are thus suitable for cation exchange in nonaqueous media. For any solvent to be employed, it is possible to tailor-make a resin with optimal cation-exchange properties as far as capacity and swelling are concerned, since it is evident that an increase in swelling in nonpolar solvents can be attained only at the cost of lowered capacity. The properties of these resins as cation exchangers will be the subject of a forthcoming paper.

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Oleophilic Ion-Exchange Polymers. III. Equilibria and Chromatographic Separation of Organic Bases by Sulfonic Acid Resins in Nonaqueous Media[1]

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Contribution from the Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York. *Received April 2, 1965*

The reactions between organic bases and an oleophilic sulfonic acid were investigated in polar and nonpolar media. The neutralization of the resin in the hydrogen form by the bases was regarded as an association–dissociation equilibrium whose constant is a measure of the strength of the base toward the resin sulfonate group. A measurable equilibrium of this type was found for diphenylamine. Assuming that base strengths toward the resin parallel their strengths in water, the selectivity coefficients, as a first approximation, may be set equal to the ratio of the respective base dissociation constants in water. The measured selectivities confirmed this qualitatively for bases of widely differing strengths. For bases of nearly equal strength, secondary binding between resin and base influenced the selectivity strongly. The effect on these equilibria of different solvents or temperatures was only minor. On the basis of selectivities, some chromatographic separations of organic bases were performed in nonpolar media. Aniline was separated from pyridine, nicotine from aniline, renoxidine from reserpine, rescinnamine, and deserpidine, and leurosine from vincaleukoblastine. In each case a chromatographic separation, at least comparable to those encountered with ordinary exchangers in water, was obtained.

Introduction

The principal deterrent to extending the techniques of ion-exchange chromatography to nonpolar solvents has been the insufficient swelling of conventional exchangers in these solvents with a resultant low capacity and extremely low rate of exchange. We have succeeded in preparing cation exchangers whose structure was modified to increase their swelling in nonaqueous solvents.[2] This paper describes ion-exchange equilibria of lauroylated and sulfonated polystyrene with different organic bases in nonaqueous media. These exchangers were prepared from polystyrene beads cross linked with 1% divinylbenzene. Lauroyl groups were attached to the styrene residues by a Friedel–Crafts reaction with lauroyl chloride. Acylation was followed by partial or total sulfonation with sulfur trioxide. Details of the preparation are reported elsewhere.[2] Fully lauroylated and partially (25–50%) sulfonated resins showed considerable swelling in all solvents tested, including saturated hydrocarbons.[2,3] Their capacities ranged from 0.8 to 1.6 mequiv./dry g.

We can represent the neutralization of a sulfonic acid resin by a base in a nonpolar medium as an association–dissociation process of the following type

$$RSO_3H + B = ROS_3^- {}^+HB \qquad (1)$$

where R signifies resin and B an organic base. The resin sulfonate group or the base are not assumed to be ionized in this medium. Equation 1 bears an analogy to the dissociation equilibrium of bases in water.

$$H_2O + B \rightleftharpoons OH^- + HB^+$$

The constant of this latter equilibrium is taken as a measure of the strength of the base in water. Similarly, the equilibrium constant K of eq. 1 is a measure of the strength of the base towards the resin sulfonate group. Since this group is a much stronger acid than water, we can expect the position of equilibrium to be far to the right for bases which show only partial dissociation in water. In order to evaluate K we substitute concentrations for activities

$$K = \frac{[RSO_3^- {}^+HB]}{[RSO_3H][B]} = \frac{\bar{X}}{(1 - \bar{X})[B]}$$

where $\bar{X} = [RSO_3^- {}^+HB]/([RSO_3^- {}^+HB] + [RSO_3H])$ is the fraction of exchange sites occupied by the base. The concentration of free base in the resin phase [B] is taken, as a first approximation, to be equal to the concentration (c) of base in the solution outside of the resin. Thus $K = \bar{X}/(1 - \bar{X})c$.

If we expose two bases B_1 and B_2 to the resin, the following simultaneous equilibria will result.

$$RSO_3H + B_1 = RSO_3^- {}^+HB_1 \quad K_1$$
$$RSO_3H + B_2 = RSO_3^- {}^+HB_2 \quad K_2$$

(1) Taken from the dissertation submitted to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1964.

