_B{}^A \qquad (Z_A = Z_B) \tag{12.24}$$

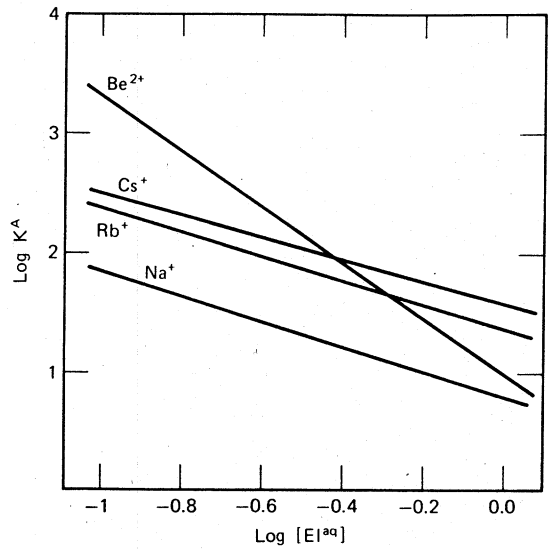


Figure 12.6. The effect of eluent concentration upon K^A. A hydrogen form cation exchanger with 12% divinylbenzene was utilized in conjunction with an HCl eluent. Reprinted from Ref. 10, by courtesy of the American Chemical Society.

An example of this approach is depicted in Fig. 12.6. Plots of log K^A against log $[El^{aq}]$ yield straight lines with slopes of $-|Z_A|$. For species of the same charge, the difference in log K^A is constant although $[El^{aq}]$ is varied. At low concentrations of eluent, the K values are large, leading to wide separation of peak centers. At higher concentrations of eluent, the retention volumes result in closer peak centers.

It is clear that for a column of given efficiency and dimensions an eluent concentration can be chosen that will provide the desired separation of solutes. An alternative approach is the utilization of stepwise changes in eluent concentration. An eluent concentration is chosen so that the first eluted peak has a desirable retention volume. Subsequent peaks, which would have excessively large retention volumes at this initial eluent concentration, are removed from the column by appropriate increases in eluent concentration. This technique has been modified by slowly increasing the eluent concentration during the course of a separation. The resulting procedure, called *gradient elution*, is formally equivalent to temperature programming in gas-liquid chromatography (see Chapter 5).

When the ions to be separated are of different charge, the situation is somewhat more complex but offers more options for separation. At low eluent concentrations K^A is usually higher for the higher-charged species (if all other factors are about the same; see Eq. 12.11). The slope of the log K^A

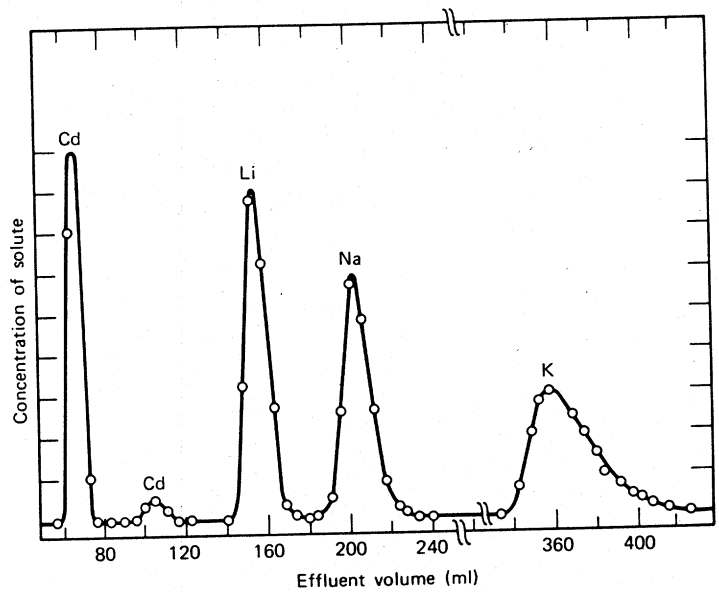


Figure 12.7. Separation of some cations with 0.7 *M* HCl as an eluent. About 5 hr was required for the separation. Reprinted from Ref. 11, by courtesy of Plenum Publishing Corporation.

versus log [El] line is steeper for the ion of greater charge. Somewhere in the graph a line for a species of high charge crosses the line for a species of lower charge. Thus, at low concentrations of eluent, the solute of lowest charge tends to be eluted first; at some intermediate concentration no separation is possible; and at a higher concentration the solute of greater charge may be eluted first. (Some anomalous effects, such as curvature of the lines at high eluent concentrations, have been encountered, but the aforementioned trends are usually observed.) During the course of stepwise or gradient elution, the solute of higher charge may move more slowly, then at the same rate, and finally faster through the column than a solute of lower charge. A classical separation of some cations is depicted in Fig. 12.7.

12.52 pH

The elution patterns of weak acids or their salts may be influenced markedly by changes in pH (see secondary chemical equilibria, Section 2.13). Weak bases or their salts are similarly affected, but strong acids, bases, and their salts are not influenced by pH. The dissociation of a weak acid may be described by

$$HA \rightleftharpoons H^+ + A^-; \qquad K_{eq} = \frac{[H^{aq}][A^{aq}]}{[HA^{aq}]} \tag{12.25}$$

The anion is free to exchange with eluent anions in the resin, as in the case

$$A^- + (R^+ + El^-) \rightleftharpoons (R^+ + A^-) + El^-; \qquad K_{El}{}^{A} = \frac{[A^r][El^{aq}]}{[A^{aq}][El^r]}$$

Then

$$K^A = D = \frac{[A^r]}{[HA^{aq}] + [A^{aq}]} = \frac{K_{El}{}^{A}[El^r]}{[El^{aq}]} \cdot \frac{K_{eq}}{K_{eq} + [H^{aq}]} \qquad (12.26)$$

