THE USE OF ION EXCHANGERS IN THE ANALYSIS OF SALTS OF WEAK ORGANIC BASES AND WEAK ORGANIC ACIDS

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The determination of the amount of alkaloid in alkaloidal salts is often undertaken by supersaturating a solution with a base and shaking out the alkaloid with ether, chloroform or other suitable organic solvents. After evaporation of the latter, the amount of the free base is determined by weighing or titration. The many manipulations necessary make this a troublesome method and, as the evaporation of the solvent may cause loss of alkaloid, a better method would be desirable.

In 1936 Franck[1] made the following observation. When an ethanolic extract of an alkaloidal drug was passed through a column of a specially prepared aluminium oxide (Merck, purissimum anhydricum), not only the colouring matters, but also the anions were adsorbed by the column, so that the resulting liquid was an almost colourless solution of the alkaloidal bases, which could be determined by titration after evaporation of the ethanol.

In recent years this promising method has been studied in many laboratories, and Reimers[2] and collaborators have worked out a method using chromatographic analysis for alkaloidal salts. This method is used to a great extent in the Danish Pharmacopœia, 1948. Bjørling[3] has also used aluminium oxide for analysis of alkaloidal salts and pointed out that some difficulties may arise from adsorption in the column. Although the use of aluminium oxide has given good results, we were interested in investigating whether the use of modern ion exchangers would not give just as good results and also extend the field of use, so that with the aid of these one could determine, not only the amount of base in salts of organic bases but also the amount of acid in salts of organic acids. Good results with this method have been obtained during recent years, and this principle has been applied to a great extent in different fields of organic analysis.

Ion Exchangers

Certain compounds possess the ability to exchange ions with a solution, in which they are themselves insoluble. Because of this property they are called *ion exchangers*. The ion exchangers are denoted *cation* or *anion* exchangers, according to whether the ions which they exchange with the solution, are cations or anions. An ion exchanger can be defined as a high molecular, polyvalent, insoluble and indiffusible ion, of which the polyvalent charge is in equilibrium with relatively small ions of opposite charge. The ion-exchanging groups in anion-exchangers are usually amino groups. In cation exchangers they can be, for example,

sulphonic acid groups, carboxyl groups or phenol groups. The following reaction schemes are given as an illustration.

When a solution of a salt of a weak organic base is passed through a column of an anion exchanger the process indicated in Figure 1 takes place:—

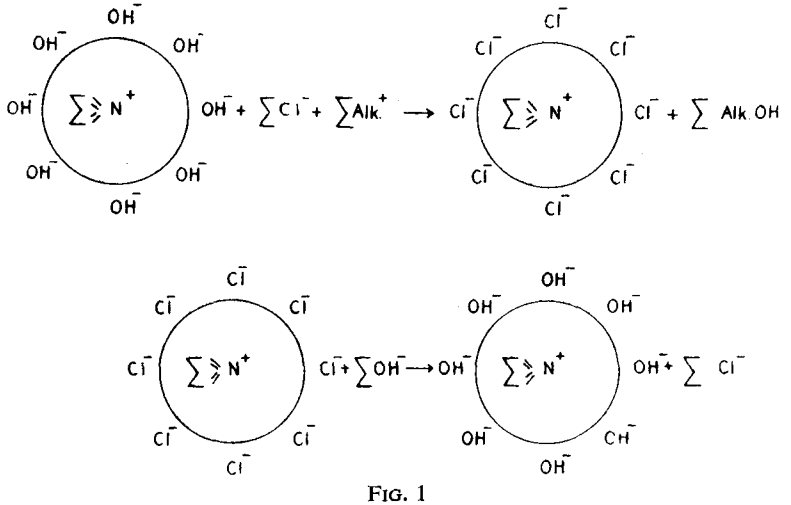

FIG. 1

The base will remain in solution and may be determined in that state.

The anion exchanger is regenerated by passing a more concentrated solution of sodium hydroxide through the column and subsequent washing with water.

The corresponding processes for cation exchangers are indicated in Figure 2.

