at levels five times the concentration of maximum activity, 0.01%. Sodium lauryl sulfate required a concentration of 0.2% to yield dialysis rate roughly equivalent to those with 0.01% DDS. Higher concentrations of sodium lauryl sulfate were not tested, since the 0.2% caused irritation in the abdomen evidenced by squirming and discomfort of the animal when the solution was introduced. It did not show any evidence of permanent damage, however. The rates obtained with sodium lauryl sulfate varied more than with any other agents used.

From these experiments it was concluded that DSS was the most promising of the wetting agents, accelerating the dialysis rate for urea to about four times that of the controls. This would constitute a significant improvement in the dialysis process.

Since DSS appeared to be the most promising agent it was also tested for its effects on the dialysis of creatinine. As seen in Table I, it also accelerates the removal of the compound, rates being about three times the controls.

The experiments with sodium desoxycholate were quite surprising. Death resulted with concentrations as low as 0.01%, and when lower concentrations were tested the effect on dialysis rate decreased as toxicity appeared to decrease. At nontoxic levels no acceleration of dialysis was observed.

The results of this work indicate that DSS may be a useful accelerator of peritoneal dialysis and is deserving of further work. The compound accelerates the dialysis of urea and creatinine, but whether it also accelerates the removal of the multitude of other substances, some known, some unknown, which accumulate in uremia must be determined by experiments which assess the effect of general uremic symptoms and long-term treatment of the diseased condition. Before DSS can be evaluated in man, of course, a measure of its absorption and accumulation in the body must be made and correlated with possible toxic effects which might result. It seems possible that once a given level of DSS is established in the system that the concentration in the dialysis fluid might be reduced without loss of effect. These are problems which must be faced in further work leading toward clinical trials.

This work also suggests the possibility of using DSS or other wetting agents in the removal of drugs such as salicylates and barbiturates which are commonly encountered in poisonings. This study is being conducted in this laboratory.

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Keyphrases

Peritoneal dialysis
Surfactants in dialysis solutions
Dialysis acceleration—surfactants
^{14}C-labeled urea—test compound
^{14}C-labeled creatinine—test compound
Liquid scintillation counting—analysis

Studies with Ion-Exchange Resins on Cinchona Alkaloids II

Effects of the Ionic Form and of the Solvent Medium

By C. V. BHAT, B. R. KAMATH, R. S. SHAH, S. S. KANHERE, and S. L. BAFNA

The effect of the ionic form of the sulfonic acid cation-exchange resins of different degree of crosslinking and of the added sulfuric acid on the equilibrium exchange of four cinchona alkaloid sulfates as well as the equilibrium uptake of four cinchona alkaloid bases by the hydrogen form of the same resins from six aliphatic alcohols has been studied and the results are discussed.

EARLIER (1) the equilibrium exchange of four cinchona alkaloid (quinine, quinidine, cinchonine, and cinchonidine) sulfates on styrene divinylbenzene copolymer based sulfonic acid cation-exchange resins of different degree of crosslinking and particle size in hydrogen form had been studied. This includes the study on the effect of the ionic form of such resins and of added sulfuric acid on the equilibrium exchange of the four cinchona alkaloid sulfates as well as the

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equilibrium uptake of the four cinchona alkaloid bases by the same resins in hydrogen form from six aliphatic alcohols at room temperature (~30°).

EXPERIMENTAL

Resins (1, 2)—Styrene divinylbenzene copolymer based sulfonic acid cation-exchange resins of degree of crosslinking (% nominal divinylbenzene content) as 2, 4, and 8 (further referred to as resins X2, X4, and X8)[1] of −20, +50; −50, +100; and −50, +100 mesh size, respectively. The resins were conditioned, regenerated, air dried, and moisture content and capacity were estimated (3, 4). The percent moisture and the capacity in meq. per oven-dry Gm. were: X2, 20.4, 5.20; X4, 24.0, 5.12; and X8, 27.0, 5.09. The different ionic forms of the resins were obtained by passing excess of the salt or hydroxide solution through the resin bed. The resins were then washed, filtered, air dried, moisture content determined, and capacity of the air-dry resin calculated from the oven-dry capacity in the hydrogen form.

Resin IR-200[2] of −10, +60 mesh size, which is presumably styrene divinylbenzene copolymer based sulfonic acid cation-exchange resin of relative degree of crosslinking of about 20 but has an expanded structure. The resin was conditioned, regenerated, air dried, and percent moisture content and capacity in meq. per oven-dry Gm. were 25.5 and 4.78.

