

567. The Absorption of Quinine by a Carboxylic Acid Ion-exchange Resin.

By L. SAUNDERS and R. SRIVASTAVA.

The rates of absorption on, and elution from, a carboxylic acid ion-exchange resin have been studied for quinine, and the most favourable conditions have been determined. These have been tested on a column of the resin and a quantitative recovery of quinine from the column has been obtained. The maximum capacity of the resin depended on the rate of running, but when a very fine resin powder (less than 60 B.S.S.) was used this rate could be very considerably increased without loss of capacity.

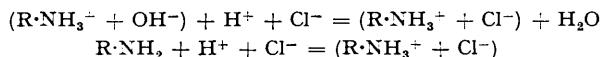
The mechanism of absorption is discussed with reference to an empirical equation for the rate of absorption.

THE possible application of weak(carboxylic)-acid ion-exchange resins to the purification and separation of organic bases has been suggested by Winters and Kunin (*Ind. Eng. Chem.*, 1949, **41**, 460) who showed that considerable absorption of alkaloids by the resin Amberlite IRC 50 does occur. They also indicated that non-aqueous solvents could be used with this resin.

The use of the strong(sulphonic)-acid resins in alkaloid recovery (Nachod, "Ion Exchange," Academic Press, New York, 1949) and in separation of organic bases (*e.g.*, Partridge and Westall, *Biochem. J.*, 1949, **44**, 418) is established. Little work has yet been recorded on similar application of the carboxylic-acid type, although Hems (*J. Soc. Chem. Ind.*, 1948, **67**, 77) reported that a resin of this type had insufficient capacity for commercial separation of amino-acids. The weak-acid resin would appear to offer better opportunities than the strong-acid type for the delicate separation of mixtures of similar organic bases.

As a first step in the study of the absorption of alkaloids by the hydrogen form of a weak-acid resin, the interaction of alcoholic quinine solutions and the commercial resin, Amberlite IRC 50, a monofunctional carboxylic acid resin (Kunin and Barry, *Ind. Eng. Chem.*, 1949, **41**, 1269), has been examined quantitatively.

Quantitative studies of ion-exchange processes have been mainly concerned with equilibria rather than with kinetics. This is understandable with processes involving exchange of small cations on a strong-acid resin, since equilibrium is reached fairly rapidly. For a large organic base and a weak-acid resin, however, the equilibrium, if a true equilibrium exists, is only reached very slowly and kinetic considerations are important. Among the kinetic studies with ion-exchange resins which have been reported are those of Nachod and Wood (*J. Amer. Chem. Soc.*, 1944, **66**, 1380), who showed that the rate of exchange of small ions on a strong-acid resin could be expressed by a bimolecular reaction rate equation. Kunin and Myers (*J. Physical Chem.*, 1947, **51**, 1111), made a detailed examination of the kinetics of exchange of acids on a weak-base resin and found that the rate of absorption was mainly determined by the rate of diffusion of acid through the gel structure of the resin. This was shown by the fact that the amount, Y_t , of anion absorbed after a time t was related to t by a parabolic equation, $Y_t/Y_\infty = kt^{\frac{1}{2}}$. In support of this view, the rate of exchange was found to depend on the size of the resin particles. Heymann and O'Donnell (*J. Colloid Sci.*, 1948, **3**, 479) have pointed out that in the case of anion exchange between an acid solution and a weak(amine)-base resin, two mechanisms are possible :



The former is an ion exchange, whereas the latter is a molecular absorption of acid. According to these authors, there is no unambiguous method of determining which is the main mechanism.

Kressman and Kitchener (*J.*, 1949, 1211) studied the equilibria between large organic cations and the ammonium form of a strong(phenolsulphonic)-acid resin, and concluded that these equilibria can be represented by the law of mass action, and that since the affinities of bases for the resin, as measured by the equilibrium constants, increase with increasing ionic size the bases must be held on the resin by forces other than the simple Coulomb forces which hold inorganic ions on such a resin. They observed, however, that increasing ionic size reduces the rate of absorption of the organic bases. In the case of quinine hydrochloride solution, they found that equilibrium was not reached after twenty weeks' contact with the resin.