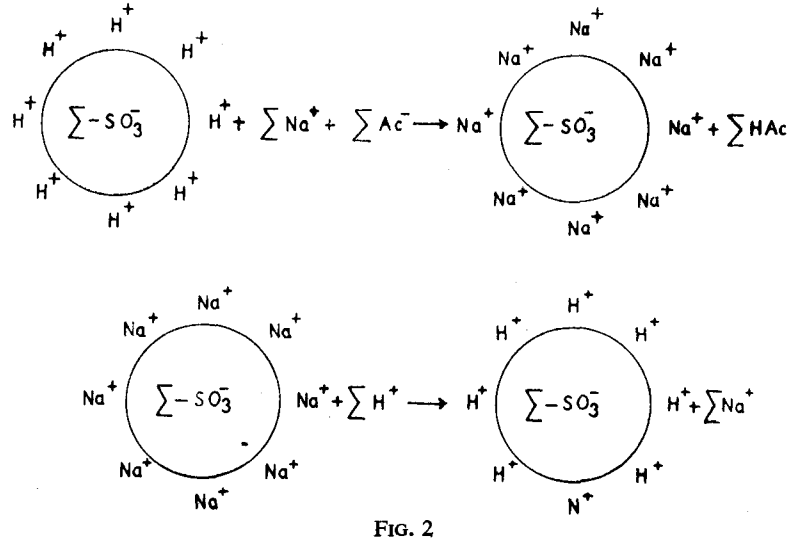

FIG. 2

The cation exchanger is regenerated by passing 4 N hydrochloric acid through the column and subsequent washing with water.

The use of ion exchange for analytical purposes was suggested as early as 1909 at the International Congress for Applied Chemistry in London,[4] and it has occasionally been brought forward in the literature during the succeeding years. An example is Folin and Bell's[5] use of ion exchange for the determination of ammonia in urine; but it was not until the nineteen thirties, when Adams and Holmes[6,7] published their work on organic ion exchangers, that these were extended for use in analytical chemistry. The modern ion exchangers, on a synthetic resin basis, are prepared both as cation exchangers (sulphonic acids, carboxylic acids and phenols) and as anion exchangers (strong or weak bases containing acyclic or aromatic amino groups).

Ion exchange resins have a field of application which extends over practically the whole *p*H scale. Since they can be obtained in a pure state for analytical purposes, and can be easily repurified after use, one has an implement for analytical chemistry having great possibilities.

Our investigations are of a preliminary nature as we have not investigated as many compounds and groups as we would have liked, but we have primarily aimed at the analysis of alkaloidal salts and salts of simple organic acids.

The Analysis of Salts of Natural Alkaloids and Other Weak Organic Bases

For the analysis of alkaloidal salts we have preferably used the strongly basic ion exchanger, Amberlite IRA-400, as we found it more suitable for this purpose than Amberlite IR-4B.

A glass tube 8 mm. in diameter and about 90 mm. long was used for the column, the bottom part of the tube was drawn out to a narrow tube and to the top was fused another glass tube 20 mm. in diameter and having a capacity of 15 ml. (Fig. 3).

Fig. 3

Before a column was prepared, the ion exchanger, which was used in the commercially available particle size, was made to swell by immersion overnight in the solvent concerned. It was then suspended in water and poured into the glass tubing, in which had been previously placed a little glass wool to act as a filter. The top of the column was finally covered with a layer of glass wool. The column was thus formed by sedimentation, and had a height of about 75 mm. Purification of the ion exchanger was carried out by passing 50 ml. of N sodium hydroxide through the column. After subsequent washing with water until the washings were colourless on the addition of phenolphthalein, the column was ready for use. Between experiments, or when not in use, the column was always filled with water by placing a stopper in the upper end of the tubing before the rinsing water had reached the top of the column.

Kunin[8] gives the following values for the capacity of the ion

exchangers which we used: Anion exchanger Amberlite IR–4B, weak base, 10 milli-equivalents/g. or 2·5 milli-equivalents/ml. Anion exchanger Amberlite IRA-400, strong base, 2·3 milli-equivalents/g. or 1·0 milli-equivalent/ml. Cation exchanger Amberlite IR 100, of the phenol-methylene sulphonic acid type, 1·75 milli-equivalents/g. or 0·65 milli-equivalents/ml. Our experiments have, by and large, confirmed the given figures.

The solubility of the ion exchangers was determined in order to obtain some idea of the stability of the ion exchanger in relation to the solvent used for the experiments. 6 ml. of regenerated and washed Amberlite IRA–400 was suspended in 75 ml. of ethanol (75 per cent.) and allowed to stand for 24 hours at room temperature. The ethanol was then filtered off and after evaporation the residue was determined. Weight of the residue 0·002 g. The solubility was further determined under experimental conditions which had more similarity to those employed in the actual determination: 500 ml. of ethanol (75 per cent.) was filtered through a column (8 mm. diameter, 120 mm. height) of regenerated and washed ion exchanger, at room temperature and the residue from the evaporation was determined. Weight of the residue 0·0024 g. The solubility of the ion exchanger in the solvents used is so small that it can be ignored.