In the formulation of Eq. 12.26, it was assumed that only the anion, and not the undissociated acid, penetrates the resin. Under the conditions of chromatography, the first two terms in the numerator are constant. When $K_{eq} \gg [H^{aq}]$, this equation reduces to the form of Eq. 12.23. Under these conditions, the acid is fully dissociated and the situation is equivalent to the exchange of salts of strong acids. When $[H^{aq}] \gg K_{eq}$—and in aqueous solution this indicates that $K_{eq} \ll 1$—the second part of Eq. 12.26 is very small. For all reasonable values of the first half of this equation, the resulting value of D nears zero under this condition. Equilibrium constants such as K_{eq} depend upon the acid HA, the temperature, and the solvent. Variation in [El] results in a small change in K_{eq}, which often can be neglected over the range in which [El] is varied in most chromatographic systems. In the intermediate range, where K_{eq} and $[H^{aq}]$ are of comparable magnitude, fixing pH results in the second half of Eq. 12.26 remaining essentially constant. Changes in [El] may be utilized to change D and hence the retention volumes. Similarly, pH may be varied to influence D. Many separations, such as that depicted in Fig. 5.2, utilize both pH and eluent concentration to control retention volumes.

Polyprotic acids (or bases) and their salts may be considered in similar terms. For the acid H_mA the dissociated species are commonly found in the resin phase, while these and the undissociated acid may be present in the external solution. Then

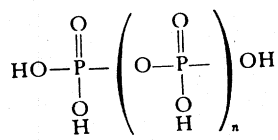
$$D = \frac{[H_{(m-1)}A^r] + [H_{(m-2)}A^r] + \cdots + [A^r]}{[H_mA^{aq}] + [H_{(m-1)}A^{aq}] + [H_{(m-2)}A^{aq}] + \cdots + [A^{aq}]} \qquad (12.27)$$

and

$$D = \frac{(K_{El}{}^{H(m-1)A}K_1[H^{aq}]^{m-1}/[El^{aq}]) + (K_{El}{}^{H(m-2)A}K_1K_2[H^{aq}]^{m-2}/[El^{aq}]^2) + (K_{El}{}^{A}K_1K_2\cdots K_m[El^{aq}]^m)}{[H^{aq}]^m + K_1[H^{aq}]^{m-1} + K_1K_2[H^{aq}]^{m-2} + \cdots + K_1K_2\cdots K_m} \qquad (12.28)$$

The terms K_1, K_2, and so on indicate the first, second, and higher dissociation constants. At virtually any pH only one or two species are present, resulting in three to five terms in equations analogous to Eq. 12.27. Consider the

homologous series of polyphosphoric acids, the salts of which are important in detergents and fertilizers. The acids have the following structure:



When $n = 2$, the species are referred to with the prefix *tripoly*. (The monomer is referred to using the prefix *ortho*, and the dimer is called *pyrophosphate*.) Another group of related compounds consists of cyclic species, with the ends joined through oxygen bridges. These are referred to with the modifier *meta*, for example, *trimetaphosphate ion*. The equilibrium constants are such that one proton is dissociated from each phosphate group at pH 5 in aqueous solution. Thus

$$D = \frac{J_{\mathrm{El}}{}^{\mathrm{H_2A}}}{[\mathrm{El}^{aq}]^{n+1}} \tag{12.29}$$

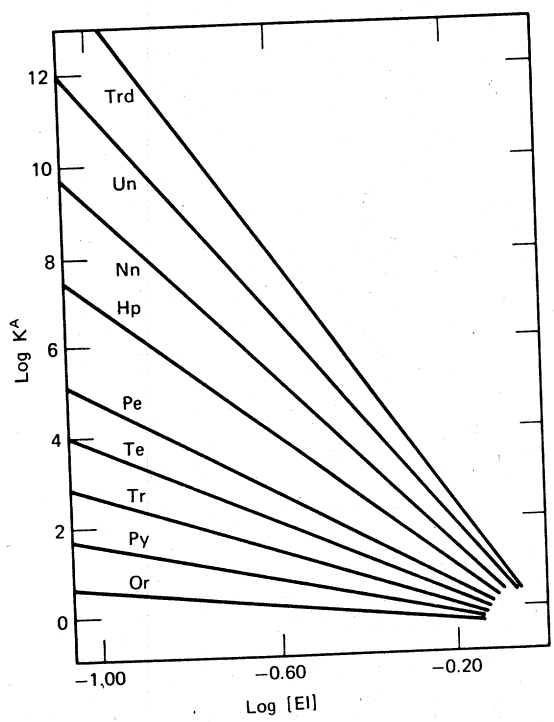


Figure 12.8. Variation of log K^A with log [El] for the linear phosphates. A KCl eluent at pH 5.0 was utilized in conjunction with an anion exchanger. Reprinted from Ref. 12, by courtesy of Pergamon Publishing Co.

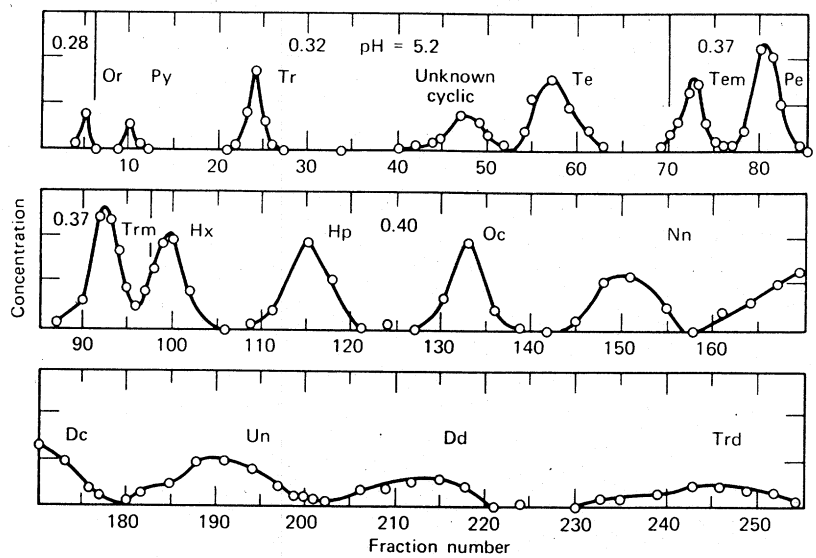


Figure 12.9. Separation of some linear and cyclic phosphates on an anion exchanger. The molarity of the KCl eluent is shown on the figure; pH was 5.0 except where noted, and fraction volumes were 26 ml. Reprinted from Ref. 12, by courtesy of Pergamon Publishing Co.