This paper describes the results of some studies of the rate of absorption of quinine base from alcoholic solutions, by a weak-acid resin. The behaviour of quinine on a column of the resin is also described.

EXPERIMENTAL.

Materials.—Amberlite IRC 50 was sieved into 20/40 and 40/60 British Standard sieve fractions. The air-dried resin was weighed and completely converted into the hydrogen form immediately before use by being soaked in hydrochloric acid made 2N. in the solvent to be used. After several hours, the acid was replaced by fresh solution, in which the resin was left overnight. Before use, the acid was poured off, and the resin washed thoroughly by decantation until the washings showed no acidity. The mean loss in weight on heating a number of samples of the air-dried resin to 110° for several hours was $37 \pm 0.5\%$.

Pure quinine (B.D.H.) was recrystallised from benzene and dried at 110°, then having m.p. 172° and $[\alpha]_D^{25} -167^\circ$ (*c*, 1 in ethanol)

Capacity of the Resin.—The capacity of this resin for small ions has been reported as 10 milliequivs./g. (Kunin and Barry, *loc. cit.*, 1949, 41, 1269). The capacities for ammonium and sodium ions were determined by shaking the resin with excess of ammonium and sodium hydroxide solutions for a week and then titrating the alkali solution with standard acid. The capacities were almost exactly the same, 10 milliequivs./g. of 110°-dried hydrogen form.

Absorption Kinetics.—In the first set of kinetic experiments 5-g. samples of the air-dried resin were converted into the hydrogen form as already described. Preliminary experiments had shown that a slightly higher rate of absorption was obtained if alcoholic acid was used for this purpose. The hydrogen-form samples were washed, quickly surface-dried on filter paper, and transferred to 250-ml. conical flasks fitted with well-ground stoppers. 100 ml. of quinine solution at 20° in ethanol or 50% aqueous ethanol were then added to each flask. After being well shaken, the mixtures were kept in a thermostat at 20° and shaken intermittently—such shaking was thought to give a better representation than continuous stirring, of column conditions of contact between solution and resin. The experiments were carried out simultaneously.

At definite time intervals, 10-ml. samples of each solution were withdrawn, rapidly analysed polarimetrically for quinine content, and then returned to the mixture. As the specific rotation of quinine varies in different solvents and also with concentration, rotation-concentration curves were determined for all the solvents used and also with various additions of hydrochloric acid and ammonia. The rotations gave the amount of quinine (*x* millimoles) absorbed by the resin in *t* hours. Measurements were continued for up to 7 days; after this time very slow absorption was still found in most cases.

In the second set of experiments, the early stages of absorption were studied by putting 0.5 g. of the hydrogen form (weighed as air-dried form) in 10 ml. of quinine solution in a polarimeter tube. Very efficient contact between resin and solution was maintained by inverting the tube frequently. At definite time intervals, the resin was allowed to settle (which it did very rapidly) and the optical rotation determined. This technique gave higher rates of absorption than the first method.

Elution Kinetics.—For determination of the rates of elution of quinine from 5-g. (air-dried) samples on which a known amount of quinine had been absorbed, the resin was rapidly washed with a small amount of solvent immediately after completion of the absorption measurement, surface-dried, and transferred to a conical flask containing 100 ml. of eluting solution. The rate of elution was followed polarimetrically, as described above.