(2) H. P. Gregor, *et al.*, *J. Am. Chem. Soc.*, 87, 5525 (1965).

(3) A. G. Tsuk and H. P. Gregor, *ibid.*, 87, 5534 (1965).

If, as before, we designate

$$\bar{X}_1 = [RSO_3^- {}^+HB_1]/([RSO_3^- {}^+HB_1] + [RSO_3^- {}^+HB_2] + [RSO_3H])$$

and take $[B_1] = c_1$ and $[B_2] = c_2$, we get $K_1 = \bar{X}_1/(1 - \bar{X}_1 - \bar{X}_2)c_1$ and $K_2 = \bar{X}_2/(1 - \bar{X}_1 - \bar{X}_2)c_2$. The quantity $(1 - \bar{X}_1 - \bar{X}_2)$ is usually too small to determine readily. Thus, only the ratio of the two equilibrium constants can be obtained experimentally.

$$\frac{K_1}{K_2} = \frac{\bar{X}_1 c_2}{\bar{X}_2 c_1}$$

This expression is identical with that of the rational selectivity coefficient K_2[1]. If we further assume that the strength of the bases in water parallels their strengths towards the resin sulfonate group, the selectivity coefficient of two bases on the resin can be predicted from the ratio of their dissociation constants in water.

Experimental Section

Materials. All resins were prepared from polystyrene beads cross linked with 1% divinylbenzene by lauroylation and sulfonation. The three resins used in this work have the following symbols and characteristics[2]: LS1′-1 (42, 78, 3.17), LS1′-7 (98, 84, 2.57), and LS1′-2 (88, 24, 0.83), where the numbers in parentheses represent, respectively, the per cent lauroylation based on styrene, the per cent sulfonation based on styrene, and the capacity in milliequivalents per dry gram.

These resins generally show markedly improved swelling in nonaqueous solvents as compared to conventional sulfonated polystyrene resins. The difference is quite pronounced between LS1′-2 resin and conventional exchangers in nonpolar solvents. This results in a much more rapid rate of base uptake for the LS1′-2 resin. In one experiment, 62 mg. of this resin, 94 mg. of a Dowex 50-WX8 resin, and 5.5 mg. of Amberlyst-15 resin were each exposed to 83 mg. of reserpine dissolved in a 1:1 mixture of 1,2-dichloroethane and cyclohexane. After 2 hr. of shaking, the uptake of alkaloid per gram of resin was as follows: LS1′-2, 0.817 mequiv., 105% of capacity; Dowex 50, 0.235 mequiv., 4.5% of capacity; Amberlyst-15, 0.234 mequiv., about 5% of capacity.

The bases and solvents used in this work were of analytical grade. Alkaloids in purified or semipurified state were obtained through courtesy of Eli Lilly Co. and the Ciba Corp.

Methods. A known weight of the resin was equilibrated with the solvent; then a solution of the base or bases in the same solvent was added. The base in solution was assayed periodically and the base on the resin was determined by difference. Sufficient time was allowed for the establishment of equilibria. Occasionally, a test of the true equilibrium state was performed by letting the same state be established starting from two opposing original conditions.

Diethylamine, ethylenediamine, *n*-butylamine, and benzylamine in water or water-miscible solvents were determined by titration with standardized hydrochloric acid solution. In water-immiscible solvents, the titration was performed with standard trichloroacetic acid in cyclohexane against bromophenol blue or bromcresol purple indicator. Pyridine, aniline, nicotine, diphenylamine, sometimes benzylamine, and the alkaloids were determined by spectrophotometry in the ultraviolet. Measurement of ultraviolet absorbancies at different wave lengths was used for the simultaneous determination of bases in pyridine–aniline and aniline–nicotine mixtures. Infrared spectra were used to identify the alkaloids leurosine and vincaleukoblastine.