Plots of log D against log $[El^{aq}]$ result in straight lines with slopes of $-(n + 1)$ (Figure 12.8), and separations can be devised as described in Section 12.51. A separation of these phosphates is depicted in Fig. 12.9. Although other species will have different pH dependence, the trends are usually similar.

12.53 COMPLEXING

Complexing agents may be used to influence retention volumes and hence separation (see Section 2.13). The aqueous rare-earth ions are difficult to separate because of their similar charge-to-size ratios. This result of the lanthanide contraction leads to similar ion-exchange distribution coefficients. However, the formation constants of these ions with a variety of complexing agents are sufficiently different so that separations are practicable. The pertinent equilibria can be written as:

$$L^- + M^{+Z_M} \rightleftharpoons ML^{+(Z_M+1)}; \qquad K_f = \frac{[ML^{aq}]}{[L^{aq}][M^{aq}]} \tag{12.30}$$

$$D = \frac{[M^r] + [ML^r]}{[M^{aq}] + [ML^{aq}]} = \frac{[M^r]}{[M^{aq}]} \cdot \frac{1 + K_f[L^r]}{1 + K_f[L^{aq}]} = \frac{J_{El}{}^M}{[El^{aq}]^{Z_M}} \cdot \frac{1 + K_f[L^r]}{1 + K_f[L^{aq}]} \tag{12.31}$$

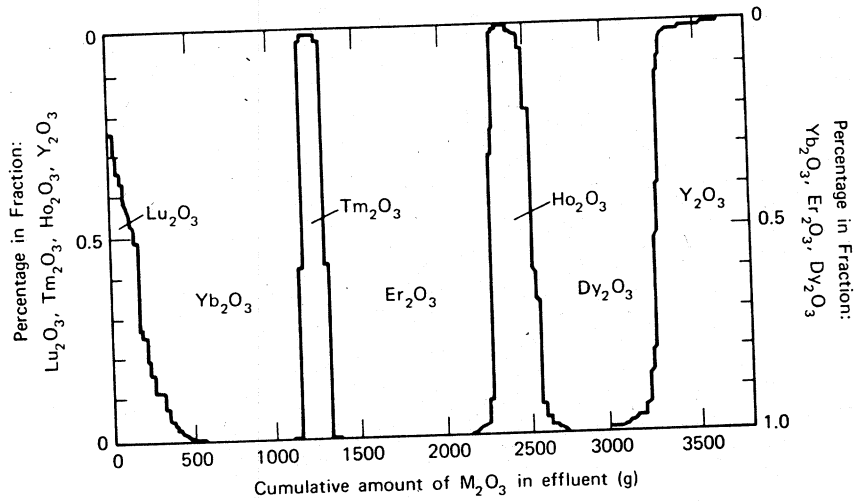


Fig. 12.10. Preparative separation of some rare-earth ions as their citrate complexes on a cation exchanger. Odd-numbered rare earths are plotted upward; even-numbered species, downwards. Concentration is expressed in terms of the oxides of the species recovered. Reprinted from Ref. 13, by courtesy of Academic Press, Inc.

The negatively charged ligand is excluded from cation exchangers by the fixed charges. Thus the numerator of the second part of Eq. 12.31 is smaller than the denominator. Complexing in this fashion leads to a reduction in D and retention volume. In a series such as the lanthanides, the species with the smallest unhydrated crystal radii have the highest K_f and are most affected by complexing agents. An example of the well-known preparative separation of these materials is shown in Fig. 12.10. Retention volumes may be influenced simultaneously by use of a noncomplexing eluent. Control of pH must also be provided, since the concentration of ligand ions is dependent on this parameter through the equilibrium

$$HL \rightleftharpoons H^+ + L^-; \qquad K = \frac{[H^{aq}][L^{aq}]}{[HL^{aq}]} \tag{12.32}$$

Strong ligands that are polyprotic or cations that can be complexed by a number of anionic species may result in complexes with negative charge. These are excluded from cation exchangers and have effective D values of zero. They may, however, be sorbed on anion exchangers.

Kraus and his coworkers have carried out extensive investigations of the effects of complexing agents on the elution behavior of ionic forms of the elements. They popularized the use of "periodic tables" such as Fig. 12.11. The symbol D_V is equal to the retention volume V_R divided by the bed volume