Column Studies.—The behaviour of quinine on a column of Amberlite IRC 50, was examined. 50 G. of the air-dried form of the resin (20/40 B.S.S.) were converted into the hydrogen form with acid in 50% ethanol, and packed wet, in successive small portions without tamping, into a Pyrex-glass tube 30 cm. long and of 2.5-cm. internal diameter. The bottom of this tube was sealed to a capillary tap and packed with a small quantity of glass wool. A siphon device was fitted to prevent drying out of the resin in overnight running. 50 G. of resin occupied 20 cm. of the column length. A 2-cm. layer of liquid was maintained above the resin to prevent uneven absorption, and the solutions were added from a tap funnel. The total volume of liquid in contact with the resin in the column was 29.5 ml.

After being packed into the column, the resin was thoroughly washed with 2N-hydrochloric acid in 50% ethanol, and then with 50% ethanol until the issuing liquid showed no acidity. To check that no material was dissolved from the resin by ethanol, 100 ml. of this liquid were run through the column very slowly (24 hours), and the eluate was collected and evaporated to dryness. The residue, if any, was <0.1 mg.

Results.

The combined results of the absorption kinetic experiments showed that the following factors influence the rate of absorption of quinine on Amberlite IRC 50: (i) The initial concentration of solute (*a* millimoles/100 ml.). (ii) The nature of solvent, absorption from 50% ethanol solution being more rapid than that from pure ethanol for a given value of *a*. (iii) The method by which the resin was converted into the hydrogen form; aqueous 2N-acid produced a less effective absorbent than alcoholic 2N-acid. (iv) The amount of base already absorbed on the resin (*x* millimoles). (v) The stirring conditions. (vi) The particle size of resin. (vii) The initial pH of solution.

The amounts (*x* millimoles) absorbed in time (*t*) are shown in Figs. 1 and 2.

Fig. 1 shows that the initially rapid rate of absorption later decreased greatly. After 28 hours it was almost independent of the initial quinine concentration *a*. After 7 days slight absorption was still detectable in some cases. The relation between the rate of absorption dx/dt and *t* was studied in detail for the ethanol solutions, in which a wide variation of *a* was possible. No significant constants were found by applying first- or second-order reaction velocity equations to the results. An empirical relation, however, represented the results quite closely, for values up to 24 hours, namely:

$$dx/dt = ka(a - x)/x^2 \quad \dots \dots \dots (1)$$

where k = constant, a = initial solution concentration in millimoles/100 ml., x = millimoles absorbed by 5 g. of resin, and t = time in hours.

For the early stages of absorption, $(a - x)$ approximately equals a and by this substitution equation (1) can be integrated to give the simple solution :

$$x = (3ka^2t)^{\frac{1}{2}} \quad \dots \dots \dots (2)$$

or

$$x = k't^{\frac{1}{2}} \quad \dots \dots \dots (3)$$

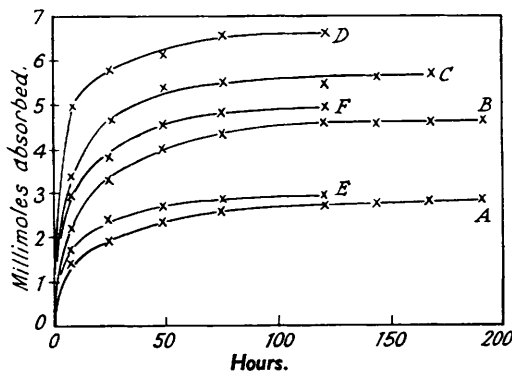
where $k' = (3ka^2)^{\frac{1}{2}}$.

From equation (1), the mean value of k was found to be 0.014 with a standard deviation (s) of 0.004 among twelve results. By direct application of equation (2) to the experimental measurement up to 7 hours, k was found to be 0.012 and s 0.002. The higher variance of the mean value from equation (1) reflects the error in the graphical differentiation of a curve whose slope is changing rapidly; the theoretical implications of this equation are discussed later.