Results

When a resin in the hydrogen form was exposed to a solution of a base, the latter was removed. The speed of this process depended primarily on whether the resin swelled appreciably in the solvent, but base concentration, stirring, and temperature were also of influence. When the systems reached equilibrium, the uptake of all bases (with the exception of diphenylamine) was equal to or slightly higher than the capacity of the resin, irrespective of differences in solvent, swelling, or other conditions. The bases tested included diethylamine, pyridine, aniline, *n*-butylamine, and benzylamine and the solvents included water, methanol, acetone, cyclohexane, and toluene.

The uptake of diphenylamine, an extremely weak base ($pK_a = 0.9$), was only partial. Figure 1 shows the course of neutralization of LS1′-1 resin by diphenylamine in cyclohexane. Out of a total of 7.50 mequiv. of base in solution, only 3.13 mequiv. was bound by the resin, which represented 58% of the available capacity. When diethylamine was added to the system, it was quickly removed from solution, and diphenylamine was released until the amount still on the resin amounted to 50% of the reduced available capacity. A further addition of diethylamine resulted in a further release of diphenylamine until an occupancy of 52% of available sites was once again established. In similar experiments in methanol and acetone, diphenylamine tended to occupy 35–40% of the cation-exchange sites available to it. Thus, diphenylamine furnishes an example for the association–dissociation equilibrium as pictured in eq. 1.

Base uptake over capacity was due to nonion-exchange sorption. This sorptive uptake was concentration dependent, and in dilute solutions was found to be directly proportional to the solution concentration. Since this sorptive uptake is due to interactions between the base and the resin matrix, bases show individual variations. Among the bases of smaller molecular weight, aniline showed the strongest tendency for nonion-exchange sorption. The slope of the capacity (in mequiv. $g.^{-1}$) *vs.* the base concentration in water (in mequiv. $l.^{-1}$) was 0.0145 (the same within experimental error) for aniline in water on both resins LS1′-1 and LS1′-7, while pyridine on the latter resin had a slope of 0.0050. In further work involving equilibria, care was taken to have rather dilute final solutions in equilibrium with the resin to minimize the contribution of nonionic sorption.

It was generally observed, for bases of low molecular weight, that whenever the pK_a values of the bases in water differed by 2–3 units or more, the stronger base replaced the weaker one on the resin essentially quantitatively, and regardless of the nature of the solvent. Thus, diethylamine replaced pyridine, aniline, and di-

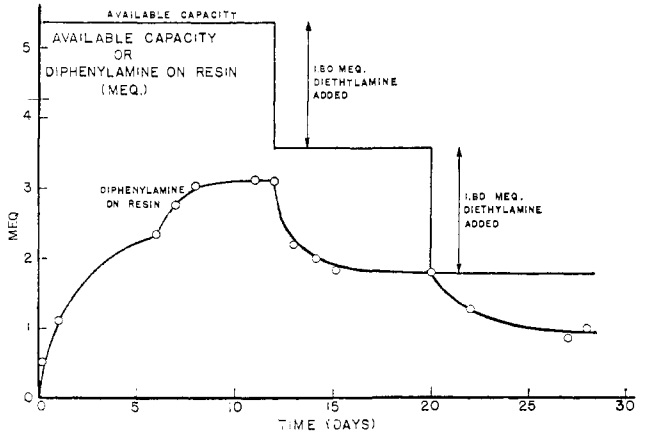

Figure 1. Neutralization of sulfonic acid resin LS1′-1 by diphenylamine in cyclohexane and its subsequent displacement by added diethylamine.

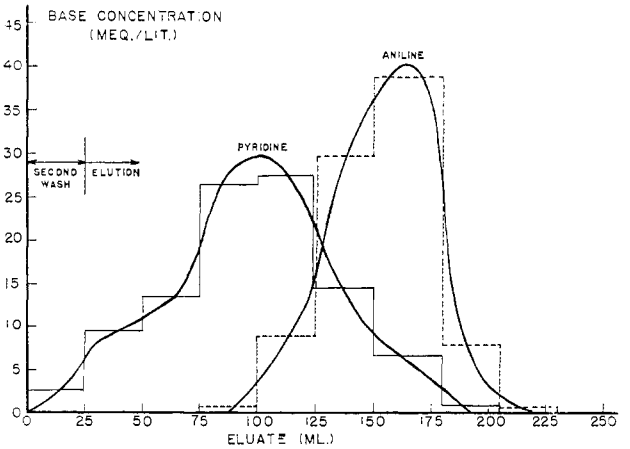

Figure 3. Chromatographic separation of pyridine from aniline on resin LS1′-2 by elution with 0.04 *N* *n*-butylamine in *n*-heptane.