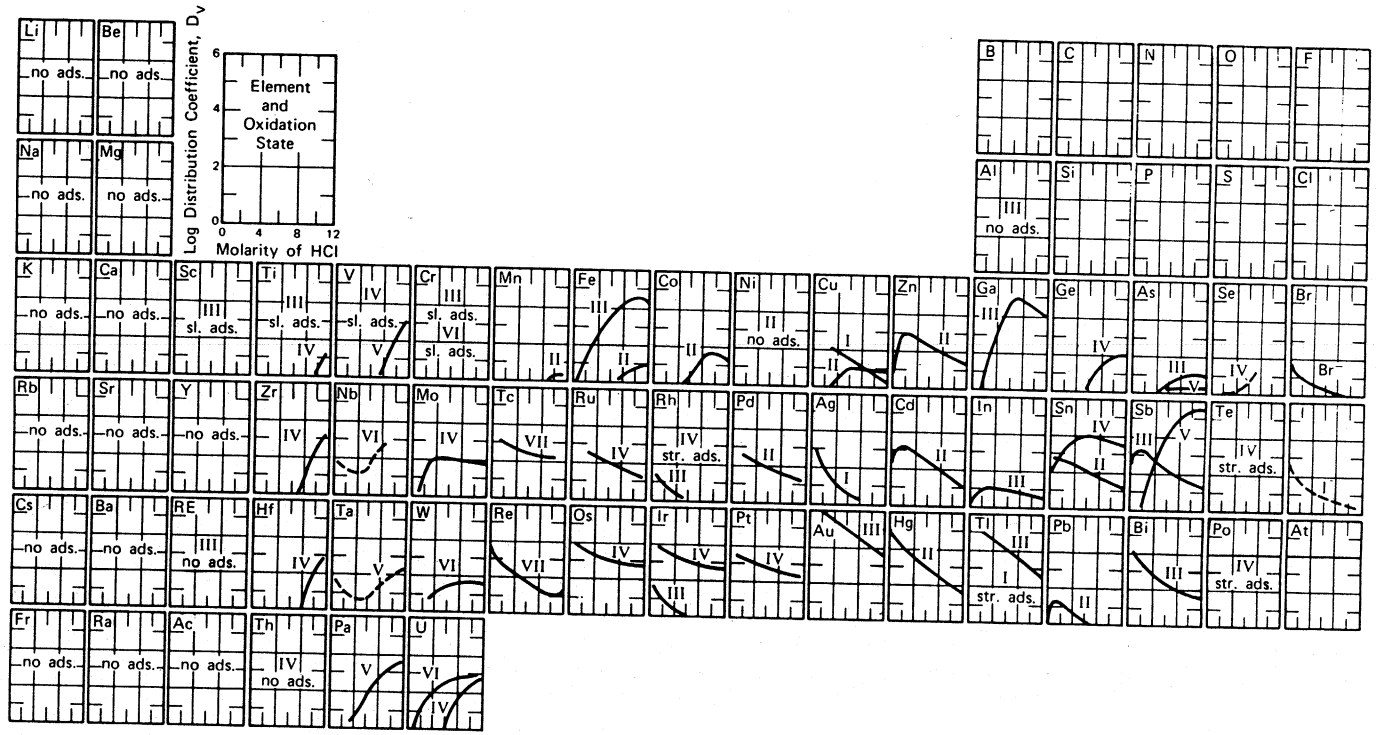


Figure 12.11. Distribution coefficients for the elements on an anion exchanger as a function of the HCl eluent concentration: no ads. = no adsorption, $0.1 < M$ HCl < 12; sl. ads. = slight adsorption in 12 M HCl ($0.3 \leq D \leq 1$); str. ads. = strong adsorption; $D_v \gg 1$. Reprinted from Ref. 14, by courtesy of United Nations Press.

($V_M + V_S$) and is proportional to D. Five types of behavior are noted: (1) no adsorption by the anion exchanger, (2) sorption increasing with complexing agent concentration, (3) sorption decreasing with complexing agent concentration, (4) systems displaying a maximum in D_V, and (5) systems displaying a relative minimum. The first case relates to species that do not form chloride complexes. Case 2 reflects systems with relatively low formation constants for production of the complex anion in which a considerable concentration of HCl is required before the exchangeable species is produced. In case 3, which is often a special form of case 4, the ion usually displays a large formation constant which results in anionic species at low chloride concentrations. Increasing chloride concentration tends to displace the solute from the resin, since the chloride ion is the eluent. Examination of distribution coefficient curves indicates a maximum at a low acid molarity. Other cases with more obvious maxima involve a low degree of complexing at low ligand concentration. Increasing this concentration leads to anions capable of ion exchange with the resin. At high concentration of ligand, the ligand acting as eluent removes the complex from the resin, as in the previous case. Sometimes species of higher negative charge are formed; at these high ligand concentrations, they tend to be removed from the resin with the factor $[El^{aq}]^{|Z_A|}$. This is analogous to the discussion in Section 12.51. In case 5, the systems display minima but this phenomenon is not well understood.

Electrically neutral species that are able to complex ions may be separated by the exchange process. A well-known example involves the separation of glycols, including some sugars, through the charged species that result from their borate adducts. An anion exchanger in the borate form and a buffered sodium borate eluent were utilized (15). "Ligand exchange" is the name given to the approach in which separations of ligands are produced by their interaction with central ions sorbed by a resin. The eluent contains another ligand that competes for central ions with the ligands to be separated. An example is the separation of amino acids on a cation exchanger in the zinc or cadmium form (16). The acids compete with ammonia in the eluent for sites on the cations. Removal of metal ions from the resin is compensated for by adding these species to the eluent. Another approach has involved the use of chelating resins that bind metal ions strongly, reducing the need for replacement ions in the eluent. Use of metal-ion orbitals in this binding reduces the number of available sites and hence the resin capacity, but this term is usually larger than the capacity of ion exchangers in ordinary separations.

12.54 NONEXCHANGE APPLICATIONS

Ion-exchange resins have been utilized as stationary phases for the separation of nonelectrolytes. Sometimes species may be resolved by elution with

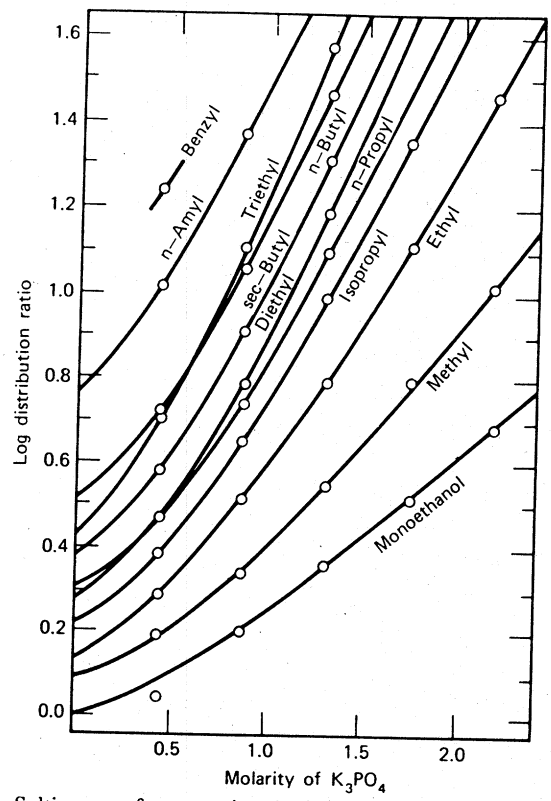


Figure 12.12. Salting out of some amines by K_3PO_4 onto a cation exchanger in the K^+ form. Reprinted from Ref. 17, by courtesy of Elsevier Publishing Co.