Chemicals and Solvents (5)—Quinine sulfate (Government quinine factory, Madras), quinidine sulfate (P. B. Howard, London), cinchonine sulfate (B. D. H. London), and cinchonidine sulfate (Fluka, A.G., Switzerland) were crystallized several times from hot water and stored in well-stoppered colored bottles. The composition was $Q_2H_2SO_4 \cdot nH_2O$ where Q denotes the alkaloid base. This was established from estimation of water content by drying in an oven (100 ± 3°), sulfate estimation as barium sulfate gravimetrically and estimation of the precipitated alkaloid base by weighing and by ultraviolet absorption in alcoholic solution.

For the preparation of the cinchona alkaloid bases about 0.5 *N* sodium hydroxide solution was added to alkaloid sulfate solution in slight excess, heated to about 80°, filtered hot, washed free of alkali, recrystallized (quinine from 40% v/v aqueous ethyl alcohol, quinidine from 80% aqueous ethyl alcohol, and cinchonine and cinchonidine from distilled ethyl alcohol), dried at 100 ± 2°, and stored.

The alcohols were of C.P. grade. Absolute ethyl alcohol was prepared by refluxing distilled ethyl alcohol in the presence of anhydrous calcium oxide for 6 hr. and then distilling it.

Procedure—The alkaloid sulfate (1 mole equal to two equivalents) solutions were prepared by dissolving weighed amounts of the respective alkaloid sulfates (1) in distilled water in volumetric flasks. The concentration of the solutions was rechecked gravimetrically by sulfate estimation as barium sulfate and by ultraviolet absorption (5). The alkaloid base (1 mole equal to one equivalent) solutions were prepared by dissolving the weighed amount of the alkaloid bases in the respective alcohols in the volumetric flasks. The concentration of the solutions was rechecked by ultraviolet absorption. To study the equilibrium of alkaloid sulfates and bases with the resins, weighed amounts of air-dried resins were contacted with the aqueous sulfate solutions or the solutions of the bases in the alcohols of known concentration in well-stoppered flasks with frequent shaking at room temperature (~30°). Preliminary work was carried out to find the approximate time within which equilibrium was attained. After sufficiently more time than this (about 4–40 days depending on X), the solutions were analyzed for alkaloid concentration by ultraviolet absorption. The ultraviolet absorption measurements were made with a Beckman model DU spectrophotometer using 10-mm. matched quartz cells. Preliminary work also indicated that for small changes in temperature the value of P_R did not change significantly.

[1] Dowex 50W, Dow Chemical Co., Midland, Mich.
[2] Amberlite 1R-200, Rohm and Haas Co., Philadelphia, Pa.

RESULTS AND DISCUSSION

Effect of the Ionic Form of the Resin—The synthetic organic ion-exchange resins (6, 7) consist of an irregular, three-dimensional network of hydrocarbon chains, to which ionogenic groups are attached and the surplus electric charge is balanced by mobile counter ions. The hydrocarbon network is hydrophobic but the ionogenic groups are hydrophilic, and hence when the resin particle is placed in water, it sorbs water and swells to a limited extent. The amount of water sorbed and the extent of swelling would depend on the degree of crosslinking and the counter ions.

The equilibrium exchange of the four cinchona alkaloid sulfates in aqueous solution with resins X2, X4, and X8 in lithium, sodium, potassium, magnesium, and aluminum forms was studied and the calculated values of P_R were practically constant when P_A was varied. Table I gives an illustration of the type of results obtained, and the values of P_R obtained from such data are given in Table II.

It is suggested that the value of the equilibrium

Table I—Equilibrium Exchange of Quinine Sulfate with Resin X4 in K Form

$[\bar{M}]_i$	$[A]_i$	$[\bar{A}]_e$	P_A	P_R
1.32	2.16	0.57	26.4	43.2
2.21	2.16	0.97	44.9	43.9
3.08	2.16	1.33	61.6	43.2
3.34	2.08	1.44	69.2	43.1
4.46	2.08	1.92	92.3	43.1

Table II—Values of P_R for Equilibrium Exchange of Cinchona Alkaloid Sulfates with Resins in Different Ionic Forms

Ionic Form →		Li	Na	K	Mg	Al
Alkaloid Sulfate	Resin			P_R		
Quinine	X2	65	65	61	50	31
	X4	50	45	43	36	25
	X8	37	30	28	23	22
Quinidine	X2	66	62	56	44	28
	X4	51	43	39	32	20
	X8	38	29	27	21	18
Cincho-	X2	—	82	68	—	—
nine	X4	—	65	60	—	
	X8	—	42	44	—	—
Cinchoni-	X2	95	85	70	—	—
dine	X4	75	62	62	—	—
	X8	51	47	42	—	

constant for the exchange of the cation QH^+ is large and the equilibrium

$$\overline{M^{+y}} + y\overline{QH^+} \rightleftharpoons M^{+y} + y\overline{QH^+}$$

($\overline{M^{+y}}$ and $\overline{QH^+}$ denote the cations in the resin phase and M^{+y} and QH^+ denote the cations in the solution phase; y denotes the valence of M) is shifted very much to the right; however, all the replaceable ions in the resin phase are not accessible for exchange or the available capacity is only a fraction of the total capacity, probably due to the size of the organic counter ions. It is likely that the marked shift of the equilibrium to the right is aided by nonexchange interactions (1, 3).

