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A Simple Method for the Separation of Amines on a Preparative Scale

ARNE BRÄNDSTRÖM

AB Hässle, Fack, S-431 20 Mölndal 1, Sweden

Mixtures of amines are often readily separated on a preparative scale by extractions at suitable pH values. These pH values may be obtained directly, without any calculation, from a titration curve measured in a two-layer solvent system.

In common laboratory practice amines are separated from neutral and acidic compounds by extracting them from an organic layer to an aqueous layer at a low pH value. The aqueous layer containing the salts of the bases is then made strongly alkaline and the bases are extracted by an organic solvent. In this separation a pH difference of 10 – 14 units is used although a difference of 4 units is sufficient for a separation on the 99 % level (99 % yield, 99 % purity) if the proper pH values are used. The method has thus the capacity for much more intricate separations than are usually performed on a preparative scale. This is demonstrated by the fact that separations of amines by extractions at carefully selected pH values have been performed in analytical chemistry for many decades.[1]

The crucial factor for a successful separation of amines is to find a proper pH value. In analytical chemistry this problem is solved by careful measurements at different pH values using the pure compounds to be separated.[1] In preparative chemistry such a procedure is often out of the question especially when the compound is prepared for the first time.

There is, however, a wide gap between making calculations from careful measurements and taking extreme values for the sake of convenience. The intention of this paper is to bridge this gap by demonstrating that mixtures of amines can often be separated by extractions at pH values easily obtained from a simple titration curve measured in a two-layer solvent system.

The method has been used for some years in our laboratories. In practice the procedure is very simple to perform and has in a dramatic way facilitated the purification of amines. In contrast to chromatografic methods it is as convenient in the kmol scale as in the mmol scale. Although the method is based on an elementary process well-known to every chemist, it seems to be necessary to present it in some detail in order to make it useful as the standard method of choice for the separation of amines.

THEORY

The distribution of a base B between water and an organic solvent is governed by eqns. 1 and 2 which are given to define the symbols used.

$$B_w + H_3O^+ \rightleftharpoons HB_w^+ + H_2O; [B]_w a_{H_3O^+} = k^*_{HB}[HB^+] \quad (1)$$

$$B_w \rightleftharpoons B_s; [B]_s = K_{DB}[B]_w \quad (2)$$

The situation might be complicated by the formation of ion pairs and adducts, which are extracted into the organic layer. This type of complication can usually be avoided, however, by a proper choice of anion and solvent. With aqueous sulfuric acid and a hydrocarbon or an ether as the solvent there is usually no formation of ion pairs or adducts.

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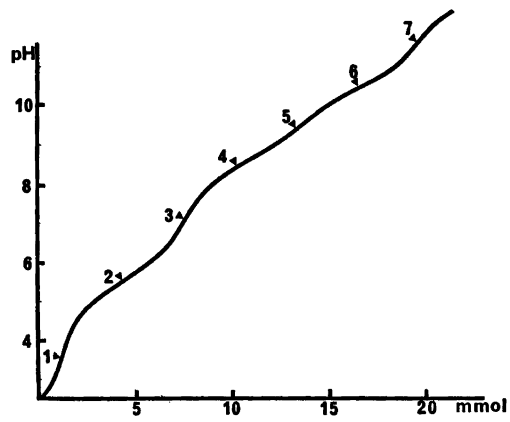

Fig. 1. Titration of a solution of a mixture of mono-, di- and tributyl amine in 20 ml of 0.5 M H_2SO_4 in the presence of 20 ml of toluene.

A combination of eqns. 1 and 2 used in the logarithmic form gives eqn. 3.

$$\mathrm{pH} = \mathrm{p}k^*_{\mathrm{HB}} + \mathrm{p}K_{\mathrm{DB}} + \log \frac{[\mathrm{B}]_s}{[\mathrm{HB}^+]_w} \qquad (3)$$

This means that $\mathrm{p}k^*_{\mathrm{HB}} + \mathrm{p}K_{\mathrm{DB}}$ has the same function in the two-layer system as $\mathrm{p}k^*_{\mathrm{HB}}$ has in the homogenous one-layer system and thus determines the shape of the titration curve obtained in a two-layer solvent system.