water, although greater selectivity can be achieved by the use of aqueous salt solutions. The solute interacts with the hydrocarbon matrix of the resin as well as with the ionic species and solvent molecules in both phases. In contrast to exchange separations, increases in eluent concentration result in increases in distribution coefficients (Fig. 12.12). This removal of solute from the aqueous phase by salt is reminiscent of "salting out" methods for the precipitation of nonelectrolytes or enhanced extraction by organic solvents of limited aqueous solubility. The mathematical form of the classical salting-out equation is similar to the following expression:

$$\log K^A = \log K_0{}^A + \kappa \tag{12.33}$$

which has been used to describe, phenomenologically, K^A in salting-out chromatography. Here K^A is the observed distribution ratio while $K_0{}^A$ is the distribution ratio with pure water, κ is a constant for a particular species and resin in a stated ionic form, and M is the molarity of salt. Some curvature noted in Fig. 12.12 is due to acid-base equilibria of the amine and potassium

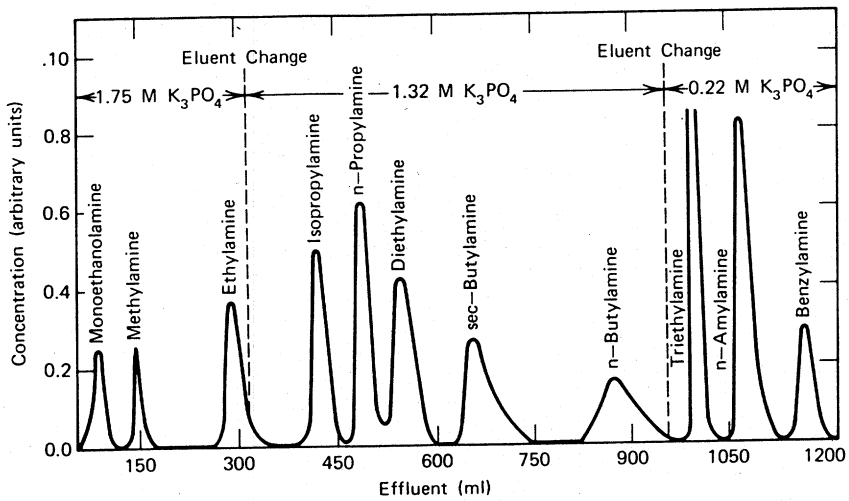


Figure 12.13. Separation of some amines by salting-out chromatography on a cation exchanger. Reprinted from Ref. 17, by courtesy of Elsevier Publishing Co.

phosphate eluent. When the concentration of salt in the eluent is high enough to fix pH, though M is varied, straight lines are observed. Other solutes less prone to acid-base equilibria show rather linear behavior. Separations involve the use of high initial concentrations of salt solutions as eluents, followed by gradient or stepwise reductions in concentration. A considerable number of compounds have been separated by this approach; one group is depicted in Fig. 12.13.

Solutes that show high affinity for the resin may be eluted by the use of organic solvents. Among the well-known examples of this approach are the separation of *n*-amyl through *n*-nonyl alcohol with aqueous acetic acid (18) and the separation of a variety of mono- and disaccharides with aqueous ethanol (19).

This and the ion-exchange approach are particularly useful for compounds of low volatility, when derivatization is troublesome and/or the solutes are thermally unstable but compatible with resin systems.

12.55 CROSS LINKING

The significance of cross linking in selectivity has been discussed and is widely recognized; its importance in chromatographic separations, however, has not always been considered. Producers of styrene-based ion exchangers use commercial divinylbenzene, which contains positional isomers of the cross-linking agent as well as ethyl styrene. The reported value for cross linking reflects the actual mole percentage of divinylbenzene isomers present

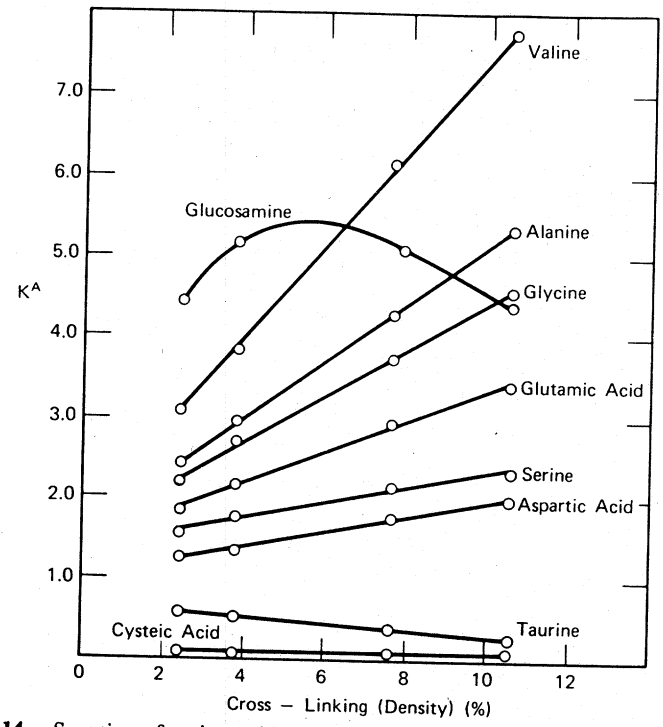


Figure 12.14. Sorption of amino acids by a cation exchanger, in the sodium form, as a function of cross linking as determined by density. Reprinted from Ref. 21, by courtesy of the American Chemical Society.

and is called the *nominal cross linking*. However, not all of the beads in a batch have the same nominal cross linking. Furthermore, incorporation of divinylbenzene into the growing bead occurs at a rate faster than that for styrene. Beads thus formed are rich in cross linking at their centers and have relatively low concentrations of cross links at their peripheries. Similarly, beads formed early in the polymerization are relatively highly cross linked.