In order to obtain as great an accuracy as possible we have not used the commercial salts of the organic bases as they contain varying amounts of water of crystallisation. We dissolved the free base, the purity of which was controlled by titrating with 0·1 N hydrochloric acid, in ethanol or methanol (50 per cent.) and neutralised this solution with 0·1 N hydrochloric acid using bromophenol blue as indicator. This indicator is particularly suitable for the titration of bases having a *p*A* value about 7 to 8 in a solution in ethanol (about 50 per cent.).[9,10]

The solution of the salt of the organic base was then filtered through a column of Amberlite IRA-400. The flask and column were rinsed with 50 ml. of ethanol (50 per cent.). In order to finish the subsequent titration in a medium which contains about 50 per cent. of ethanol, about 9 ml. of ethanol (86 per cent.) was added, this being used to rinse the narrow part of the column and the neck of the flask. This solution was now titrated with 0·1 N hydrochloric acid after the addition of 2 drops of bromophenol blue indicator, as the indicator added in the first titration was retained by the ion exchanger. This method was used in the determination of the natural alkaloids and other organic bases listed in Table I.

The quantity of ion exchanger used for the experiments corresponds to a little more than twice the amount—expressed in milli-equivalents—of the substance which was used for the experiments. In a few cases, shown under "remarks" in the table, it was necessary to use ethanol of a higher concentration (75 per cent. v/v), and even to elute with warm ethanol. In some cases (ethylmorphine, hydrocodone, oxycodone)

* pA is defined from the following equation

$$pA = pH - \log. \frac{[base]}{[salt]}$$

TABLE I

DETERMINATION OF SALTS OF NATURAL ALKALOIDS AND OTHER ORGANIC BASES USING AMBERLITE IRA-400

0·5 to 1 milli-equivalent of alkaloidal salt
Column: 8 × 75 mm.
Unless otherwise specified the elution is carried out with 50 ml. of ethanol (50 per cent. v/v)

Base	Recovered, per cent.	Remarks
Amphetamine	99·5, 99·0, 98·9, 99·0	
Atropine	99·1, 98·8, 99·1, 99·1	
	99·4, 99·4	
Brucine	99·0, 100·2, 100·0	
Butacaine	99·1, 99·3, 99·6	
Cinchonine	100·0, 100·3*	
Cincaine	99·1, 98·9, 99·1	
Cocaine	98·8, 99·0, 99·0	
Codeine (chloride)	99·4, 99·1, 99·0, 98·5	
	98·6, 98·9	
Codeine (phosphate)	99·1, 99·5, 99·1	
Diphenhydramine	98·4, 98·2, 98·9, 98·0	
	99·1, 99·3	ethanol (75 per cent. v/v
Emetine	99·6, 99·5, 99·8	
Ephedrine	99·0, 99·8, 99·7	
Ethylmorphine	99·5, 99·1, 99·1	
	98·8, 99·4	methanol (75 per cent. v/v)
Homatropine	99·8, 100·0, 100·0	
Hydrocodone	96·5, 97·0	
	98·6	ethanol (75 per cent. v/v)
	99·6, 98·9, 98·8	ethanol (75 per cent. v/v), warm
	99·8	methanol (75 per cent. v/v)
Hyoscyamine	99·6, 99·4, 99·7, 100·0	
Methadone	99·1, 99·5, 99·5	
Oxycodone	95·4	
	95·2, 94·6	ethanol (50 per cent. v/v), warm
	97·6	methanol (50 per cent. v/v)
	98·4	methanol (50 per cent. v/v), warm
	100·0, 100·2	methanol (75 per cent. v/v), warm
Papaverine	99·2, 100·8	
Pethidine	99·4, 99·5	
Procaine	99·7, 99·4, 99·2, 99·1	
Quinidine	100·0, 100·2*	
Quinine	97·7, 100·0*	
Scopolamine	100·0, 99·8, 99·9	
Strychnine	100·3, 100·8*	

* Electrometric titration.

the use of methanol gave the best results. It was found necessary to carry out a blank determination on the reagents. The amount of 0·1 N hydrochloric acid used was 0·06 ml. Also a quantitative determination of atropine was attempted using Amberlite IR-4B, the method being the same as that described above. The results showed that there was only incomplete conversion in this ion exchanger. To prove that this was the case and not adsorption of the alkaloid base to the column, the following experiment was carried out. The filtrate from the column of Amberlite IR-4B was passed through a purified column of Amberlite IRA-400. On titration of the filtrate the same amount of 0·1 N hydrochloric acid was used as before the passage through the columns.

From strychnine base, which is very slightly soluble, a solution was prepared in absolute ethanol. This contained in 10 ml. strychnine base equivalent to about 0·6 ml. of 0·1 N hydrochloric acid. The titrations were therefore carried out using 0·01N hydrochloric acid, but as the end-point was not distinct, the solutions were titrated potentiometrically.