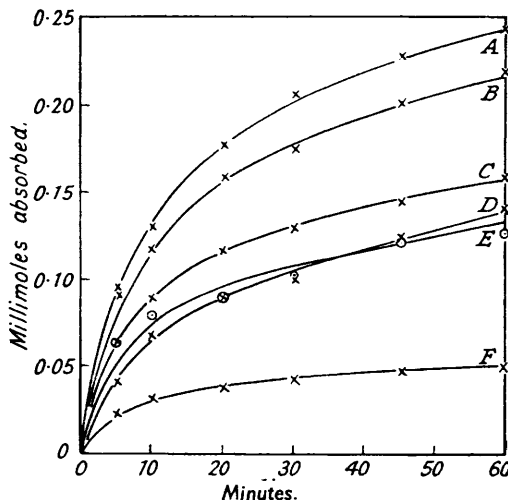
FIG. 2.

Early stages of absorption of quinine by Amberlite IRC 50. 0.5 G. of air-dried resin + 10 ml. of solution.

FIG. 1.
Rate of absorption of quinine by Amberlite IRC 50. 5 G. of air-dried hydrogen form + 100 ml. of solution.



A : a, 3.09 in ethanol. D : a, 24.7 in ethanol.
B : a, 6.17 " " E : a, 3.09 in 50% ethanol.
C : a, 12.34 " " F : a, 6.17 " " "



A : a, 3.09 in 50% ethanol; 40/60 B.S.S. resin.
B : a, 6.17 " " " 20/40 " " "
C : a, 3.09 " " " " " "
D : a, 3.09 in ethanol; " " " "
E : a, 3.09 in 50% ethanol; 20/40 B.S.S. resin;
HCl to pH 8.
F : a, 3.09 in 50% ethanol; 20/40 B.S.S. resin;
HCl to pH 7.

For 50% ethanol solutions, equation (3) was followed quite closely for a given value of a , but k' was not directly proportional to $a^{\frac{1}{2}}$ when a was varied.

In the second set of kinetic experiments, which were concerned with absorption in the first hour, equation (3) was found to hold over a wide range of experimental variations. The value of k' was, however, higher than that obtained in the first set of measurements under comparable conditions. This was due to the very efficient contact between resin and solution in the one-hour experiments. The values of k' are summarised in Table I, together with s and N (the number of results from which k' was calculated); all values except one refer to 20/40-B.S.S. resin.

The value of k' provides a useful quantitative assessment of the effect of changes in experimental conditions on absorption rate. The most favourable conditions for absorption appear to be the use of 50% ethanol as solvent with as high a value of a as possible and a small resin-particle size. Clearly, addition of acid to the quinine solution must be avoided.

The effect of pH change on the rate of absorption is considerable. At pH 8 the rate is slightly below that found without addition of acid, but, at pH 7 and below, the rate is reduced very considerably.

In order to examine the pH change occurring during absorption some further kinetic experiments were carried out by the first method, with quinine solution in 50% ethanol containing 3.09 millimoles/100 ml. The pH and the optical rotation of 10-ml. samples were measured at various times. The pH falls more rapidly than would be expected from the change in quinine content of the solution, but in the first 24 hours does not fall below 8, so that this effect will not greatly affect the rate of absorption for periods up to 24 hours.

TABLE I.

*First method, up to 8 hrs., 20°.**Second method, up to 1 hr., room temp. (16—18°).*

	<i>k'</i>	<i>s.</i>	<i>N.</i>		<i>k'</i>	<i>s.</i>	<i>N.</i>
<i>a</i> , 24.69 in EtOH	2.68	0.19	3	<i>a</i> , 3.09 in EtOH	1.24	0.14	8
<i>a</i> , 12.34 "	1.72	0.05	3	<i>a</i> , 3.09 in 50% EtOH	1.57	0.07	8
<i>a</i> , 6.17 "	1.17	0.02	3	As above + HCl to pH 8 ...	1.32	0.07	8
<i>a</i> , 3.09 "	0.72	0.01	3	As above + HCl to pH 7 ...	0.53	0.01	8
<i>a</i> , 6.17 in 50% EtOH	1.53	0.01	3	As above + HCl to pH 6 ...	0.53	0.02	8
<i>a</i> , 3.09 " "	0.82	0.05	3	As above, 40/60 B.S.S. resin	2.43	0.15	8
				<i>a</i> , 6.17 in 50% EtOH	2.18	0.05	8