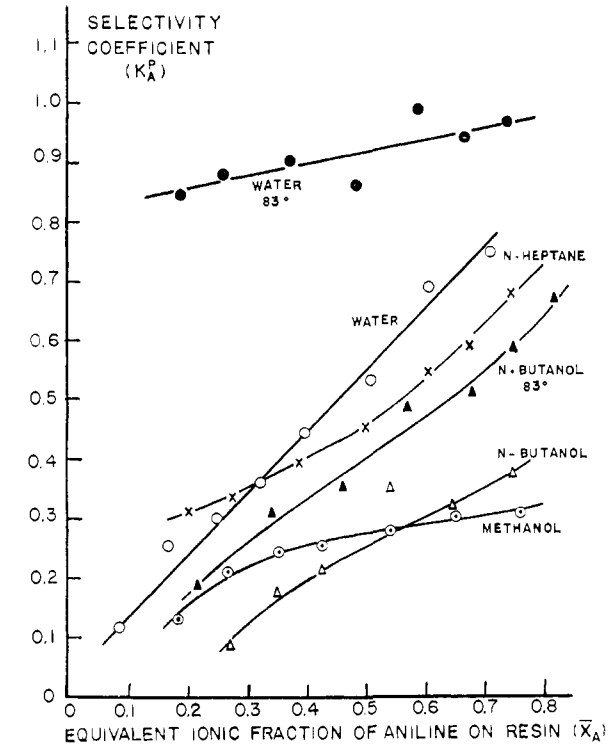

Figure 2. Phase equilibria of pyridine and aniline on resin LS1′-7 in different solvents and at 25°, unless noted otherwise.

phenylamine. Diphenylamine was replaced even by pyridine and aniline. Aniline was replaced by benzylamine, which in turn was replaced, though not completely, by *n*-butylamine.

Divalent bases provide an interesting case. Nicotine, whose pyridine nitrogen is intrinsically much weaker a base than its tertiary amine nitrogen, behaved as monobasic in exchange operations. Apparently only this latter nitrogen was operative in displacement reactions. Ethylenediamine, on the other hand, acted both as mono- and dibasic. At equilibrium, with a final solution concentration of about 0.02 *M*, the resin held 1.65 equiv./resin equiv. This represents a distribution between base in solution, base on resin singly bound, and base on resin doubly bound of 2.3, 3.8, and 2.1 mmoles, respectively. The two amine groups in ethylenediamine thus show about equal participation. Similar divalent behavior was exhibited by the dimeric indole alkaloids leurosine and vincaleukoblastine.

Pyridine–aniline equilibria were thoroughly investigated, partly because their pK_a values were close together, partly because of their solubility in most solvents, and their ease of analysis. Figure 2 shows the selectivity coefficient $K_a^P = \bar{X}_p c_a / \bar{X}_a c_p$ as a function of the equivalent ionic fraction $\bar{X}_a = \bar{n}_a/(\bar{n}_a + \bar{n}_p)$, solvent, and temperature, where subscript a refers to aniline and p to pyridine; c represents solution concentration, n represents numbers of moles, and the bar denotes quantities on the resin. The curves on the figure show only minor differences for solvents as different as water and *n*-heptane. There is no obvious connection between K_a^P and cohesive energy density or dielectric constant of the solvent. A change in temperature alters the curve, but the change is different for water and 1-butanol. The curves on Figure 2 have two features in common: they have a positive slope and K_a^P is always less than unity. The positive slope in this case means that the preference of the resin for a base gets weaker as more of the base is bound on the resin. The value of the selectivity coefficient is a reversal of the expected behavior; the resin prefers aniline even though pyridine is the stronger base. This points to strong secondary binding between aniline and the resin, which is also manifested by the pronounced nonionic sorptive tendencies of this base.