Fortunately, resin density is roughly proportional to the percentage of cross linking, and this value may readily be determined. A convenient technique utilizes a series of solutions of sodium tungstate with specific gravities from 1.200 to 1.400. A small sample of resin placed in each solution results in some fraction of the beads being suspended at the top of the solution, in the solution, or deposited at the bottom of the container (20). Thus the degree of heterogeneity of a particular batch of resin may be determined, or if large quantities are utilized the technique may serve for the fractionation of the resin.

The importance of the cross-linking parameter is depicted in Fig. 12.14. Many commercial resins vary $\pm 0.5\%$ in the degree of cross linking. This

could be significant for the separation of the amino acid alanine from glucosamine if the cross linking were 9 rather than a desirable 8.5 or 9.5. Indeed a reversal in order of elution would occur over this range of cross linking. Variation in this parameter has been cited as an important factor in irreproducibility of separations when different batches of the same resin are used. When separations are to be repeated and are carried out in many different laboratories, it is essential that enough information be given to reproduce accurately the pertinent resin conditions.

12.56 HIGH PERFORMANCE CHROMATOGRAPHY

Important separations are often carried out repetitively; in such cases it is desirable to optimize conditions. A significant example is the separation of the amino acids. When Moore and Stein (22) published their cation-exchange procedure, utilizing buffered sodium citrate eluents, it was hailed as an outstanding achievement, although about 3 days was required for the separation. Hamilton (23) and his coworkers improved this procedure, adapted it for clinical use, and increased the sensitivity of the system. As a result, complete amino acid analyses have been carried out on as little as 0.1 ml of serum. They made a careful study of the effect of pH and eluent concentration on the distribution coefficients of the solutes, utilizing a resin with cross-linking homogeneity, chosen as described in Section 12.55. Hamilton et al. showed that peak dispersion σ, in volume units, is directly proportional to column cross-sectional area, while pressure drop across the column is inversely proportional to cross-sectional area, temperature, and bead radius, but is proportional to column length and flow rate of eluent. The last term is extremely important, since the time required for an elution is inversely proportional to the flow rate for a particular set of column and solute conditions.

Under elution chromatographic conditions the flux of species B within the resin bead was shown to be approximated by the expression

$$J_{B^r} \simeq \frac{15}{dp^2} D^r([B^r]^* - [B^r]) \tag{12.34}$$

where $[B^r]^*$ is the concentration of ion B at the resin surface, and $[B^r]$ is the mean concentration of this species within the exchanger. This is apparently true when σ of the eluted peak is greater than 0.1 dp^2/D^r (24). Particle size and diffusion coefficients within the resin phase are thus important in chromatographic work, as well as in the batch systems described in Section 12.35.

Resin beads have been fractionated carefully to achieve homogeneity of cross linking and particle size, and velocity studies have been carried out as

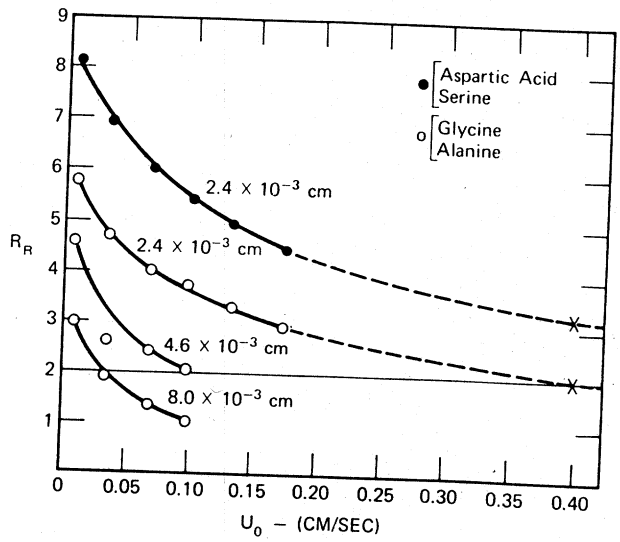


Figure 12.15. Resolution of amino acid pairs ($R_R = 4R_s$) as a function of flow rate. Average particle diameters are indicated for each curve. Reprinted from Ref. 25, by courtesy of the American Chemical Society.

depicted in Fig. 12.15. It is apparent that resolution at any velocity is greater for smaller beads. This is in agreement with conclusions drawn from Eq. 5.34; that is, the plate height contribution due to the stationary phase is directly proportional to the square of the particle diameter. An example of the separation of amino acids attained by Hamilton was given in Fig. 5.2.

Utilization of small particle diameters and high flow rates, resulting in short elution times, has led to large pressure drops across columns. These, in turn, have necessitated the development of pumps capable of maintaining constant flow rates at the high pressures required. An especially rapid separation, in which 7 to 14-μ beads of cation exchanger and a flow rate of 80 ml/hr were utilized, is shown in Fig. 12.16. The desired column conditions required a pressure of 4600 psi but resulted in a separation equivalent in time scale to those usually encountered in gas-liquid chromatography.

A related approach has involved the use of thin layers of ion exchangers coated over inert supports. The utility of this approach can be predicted from Eq. 5.28:

$$H_S = \frac{qk'\, d^2 v}{D_S(1 + k')^2} \tag{5.28}$$

It is apparent that the plate height contribution from the stationary phase is proportional to the square of the depth d of the layer. One approach to improving efficiency in this manner was shown by Horvath et al. (27), who

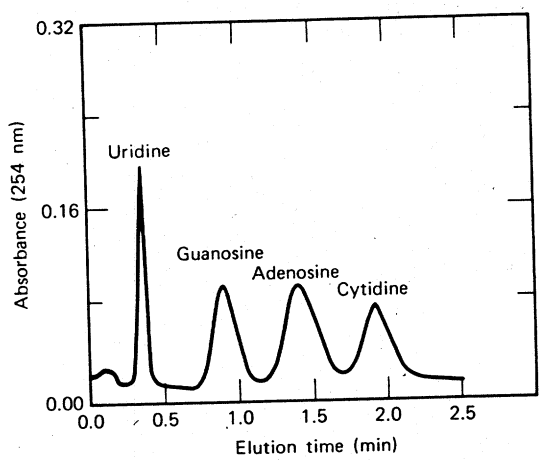


Figure 12.16. Separation of some nucleosides by cation-exchange chromatography. Reprinted from Ref. 26, by courtesy of Elsevier Publishing Co.