The method was as follows: 10 ml. of the solution was measured, and 6 ml. approx. of 0·01 N hydrochloric acid and 4 ml. of water were

added. The solution was passed through the column of Amberlite IRA–400 (diameter 0·7 mm., height 40 mm.) and this was washed with 40 ml. of warm ethanol (50 per cent.). After the addition of 9·5 ml. of ethanol (86 per cent.) the solution was titrated potentiometrically. The blank was determined by diluting 6 ml. approx. of 0·01 N hydrochloric acid with 4 ml. of water and 10 ml. of absolute ethanol and passing this solution through the ion exchanger. The ion exchanger was then washed with 40 ml. of ethanol (50 per cent.), 9·5 ml. of ethanol (86 per cent.) was added to the filtrate and the solution was titrated potentiometrically.

The alkaloids cinchonine, quinidine and quinine, which cannot be accurately titrated by the use of bromophenol blue as indicator, because of the buffer action at the end-point, were also titrated potentiometrically. The method was the same as for strychnine except that larger amounts of alkaloid were used for the determination, and therefore the column of the ion exchangers used was as described in the general method. The amount of ethanol (50 per cent.) used for washing was 50 ml. and the titration was carried out with 0·1 N hydrochloric acid.

Physostigmine salicylate was decomposed (strong red coloration) by Amberlite IRA-400 and only about 60 per cent. was recovered.

Histamine, carbacholine and homatropine methyl bromide were tested by the ordinary method, but have not given satisfactory results.

For morphine, due to the fact that this alkaloid contains phenol groups, IRA–400 could not be employed. An experiment was made with a large column of IR-4B, but the results were not satisfactory. Only 96·5 and 96·8 per cent. was recovered using methanol (75 per cent.) for elution.

The Analysis of Weak Organic Acids

Bjørling[11] used Amberite IR–100H for the determination of the amount of acid in some sodium and calcium salts of organic acids. The results were generally good for salts of lactic acid, tartaric acid, citric acid, gluconic acid, sulphosalicylic acid, glycerophosphoric acid, and amidopyrine methanesulphonic acid (novalgin), but the method could not be utilised for salts of propionic or benzoic acids. It should also be mentioned that Wiesenberg[12] has used the same method in the analysis of different inorganic salts and sodium acetate in the determination of *N*-acetyl compounds. We have thoroughly investigated the method and can confirm Bjørling's results but we have found that salts of propionic acid, butyric acid and benzoic acid can also be analysed in this way, when water containing 15 to 30 per cent. of ethanol is used for elution. The column was prepared as described on page 568 and the ion exchange resin Amberlite IR–100H was used. The solution of the salts were prepared from the pure, titrimetrically determined organic acids, of which a known amount was neutralised by sodium or calcium hydroxide. Formic acid, acetic acid and malonic acid could be directly eluted with water, whilst this was not the case with the other organic acids examined. By elution with dilute ethanol (15 to 30 per cent.) all the acids examined could be determined quantitatively, as shown in Table II.

An amount of acid was used which corresponded to about 15 ml.

TABLE II

ANALYSIS OF SODIUM AND CALCIUM SALTS OF ORGANIC ACIDS USING AMBERLITE IR-100H

1·5 milli-equivalents of acid
Column: 11 mm. × 65 mm.
Eluted with 70 ml. of water or ethanol

Acid	Eluted with	Recovered per cent.
Formic	water	99·0
	ethanol (15 per cent.)	99·5, 100·0
Acetic	water	99·4, 99·4
	ethanol (15 per cent.)	100·0
Propionic	water	99·7, 99·7
	ethanol (15 per cent.)	100·0, 100·0
Butyric	water	87·1
	ethanol (20 per cent.)	96·3
	ethanol (30 per cent.)	99·3
	ethanol (40 per cent.)	99·9
Malonic	water	99·7, 100·3
Lactic	water	98·6, 98·7, 99·1
	ethanol (15 per cent.)	99·2
Gluconic	water	98·2, 98·3, 99·6
	ethanol (15 per cent.)	99·9, 100·0
Lævulic	water	98·2, 98·3, 99·6
	ethanol (15 per cent.)	99·9, 100·0
Benzoic	ethanol (15 per cent.)	89·2, 90·1
	ethanol (30 per cent.)	100·0

of 0·1 N base. The solutions were filtered through a column of Amberlite IR-100H; the amount of eluate was about 70 ml. This was titrated with 0·1 N base (indicator phenolphthalein).

The analytical technique used is easy to carry out and gives good results for all the compounds examined; a more extensive investigation on the use of the method for pharmaceutical problems of an analytical nature would be highly desirable.

SUMMARY

1. The analysis of some salts of weak organic bases and weak organic acids using synthetic organic ion exchangers (Amberlites) is described.

2. The method has given good results and as the Amberlites are commercially available of a purity suitable for analytical purposes, may easily be regenerated and do not give rise to difficulties from adsorption, they are recommended for rapid analyses of the salts mentioned.

3. A disadvantage is that the presence of neutral salts, e.g. sodium chloride, affects the results.

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