For resins X2, X4, and X8 in lithium, sodium, and potassium forms, the values of P_R for the four cinchona alkaloid sulfates are in the order Li > Na > K which is also the order of the values of water content of the swollen resins (6, 7). For resins in the ionic forms of ions of different valence (sodium, magnesium, and aluminum), the order of the P_R values is monovalent > divalent > trivalent. The value of P_R decreases as the degree of crosslinking of the resin increases. This may be attributed to the decrease in the swollen volume of the resin as the degree of crosslinking increases and hence the number of accessible exchange sites for the organic cations in the interior of the resin decreases.

In general, the results (Table II) indicate that the P_R values for the optical isomers (quinine, quinidine cinchonine, and cinchonidine) are not substantially different. But the values of P_R for quinine and quinidine sulfates are lower than those for cinchonine and cinchonidine sulfates for the resin in the same ionic form. A possible reason for this should be the difference in the size of quinine or quinidine as compared to that of cinchonine or cinchonidine.

Effect of Added Sulfuric Acid—The equilibrium exchange of the four cinchona alkaloid sulfates with the hydrogen form of the resins X9, X8, and IR-200 with added sulfuric acid (1 N and 0.1N) was studied at room temperature. Table III gives the effect of added sulfuric acid on the equilibrium exchange of quinidine sulfate and cinchonine sulfate. The results for quinidine sulfate and cinchonine sulfate were practically the same as those for quinine sulfate and cinchonidine sulfate.

The values of P_R either decrease to a small extent or are constant with increase in P_A. The nonexchange interactions would tend to increase the extent of exchange with increase in $[A]_e$. This may be feasible to some extent by further expansion of and/or further separation between the segments in the swollen or expanded resin network and should depend on the degree of crosslinking and the extent to which the exchange has already occurred. If the further expansion and/or segment separation is sufficient to accommodate some more organic cations by exchange, P_R should increase with increase in $[A]_e$ or decrease in P_R. On the other hand, if the further expansion and/or segment separation is too small to accommodate some more organic cations by exchange, P_R should remain practically constant with increase in $[A]_e$ or decrease in P_A. The difference in the values of P_R of quinine sulfate and quinidine sulfate and those of cinchonine sulfate and cinchonidine sulfate is either relatively small or practically nil when the concentration of the added sulfuric acid is relatively large (0.1 N to 1 N). The difference in the values of P_R in the presence and absence of added sulfuric acid may possibly be due to the regenerative effect of H^+ ions and the deswelling of the resin particles for the gel-type resins (X4 and X8) and mainly due to the former for expanded structure resin IR-200.

Table IV—Equilibrium Uptake of Quinine from *n*-Propyl Alcohol by Resin IR-200 in Hydrogen Form

$[\bar{H}]_i$	$[A]_i$	$[\bar{A}]_e$	P_A	P_R
11.9	14.4	2.73	19.0	23.0
20.2	14.4	4.68	32.5	23.2
25.2	14.4	5.95	41.3	23.6
27.4	14.4	6.40	44.4	23.4
31.6	14.4	7.42	51.5	23.5
37.7	14.4	8.97	62.3	23.8

Effect of Solvent Medium (Aliphatic Alcohols)—The equilibrium uptake of the four alkaloid bases, quinine, quinidine, cinchonine, and cinchonidine, from dilute solution in six aliphatic alcohols (methyl alcohol, absolute ethyl alcohol, *n*-propyl alcohol, *n*-butyl alcohol, *t*-amyl alcohol, and *n*-hexyl alcohol) by resins X2, X4, X8, and IR-200 in hydrogen form was studied at room temperature. The value of P_R was practically independent of P_A. Table IV gives an illustration of the type of results obtained. The values of P_R obtained from such data are summarized in Table V; it also includes the values of P_R obtained for *n*-amyl alcohol by plotting P_R against the number of straight chain carbon atoms in the *n*-alcohol molecule for each resin.

The values of P_R for the optical isomers were not significantly different. The values of P_R for quinine or quinidine are different from those for cinchonine or cinchonidine in methyl alcohol. In ethyl alcohol (absolute) and *n*-propyl alcohol the values of P_R for the four bases are fairly close for each resin.