Chromatographic Separations. Information obtained during the earlier part of this investigation was put to use in an attempt to separate bases in anhydrous nonpolar solvents by cation-exchange chromatography. With the use of LS1′-2 resin, whose swelling spectrum is broad, the choice of solvent is arbitrary, but *n*-heptane was selected since it was considered to be among the most challenging, being of a low order of swelling power.

For the separation of pyridine from aniline, 5.0 g. of LS1′-2 resin in the H^+ form was equilibrated with *n*-heptane and poured into a 0.8-cm. diameter chromatographic column. The column was charged with a mixture of pyridine (2.56 mmoles) and aniline (2.63 mmoles) in 25 ml. of *n*-heptane. The progress of neutralization of the resin was visible because of the color

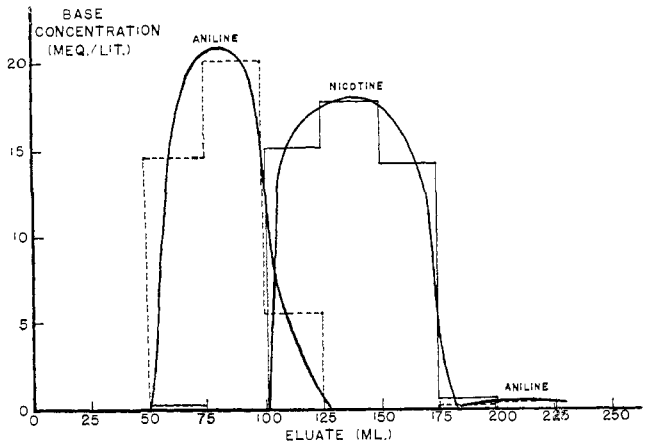

Figure 4. Chromatographic separation of aniline from nicotine on resin LS1'-2 by elution with 0.02 *N* *n*-butylamine in *n*-heptane.

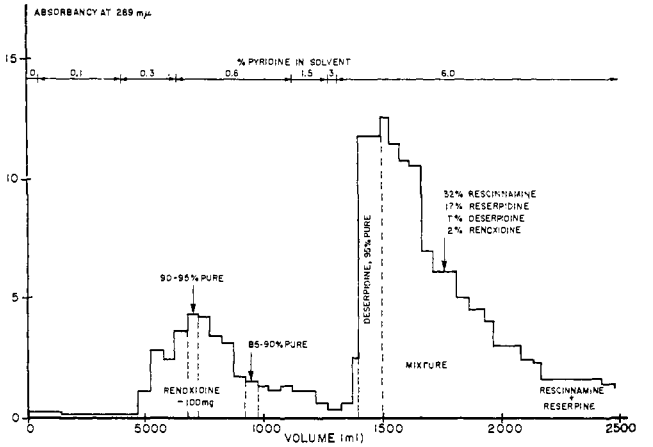

Figure 5. Chromatographic separation of about 100 mg. each of reserpine, deserpidine, rescinnamine, and renoxidine on a 1-g. column of resin LS1'-2 (originally in hydrogen form) by elution with pyridine in 1:1 dichloroethane–methanol.

change from the brown H^+ form to the yellow amine form. As a consequence of the high concentration of the charge, nonionic sorption was considerable, and the bases were first held by the upper half of the resin bed. Upon washing with pure solvent the bases slowly spread over the entire bed, and finally, since the bases were in excess of bed capacity, a breakthrough occurred. This breakthrough (second wash, Figure 3) was pure pyridine. The resin was stripped by passing a 0.04 *N* solution of *n*-butylamine in *n*-heptane through it. Figure 3 shows the analysis of the fractions. Over 95% of the bases was recovered in the fractions. The differences in nonionic sorptive tendencies between the bases aided the separation here, since aniline was retained and thus delayed. As a consequence, the separation is quite good even though the resin was overloaded (to 133% of capacity) and was of large particle size (24–40 mesh).

In the separation of aniline from nicotine, even though the difference in base strength is pronounced, the stronger nonionic sorption of aniline hindered the separation. The resin had to be ground to −70 mesh, and overloading had to be avoided to obtain a satisfactory separation (Figure 4).