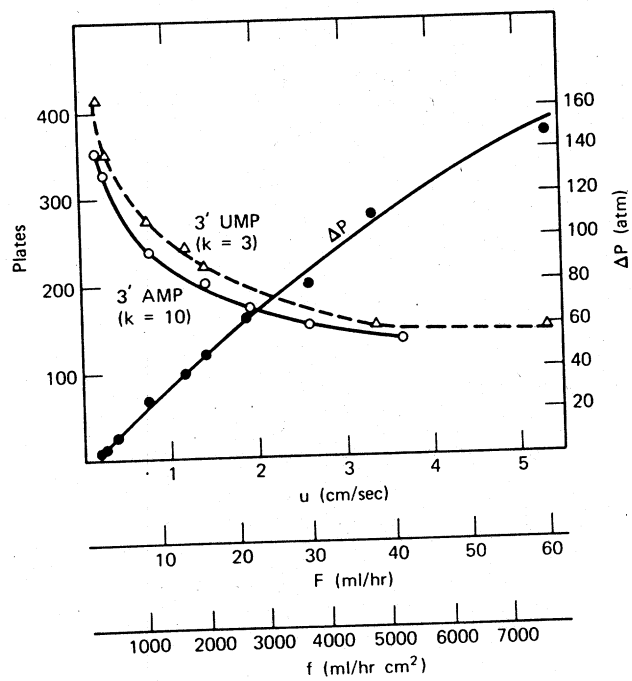


Figure 12.17. Change in number of plates and pressure drop as flow rate is changed for two nucleotides on a pellicular anion exchanger. 3′UMP = uridine-3′-phosphate, 3′AMP = adenosine-3′-phosphate. Reprinted from Ref. 27, by courtesy of the American Chemical Society.

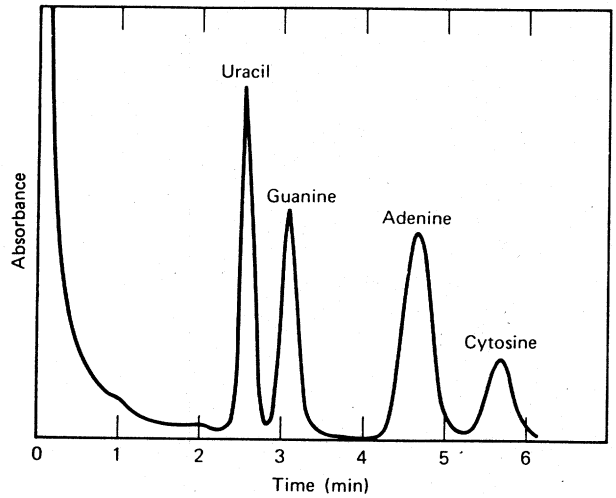


Figure 12.18. Separation of uracil, guanine, adenine, and cytosine on a pellicular cation exchanger. Reprinted from Ref. 28, by courtesy of the American Chemical Society.

coated glass beads with styrene and divinylbenzene and polymerized a thin layer around the glass core. Functionality was produced as described in Section 12.2. The "pellicular exchangers" thus obtained were utilized for the separation of a variety of charged solutes of biological interest. Figure 12.17 depicts the decrease in the number of plates as the flow rate and pressure drop across the column were increased. Figure 12.18 represents the separa-

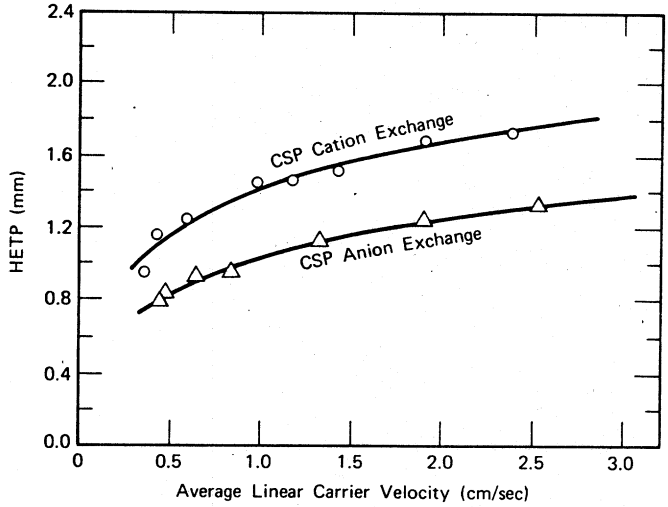


Figure 12.19. Change in HETP (H) as flow rate is varied for uridine-5′-monophosphate on a CSP cation exchanger and 2-aminobenzimidazole on a CSP anion exchanger. Reprinted from Ref. 29, by courtesy of the publishers of *J. Chromatog. Science*.