Table III—Effect of Added Sulfuric Acid on the Equilibrium Exchange of Cinchona Alkaloid Sulfates with Sulfonic Acid Resins in Hydrogen Form

Alkaloid →	Quinidine Sulfate						Cinchonine Sulfate					
H_2SO_4 →	0.1 N			1 N			0.1 N			1 N		
Resin	$[\bar{A}]_e$	P_A	P_R	$[\bar{A}]_e$	P_A	P_R	$[\bar{A}]_e$	P_A	P_R	$[\bar{A}]_e$	P_A	P_R
X4	0.53	51.2	45.3	0.23	22.5	29.7	0.37	38.3	46.6	0.29	30.5	25.2
	0.69	66.3	44.3	0.34	32.5	28.8	0.66	68.3	42.1	0.36	37.9	23.7
	0.84	81.2	43.4	0.52	50.2	26.9	0.80	83.2	40.8	0.42	43.9	21.7
X8	0.30	29.0	39.8	0.11	10.4	29.3	0.31	32.3	42.8	0.22	23.1	29.9
	0.45	42.6	39.5	0.41	39.3	27.6	0.46	48.4	41.3	0.40	41.4	26.8
	0.59	55.9	39.1	0.59	56.5	26.4	0.60	62.1	39.8	0.47	49.4	25.5
	0.72	68.6	38.4	—	—	—	0.71	73.8	38.0	—	—	—
IR-200	0.31	33.3	25.3	0.26	27.3	16.9	0.34	34.7	27.4	0.36	36.5	17.4
	0.44	46.6	25.2	0.34	36.4	16.5	0.46	47.1	26.8	0.45	46.3	16.7
	0.63	67.5	24.4	0.59	63.4	15.3	0.57	58.5	26.1	0.55	55.7	15.9

TABLE V—VALUES OF P_R FOR THE UPTAKE OF CINCHONA ALKALOID BASES FROM ALIPHATIC ALCOHOLS BY SULFONIC ACID CATION-EXCHANGE RESINS IN HYDROGEN FORM

Alkaloid → / Resin → / Alcohol	Quinine or Quinidine				Cinchonine or Cinchonidine			
	X2	X4	X8	IR-200	X2	X4	X8	IR-200
Methyl	42	33	23	30	67	38	26	34
Ethyl (abs.)	34	26	16	30	—	25	17	33
n-Propyl	23	16	09	27	24	18	11	31
n-Butyl	24	15	07	28	32	20	09	33
n-Amyl	29	14	07	30	44	25	10	33
tert-Amyl	18	11	08	28	25	23	13	37
n-Hexyl	37	14	08	32	63	29	11	39

With further increase in the chain length of the alcohol molecule (*n*-butyl and *n*-hexyl alcohols), the difference in the P_R values of quinine and quinidine and those of cinchonine or cinchonidine again becomes significant. A possible reason for this type of behavior should be the size of the organic counter ions relative to the swollen volume of the resin particle in the different alcohols. The value of P_R decreases with increase in the value of X for the gel-type resins X2, X4, and X8 due to the decrease in the swollen volume of the resin with increase in X. With increase in the chain length of the alcohol molecule, for resin of lower X, X2, the value of P_R for the four bases first decreases and then increases. With increase in the value of X, that is for resins X4 and X8, with increase in the chain length of the alcohol molecule, the value of P_R first decreases and then remains almost unchanged. With resin IR-200 which has expanded structure, the value of P_R first decreases and then increases with increase in the chain length of the alcohol molecule. The comparison of the values of P_R for *t*-amyl alcohol and the calculated values of P_R for *n*-amyl alcohol indicates that for resin of lower degree of crosslinking, X2, the value for *n*-amyl alcohol is higher than that for *t*-amyl alcohol. For resins of higher degree of crosslinking, X4 and X8 and for resin IR-200, the values of P_R for *n*- and *t*-amyl alcohols are fairly close. The variation in the values of P_R for the series of alcohols should be attributed to the variation in the swollen volume of the resin in the alcohols.

Nomenclature—

$[A]_i$ = initial concentration of the alkaloid sulfate or base solution in meq./l.

$[\bar{A}]_e$ = the meq. of alkaloid in the resin phase per liter of solution, at equilibrium.

$[A]_e$ = the meq. of alkaloid sulfate or base in the solution outside the resin phase, per liter of solution, at equilibrium.

$[\bar{M}]_i$ = the meq. of resin per liter of the solution in the M form, initially.

P_A = $100[\bar{A}]_e/[A]_i$ = the % exchange of alkaloid sulfate or base at equilibrium.

P_R = $100[\bar{A}]_e/[\bar{M}]_i$ = the % resin capacity exchanged at equilibrium.

X = the relative degree of crosslinking (% nominal divinylbenzene content).

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Keyphrases

Cinchona alkaloids
Ion-exchange resins, cinchona alkaloids—equilibrium exchange
UV spectrophotometry—analysis