Attempts were also made to separate some indole alkaloids. The solvent in these separations was 1,2-dichloroethane, to which an equal volume of methanol was added. The role of the methanol was solely to reduce the density of the solvent to below that of the resin. Figure 5 shows the separation of a mixture of four alkaloids of the reserpine class. Elution was performed with pyridine, a base weaker than the alkaloids; therefore, relatively higher concentrations were needed. Pyridine was removed from the fractions by evaporation to dryness and the alkaloids were identified by their ultraviolet spectra. Four fractions were analyzed also by thin layer chromatography, through courtesy of CIBA Corp. These fractions are marked on Figure 5, along with their approximate alkaloid distributions, as obtained from this assay. With the exception of renoxidine, the structures of the alkaloids in the vicinity of the basic nitrogen are identical, and differences in pK_a values are probably exceedingly small. Renoxidine, which is an N-oxide, can be expected to have a lower pK_a value. The separation proceeded according to these expectations. Renoxidine was eluted at lower

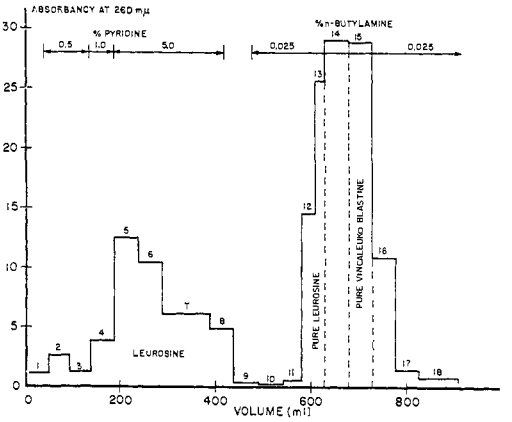

Figure 6. Chromatographic separation of 422 mg. of an approximately equimolar mixture of leurosine and vincaleukoblastine on a 1-g. column of resin LS1'-2 (originally in hydrogen form) by elution with pyridine followed with *n*-butylamine in 1:1 dichloroethane–methanol.

pyridine concentrations, and it was clearly separated from the others. The other alkaloids required more pyridine, and they came off close to each other. One pure fraction of deserpidine was obtained, followed closely by a mixture of rescinnamine and reserpine.

The separation of two vinca alkaloids was more clean-cut. We obtained an approximately equimolar mixture of leurosine and vincaleukoblastine through courtesy of Eli Lilly and Co. About 0.525 mmole of this mixture was dissolved in a 1:1 dichloroethane–methanol mixture, and the solution was charged onto a column containing the resin used previously for the separation of reserpine alkaloids. (The resin was reconverted into the H^+ form with a solution of concentrated HCl in methanol.) The appearance of colored bands on the resin indicated separation. The course of the elution of these alkaloids is shown in Figure 6. Only a limited quantity of alkaloid could be eluted from the resin by pyridine. Fraction 6 was analyzed by infrared spectroscopy and was identified as leurosine by the complete absence of the characteristic vincaleukoblastine peak at 10 mμ. The total quantity of leurosine eluted by pyridine amounted to only 0.155 m-

mole. Consequently, about 0.37 mmole of the alkaloids, some of it leurosine, was still on the resin. Since the resin capacity was about 0.78 mequiv., it was concluded that these dimeric vinca alkaloids occupy two resin sites per mole. It is also apparent that pyridine is not capable of replacing these alkaloids on the resin, and that the leurosine appearing in fractions 1 through 8 is merely a breakthrough. Since the pK_a values of these alkaloids were reported[4] as 5.4–5.5 for the first ionization, we have to conclude that the selectivity of the resin toward these alkaloids is larger than expected from base strength. The increased selectivity may be a consequence of the divalent nature of the molecule. When elution was continued with a dilute solution of *n*-butylamine, the balance of the alkaloids was liberated. The individual fractions were assayed by thin layer chromatography, through courtesy of Eli Lilly and Co. Fractions 12 and 13 were pure leurosine, fraction 15 was pure vincaleukoblastine (confirmed also by infrared spectroscopy), and fraction 14 was an about equal mixture of the two. Fraction 16 contained vincaleukoblastine with about 15% impurities and fraction 17 contained only a combination of minor impurities. Since these alkaloids are extremely similar in many of their physical and chemical characteristics, notably in their pK_a values, this sharp separation is quite unexpected. A possible reason for this strong difference in selectivity may be a difference in the relative steric position of the two valence sites in the two alkaloids.