Assume that a mixture of the amines T, D and M are dissolved in a slight excess of aqueous sulfuric acid. If a portion of this solution is added to an equal volume of a solvent, immiscible with water, and this mixture is titrated with a strong base, a titration curve of the type given in Fig. 1 is obtained. We can observe some more or less pronounced break-points numbered 1, 3, 5 and 7. These are the equivalent points in the titration of the ions HSO_4^-, HT^+, HD^+ and HM^+ respectively. Some other points are also marked on the curve. Point 2 is situated midway between points 1 and 3. At this point eqn. 4 is

$$w[\mathrm{HT}^+]_w = s[\mathrm{T}]_s + w[\mathrm{T}]_w \qquad (4)$$

valid, where w is the volume of the aqueous layer and s is the volume of the solvent layer. A combination of eqns. 3 and 4 gives the pH at point 2 and by analogy those at points 4 and 6. These are given in eqn. 5.

$$\mathrm{pH}(2) = \mathrm{p}k^*_{\mathrm{HT}} + \mathrm{p}K_{\mathrm{DT}} - \log\left(\frac{1}{K_{\mathrm{DT}}} + \frac{s}{w}\right) \simeq \mathrm{p}k^*_{\mathrm{HT}} + \mathrm{p}K_{\mathrm{DT}} - \log\frac{s}{w}$$

$$\mathrm{pH}(4) = \mathrm{p}k^*_{\mathrm{HD}} + \mathrm{p}K_{\mathrm{DD}} - \log\left(\frac{1}{K_{\mathrm{DD}}} + \frac{s}{w}\right) \simeq \mathrm{p}k^*_{\mathrm{HD}} + \mathrm{p}K_{\mathrm{DD}} - \log\frac{s}{w}$$

$$\mathrm{pH}(6) = \mathrm{p}k^*_{\mathrm{HM}} + \mathrm{p}K_{\mathrm{HM}} - \log\left(\frac{1}{K_{\mathrm{DM}}} + \frac{s}{w}\right) \simeq \mathrm{p}k^*_{\mathrm{HM}} + \mathrm{p}K_{\mathrm{DM}} - \log\frac{s}{w} \qquad (5)$$

The approximations are the better, the higher the value of K_{DB}.

We can see that it is a combination of protolytic and hydrophilic properties that determines which of the amines is liberated from the mixture and which remains in the aqueous layer. There is no accepted short name for this combination of properties. Since it is the affinity between the proton and the amine that keeps the compound in the aqueous layer, the name protophilic will be used for this property in this paper, and the name protophilic constant will be used for the product $k^*_{\mathrm{HB}}K_{\mathrm{DB}}$.

Fig. 1 is readily recalculated to the curve presented in Fig. 2, which gives the fractions at which each compound is present in the different forms as a function of the quantity of alkali added to the mixture. Fig. 2 is very informative and can be used as a reference curve for any separation of amines. Together with eqns. 3 and 5, the two figures 1 and 2 provide a very

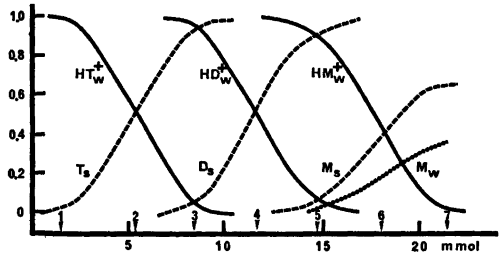

Fig. 2. Fractions of each form of the different amines T, D and M as a function of the amount of alkali added.

suitable means of predicting to what degree a separation of a base mixture is possible.

Every separation of amines can be divided into the following three steps.

1. Removal of protophilic amines.
2. Removal of amines with low protophilicity.
3. Purification of a middle fraction.

These steps will now be considered in detail.

Removal of protophilic amines

If the mixture is dissolved in aqueous sulfuric acid, it is convenient to start with a separation of T from the rest of the mixture. If the mixture contains neutral and acidic impurities, they may be removed by extraction with an organic solvent at a pH value below that at point 1. A new organic layer is then added followed by another portion of alkali sufficient to bring the well-stirred mixture to point 3. From Fig. 2 we can see that the bulk of T is in the organic layer at this point whereas the bulk of D and M is in the aqueous layer. A separation of the layers thus means a good separation of the protophilic bases D and M from a less protophilic base T.

From Fig. 2 we can also see that if the break-point is taken between points 2 and 3, a decrease in yield is obtained but the purity of the product is much better. The opposite effect is observed if the break-point is taken between points 3 and 4. Depending on whether our preference is in high yield or high purity we thus have the possibility of improving the situation somewhat. The break-point should, however, always be taken in the vicinity of point 3, which is usually easy to detect on the titration curve.