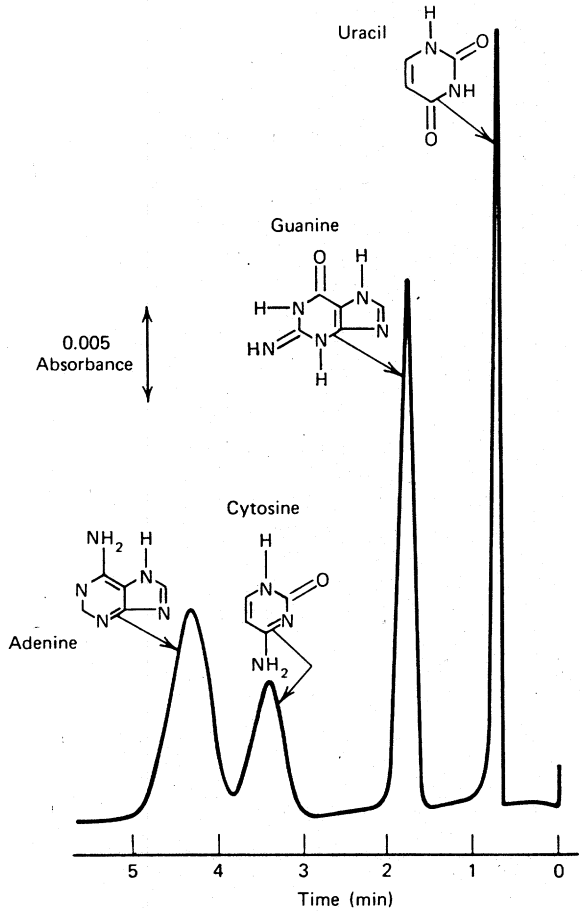


Figure 12.20. Separation of uracil, guanine, cytosine, and adenine on a CSP cation exchanger. Reprinted from Ref. 30, by courtesy of the publishers of the *J. Chromatog. Science.*

tion of some base components of RNA, achieved with a pellicular cation exchanger. Use of this sort of exchanger with relatively large particles allows rapid separations without extremely large pressure drops; however, pellicular exchangers have lower capacities than pure resin beads of similar radius, so that small amounts of sample are required.

Another approach based on similar theoretical reasoning was developed by Kirkland (29), who introduced the use of fluoropolymers with sulfonic acid or tetraalkylammonium chloride functional groups. These consist of a porous crust which surrounds a siliceous core. The materials, dubbed controlled surface porosity (CSP) exchangers, apparently have high performance

characteristics, as depicted in Fig. 12.19. They have been used for many separations, one of which is shown in Fig. 12.20.

Obstacles to high performance in liquid chromatographic systems, such as inadequate fluid-pumping devices and low-efficiency stationary phases, appear to have been overcome in principle. However, the requirement for continuous monitoring of effluents has been met only partially, although many advances have been made in recent years and refractive index and ultraviolet absorption monitors with high performance characteristics are now available. These monitoring devices are used widely but are thought to be of limited utility when compared with the thermal conductivity and flame ionization detectors used in gas chromatography. It is hoped that future developments in the area of monitoring devices will lead to high-performance instruments of broader utility than those now available.

12.57 ION EXCHANGE MEMBRANES

These materials have become extremely important in large-scale separations. The emphasis is on deionization and removal of small ions from solutions containing macroions. Little or no effort is made to utilize resin selectivity. The membranes are polymeric materials, often formed on nylon gauze, and contain fixed groups and mobile counterions. In the system shown in Fig. 12.21, cations can pass through cation exchangers, but anions are excluded by the fixed charges on the membrane. The converse applies to

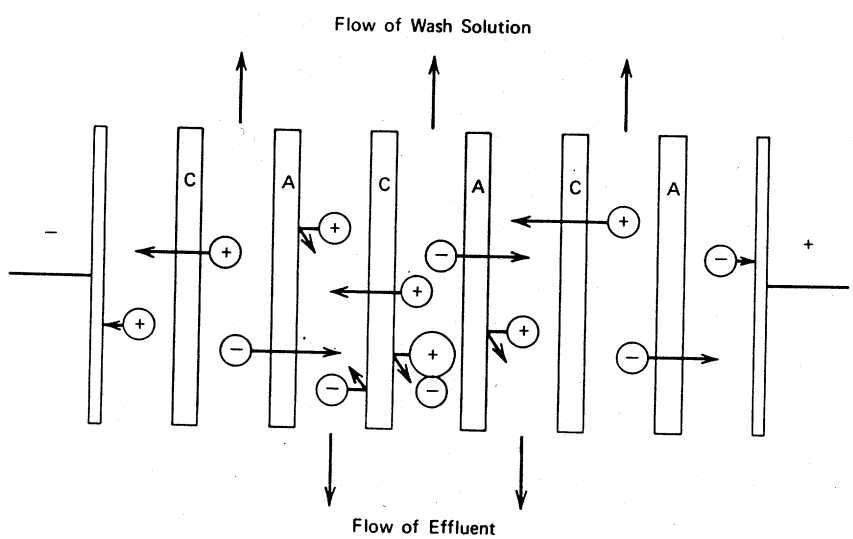


Figure 12.21. Membrane system for deionization of solvents with countercurrent flow.

anion-exchange membranes. In this manner, alternate compartments concentrate or deionize the solution. Countercurrent flow through the system provides for the collection of deionized liquid at one end and concentrated solution at the other. Large ions, as indicated in the central compartment, cannot penetrate the pores of the membrane; this effect is of use in the continuous demineralization of proteins. In another application, one ion may be exchanged for another in solution. Consider a system with two anion-exchange membranes and three solution compartments. Anions in the central compartment are transported toward the anode. These anions are replaced by a desired species from the cathode compartment. This exchange is made with no change in the equivalent concentration in the central compartment.

The use of ion-exchange membranes in various separation processes is discussed in Chapter 16 on membrane separations. Such applications appear to be so promising that predictions have been made that the use of ion-exchange membranes (in fuel cells, in desalinization of water, and in membrane electrodes) will eventually far exceed that of ion-exchange beads.

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List of Symbols

A	counterion
B	counterion initially present in the resin
D_v	retention volume divided be the bed volume
E_{Donnan}	Donnan potential
El	eluent ion
J	flux
J_{El}	constant in Eqs. 12.23 and 12.24
K_{eq}	dissociation constant
K_f	complexing constant
K_0	equilibrium constant with pure water in salting-out chromatography
L	ligand
m	number of dissociable species
M	metal
q	resin capacity
R	fixed functional group in the resin
$t_{1/2}$	half time for complete conversion
v	partial molar volume
Z	electrical change of the species
δ	film thickness
η	electrochemical potential
κ	constant in Eq. 12.33
π	osmotic pressure
ρ	internuclear distance
ϕ	electrical potential

Superscripts

aq	aqueous phase
r	resinous phase
$\circ$	thermodynamic quantity expressed with activities