Equilibrium Values of Absorption.—In all but the most concentrated ethanol solution of quinine, very slow absorption on to the resin still continued after 7 days of contact. The maximum amount of quinine absorbed (after 7 days' contact) was found to be 2.06 millimoles/g. of 110°-dried hydrogen form.

TABLE II.

Percentage elution of quinine from resin by various solutions.

Initially, 1 millimole of quinine/g. of resin.				Initially, 0.3 millimole of quinine/g. of resin.			
<i>t</i> , hrs.	2 <i>N</i> -HCl, aqueous.	2 <i>N</i> -HCl in 50% EtOH.	Conc. HCl.	<i>t</i> , hrs.	0.5 <i>N</i> -NH ₃ .	<i>N</i> -NH ₃ .	2 <i>N</i> -NH ₃ .
1	47.6	45.9	58.2	1	37.5	47.2	78.0
3	51.1	57.6	67.0	2	60.3	65.4	98.3
6	59.3	67.1	70.5	3	69.8	80.2	99.7
24	61.7	76.6	76.4	7	78.4	98.4	—
48	66.0	88.0	87.6	24	95.0	—	—

Elution.—The results of the studies of rates of elution of quinine from the resin are shown in Table II. Although the results with hydrochloric acid and ammonia are not exactly comparable, the incompleteness of acid elution was confirmed by work with a resin column. From the above results it is seen that alcoholic acid is again more effective than aqueous acid of the same strength. Complete elution in a reasonably short time can therefore be expected with *N*- or 2*N*-ammonia in 50% ethanol under column elution conditions.

Column Studies.—Aqueous-ethanolic solutions of quinine, of concentration 6.17 millimoles/100 ml., were run on to the resin column already described, at various rates, and the width of the band formed was measured by examining it in ultra-violet light. The band could often be seen under the ordinary laboratory lighting owing to the distinctive appearance of resin particles loaded with quinine. Some results are shown in Table III. It is seen that the working capacity of the resin for slow flow is 0.9 and for more rapid flow 0.3 millimole/g. The rate of flow of solution on to the resin could be considerably increased by using a resin of smaller particle size, without loss of capacity.

TABLE III.

[*w* = g. of air-dried resin involved in band (calc.); *t* = time in hours taken to run on solution; *m* = millimoles of quinine; *x* = millimoles quinine per 5 g. of resin in band.]

<i>t</i> .	<i>m</i> .	Band width, cm.	<i>w</i> .	<i>x</i> .	<i>k'</i> = <i>x/t</i> ^{1/2} .
5	3.09	4	10	1.54	0.90
75	7.72	4	10	3.76	0.89
96	7.72	3.5	8.8	4.39	0.96

The *k'* value is closer to the value found for a solution of *a* = 6.17, as determined by the first kinetic method, than to the value found by the second method (see Table I), suggesting that intermittent shaking may give a better representation of column absorption conditions than continuous agitation, though *k'* may then not have the same significance in the kinetic experiment.

When the quinine band was washed with 100 ml. of 50% aqueous ethanol, only a very slight movement was observed, showing that the alkaloid was firmly held on the resin.

When the column was eluted with hydrochloric acid solutions of various strengths, in 50% ethanol, the quinine band moved down the column with a sharp lower boundary but the upper boundary was diffuse. After the main band had been eluted from the column, quinine could still be detected in ultra-violet light throughout the resin.