Conclusions

The results in this paper have shown that once an ion exchanger is modified to permit its swelling in nonpolar solvents, its behavior in polar and nonpolar solvents becomes rather similar. The exchanging species need not be ionic in solution, just capable of forming a salt with the ionic group of the resin. If the exchanger possesses a swollen, open structure, the solvent effects on exchange rates and selectivities become minor.

The postulated mechanism of nonaqueous ion exchange, namely that of an association–dissociation equilibrium whose constant is dependent on the base strength of the exchanging species, is supported by the results with diphenylamine. The prediction of selectivity coefficients from the ratio of base dissociation constants in water involves further assumptions and can be expected to have only limited validity. These predictions were right, qualitatively, with bases of widely varying strengths, and also for the reserpine alkaloids. The vinca alkaloids showed pronounced selectivity with no difference in base strength, pointing out the importance of some secondary contribution, perhaps owing to their divalent nature. In the case of pyridine and aniline the strong secondary binding of aniline rendered the prediction wrong, even qualitatively. Based on base dissociation constants in water, a K_a^p value of about 4.5 was expected, but one in the neighborhood of 0.5 was obtained. Also, the derivation based on base strengths alone fails to explain the variation of the selectivity coefficient with the equivalent ionic fraction, which in the case of pyridine and aniline was considerable.

Results in this paper showed that our oleophilic resins were capable of rapid removal of basic substances from organic solvents, and that they were also suitable for the separation of certain bases in organic solvents by column chromatography. The strength of the eluting agent could be varied by using eluting bases of different pK_a values at different concentrations.

Acknowledgment. This work was supported by a grant from the National Institutes of Health. We wish to express our gratitude to Dr. Paul R. Ulshafer of CIBA Pharmaceutical Co. and to Dr. Albert J. Barnes of Eli Lilly and Co. for their help in obtaining and analyzing the alkaloid samples.

(4) G. H. Svoboda, T. S. Johnson, M. Gorman, and N. Neuss, *J. Pharm. Sci.*, **51**, 707 (1962).

The Chemistry of the Radical Anion of Tetraphenylethylene

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Contribution from the Chemistry Department, The New York State College of Forestry at Syracuse University, Syracuse, New York. *Received August 3, 1965*

The reaction of the disodium salt of tetraphenylethylene, $T^{2-},2Na^+$, with its parent hydrocarbon, T, has been investigated spectrophotometrically and conductometrically in tetrahydrofuran in the temperature range +20 to −70°. The conductance studies showed that at 20° the dissociation constant $K_{D,2}$ ($T^{2-},2Na^+ \rightleftarrows T^{2-},Na^+ + Na^+$) is about $^1/_{100}$ times that of the corresponding dissociation constant $K_{D,1}$ of the related radical ion, T^{-},Na^+. The exothermicity of dissociation $-\Delta H_{D,2}$ decreases from 7.2 at 20° to 0.9 kcal./mole at −70°, whereas $-\Delta H_{D,1}$ is substantially lower and changes in this range only slightly, viz. from 1.3 to 0.7 kcal./mole. This, as well as other evidence, indicates that $T^{2-},2Na^+$ forms a contact ion pair, whereas T^{-},Na^+ forms a solvent separated pair. The equilibrium constants K_1 ($2T^{-},Na^+ \rightleftarrows T^{2-},2Na^+ + T$) and K_2 ($T^{-},Na^+ + T^{-} \rightleftarrows T^{2-},Na^+ + T$) were determined over a wide temperature range, providing data for the respective ΔH_1, ΔH_2 and ΔS_1, ΔS_2. The results are interpreted in terms of the different stereochemical structures of $T^{2-},2Na^+$ and T^{-},Na^+.

The addition of alkali metals to tetraphenylethylene, T, was first studied by Schlenk[1] in 1914. The product was identified as a dianion

$$Ph_2\check{C}\text{–}\check{C}Ph_2,2Na^+ = T^{2-},2Na^+$$

(1) W. Schlenk, J. Appenrodt, A. Michael, and A. Thal, *Ber.*, **47**, 473 (1914).