The purity of T can be further increased by repeating the process. This is simply done by adding an equal volume of water to the organic solution and then aqueous sulfuric acid in small quantities with vigorous stirring to give a pH value close to that at point 3. The layers are then separated. The organic layer now contains highly purified T.

The yield and purity of T that can be expected are readily calculated by means of eqn. 3. The pH value needed is that at point 3 and the protophilic constants are equal to the pH values at points 2, 4 and 6 according to eqn. 5.

Removal of bases with low protophilicity

If the addition of alkali is continued from point 3 to point 5 and the layers are separated, the organic layer contains the bulk of D, the total quantity of T left in the aqueous layer in the separation at point 3 and a minor quantity of M. From Fig. 2 we can also see that the aqueous layer contains the bulk of M present as M_w and HM^+ and a minor quantity of D present as HD^+.

The purity of M in the aqueous layer can be highly improved by the extraction with a fresh portion of the organic solvent and a small quantity of base to give a pH value in the vicinity of point 5.

On the other hand, the removal of M from the organic layer can be improved if water and a small quantity of aqueous sulfuric acid are added to give a pH value around that at point 5.

From Fig. 2 we can see that the aqueous layer at point 5 contains both HM^+ and M. For the separation this is of no importance but if K_{DD} had been low, < 10, the aqueous layer would have contained D in the base form and a separation of D from M would have been difficult.

Isolation of the middle fraction D

The aqueous solution containing T, D and M is mixed with an equal volume of the solvent and is titrated to point 3. This operation removes the bulk of T with the organic layer. The small quantities of T still present may be removed by the addition of a new portion of the solvent and alkali enough to bring the solution again to point 3. The aqueous layer now contains only D and M. M is then removed as described above.

LIMITATIONS OF THE METHOD

The method separates bases due to differences in protophilicity, in such a way that protophilic bases are removed with the aqueous layer and bases with a low protophilicity with the organic layer. This gives the following limitations of the method.

Table 1. Yield in per cent of T, D and M after one and two separations at each pH value.

Fraction	One separation						Two separations		
	Found			Calculated			Calculated		
	T	D	M	T	D	M	T	D	M
1	95	7	0	97	4	0	93	0.4	0
2	5	80	7	3	86	8	0.1	69	0.6
3	0	14	93	0	10	92	0	1	85

1. There must be a useful difference in protophilic constants between the compounds to be separated.

2. K_D for the base to be purified must be high enough (usually $>10-100$) to prevent losses with the aqueous layer when protophilic impurities are removed.

3. If an impurity with a low protophilicity has to be removed with the organic layer this compound must have a high K_D value ($>10-100$).

The break-points may sometimes be difficult to detect on the titration curve. The reasons for this may be many. The most important are that the difference in protophilic constants is too small or that the concentrations of the compounds are too different. In the latter case a good separation is still possible. The pH values for the separations have, however, to be calculated with the aid of eqn. 3. The value of the protophilic constant for the main compound B, which is needed in the equation can usually be obtained from the titration curve. If this is not possible or if the number of compounds in the mixture to be separated is too large to allow any detection of break-points, the protophilic constant has to be found by other methods. The most general way is to calculate it directly from structure. Methods for estimating pk^*_{HB} values have been published,[2] as well as methods for calculating log K_{DB} values.[3]

PROCEDURE

The base mixture to be separated is dissolved in a slight excess of aqueous sulfuric acid, preferably 0.1 – 0.5 M. A small portion of this solution is mixed with an equal volume of a solvent, preferably a hydrocarbon, an ether, or trichloroethylene. Under vigorous stirring a titration curve with potassium hydroxide is run manually or, preferably, automatically. Potassium hydroxide is better than sodium hydroxide since the potassium error is much lower than the sodium error for the glass electrode.

If the mixture is a dispersion of organic solvent in water, a smooth curve is obtained. The pH value in this dispersion is the same as that in the aqueous layer when the stirrer is stopped.

In rare cases a dispersion of water in the organic solvent may be obtained. In such a case the pH value of the stirred mixture fluctuates vigorously and it is necessary to stop the stirrer at intervals and to read the pH in the aqueous layer. This situation can often be avoided by increasing the quantity of water or the speed of stirring.

The titration curve is carefully observed and a separation of the bulk of the solution is performed as described above.

The method is demonstrated by a separation of an equimolar mixture of mono-, di- and tributylamine (M, D and T). The results are given in Figs. 1 and 2 and in Table 1. The amount of the three amines in the different fractions was analysed with GLC.

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