On elution (*i.e.*, displacement) of the quinine band with *N*- or 2*N*-ammonia, both boundaries of the band had a sharp appearance under ultra-violet light, and fluorescence did not reappear behind the band on addition of acid. The band broadened somewhat in passage down the column.

A quantitative study was carried out, in which 7.72 millimoles of quinine were put on the column in 96 hours, giving a 3.5-cm. band. This was washed with 100 ml. of 50% ethanol and then displaced with *N*-ammonia in 50% ethanol. 15-ml. fractions of eluate were collected and analysed for quinine polarimetrically. The ammonia solution was run on at a rate of 50 ml./hr. The results are shown in

Table IV. No quinine was detected in the eluate until 225 ml. of ammonia solution had been added, and elution was complete after 480 ml. The recovery of quinine from the column was 99.8%.

TABLE IV.

Displacement of quinine by N-ammonia in 50% ethanol, from a column.

(7.72 Millimoles of quinine were put on the column and 7.71 millimoles were recovered.)

15-ml. fraction no. ...	1-14	15	16	17	18	19	20	21	22	23
Quinine, millimoles ...	Nil	0.017	0.033	0.040	0.064	0.228	0.394	0.487	0.631	0.782
15-ml. fraction no. ...	24	25	26	27	28	29	30	31	32	33
Quinine, millimoles ...	0.916	1.150	1.140	0.933	0.566	0.281	0.033	0.015	Nil	Nil

A carboxylic acid resin column of this type, made with resin of smaller particle size, may well be of considerable value both in preparative and in analytical work with organic bases.

Mechanism of Absorption of Quinine by the Resin.—The interaction of quinine with the resin is, in our opinion, mainly a molecular absorption process rather than an ion exchange. The empirical equation (1) indicates that the rate of absorption from ethanol is largely controlled by the rate of diffusion of the quinine molecule through the resin. The numerator of this equation measures the driving force of this diffusion and the denominator measures the impedance of the resin to further diffusion. This impedance will be made up of the following factors:

(a) If the large base molecule is only able to diffuse into certain channels in the gel structure of the resin, the rate of diffusion through them will, by analogy with viscous flow of liquid in a capillary, be inversely proportional to the length of the thread in the channel, *i.e.*, inversely proportional to x .

(b) As the resin particles are approximately spherical, the number of channels available will decrease as the base approaches the centre of the particle, *i.e.*, as x increases.

(c) A third impedance factor is the swelling of the resin as quinine is absorbed. Some preliminary work on this swelling effect has been carried out by selecting a large spherical resin particle from a sample which had been treated with alcoholic acid and washed with alcohol; this particle was lightly but firmly clamped between two optically flat glass plates and the whole assembly placed in a beaker containing alcohol to such a depth that the top of the upper glass plate was not covered; evaporation losses were minimised by means of a cover, and alcohol was added from time to time to keep the level constant. A microscope with a micrometer eyepiece was focused on the particle to give it a sharp periphery; after several hours no detectable change in the particle radius, measured in two mutually perpendicular directions, could be observed. The ethanol was then replaced by an alcoholic quinine solution (4 g./100 ml.); the absorption of quinine under these conditions was likely to be slow, but after several hours a detectable increase in the particle radius was found, and after two days a swelling of about 5% by volume was observed.

The net result of these impedance factors is expressed in the earlier stages of absorption by x^2 . In the later stages, a higher index of x is required.

The absorption process can therefore be visualised as a diffusion of base into the resin particle under a chemical potential difference enhanced by the acid-base interaction with the resin and by the van der Waals forces between the base molecule and the gel structure of the resin; the effects of viscous flow into spherical particles and the swelling of the resin cause the rate of absorption to fall off rapidly as the resin becomes saturated with base.

The authors thank Professor W. H. Linnell for his interest and support.

SCHOOL OF PHARMACY (UNIVERSITY OF LONDON),
17, BLOOMSBURY SQUARE, LONDON, W.C.1.

[Received, April 29th, 1950.]