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Ion Pair Extraction in Preparative Organic Chemistry

Part VII. Separation and Purification of Amines from Reaction Mixtures

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A rapid method is presented for the separation of amines on a preparative scale. The method is based on ion pair extraction utilizing ion pair dimerization which often is observed with salts of, *e.g.*, secondary amines. A specific example is given using a secondary amine obtained by isopropylation of the corresponding primary amine. From an equimolar mixture of the two amines the secondary one was isolated in 96 % yield and 99.99 % purity using a two-step separation in a separatory funnel. Finally the importance of dimerization on separation is demonstrated by two theoretical cases.

In common practice bases are separated and purified using the protolytic reaction and base partition. The conditions are regulated by pH and the choice of solvent. The ion pair extraction gives a much better possibility.

A comparison between the two reactions

$$OH^- + HB^+ \rightleftharpoons H_2O + B_{org}$$
$$\text{and} \quad X^- + HB^+ \rightleftharpoons HBX_{org}$$

reveals that in the ion pair extraction the reaction is regulated by X^- in the same way as the extraction of a base is regulated by pH. With the ion pair extraction we have two additional advantages.

1. The ion X^- can be varied in an almost unlimited way [1–5] corresponding to differences in the equilibrium constants by a factor of more than 10^{10}.

2. Some ion pairs of secondary amines undergo dimerization in the organic layer [3] according to the reaction

$$2HBX_{org} \rightleftharpoons H_2B_2X_{2org}$$

This highly improves the degree of extraction and can be used to enhance separation factors.

In the separation of two amines with a high difference in molecular weight or lipophilic properties the procedure is very simple. The mixture is dissolved in strong hydrochloric acid and the high molecular weight amine is extracted

with chloroform or methylene chloride as an ion pair. Amines of a somewhat lower molecular weight may be extracted if an excess of a more readily extracted anion such as nitrate or perchlorate is added to the solution before extraction.

To have a serious discussion of the extraction behaviour of amines with similar lipophilic properties it is necessary, however, to know at least the magnitude of the constants for the reactions involved. The protolytic reaction constants are available for an enormous number of amines, and good predictions can be made for most compounds. A great number of partition coefficients have also been measured, and a rule for prediction has recently been advanced.[6] Some ion pair extraction constants have been measured, and rather good predictions can already be made.[7] Even a measurement of the constants is not very cumbersome.

Table 1. Properties of alprenolol (A) and noralprenolol (NA).

Compound	Protolysis pK'_{HB}	Base partition $\log k_{d(B)}$	Ion pair extraction		
			$\log E_{HBCl}$	$\log k_2$	$C_{HBCl\ org} \times 10^4$
A	9.66	3.59	−1.15 [a]	4.44	1—250
NA	9.14	1.7	−2.7 [b]	—	0.2—3.5

Ionic strength of the aqueous phase: [a] 1.0; [b] 1.5. Organic solvent: chloroform.

The method is demonstrated on the separation of alprenolol from the corresponding nor compound. The structures and constants for the two compounds are given in Fig. 1 and Table 1, respectively.

DISCUSSION OF SEPARATION

The following symbols are used:

HB^+ and B = amine in protonated and unprotonated form.
X^- = anion.
[B] and $[B]_{org}$ = actual concentrations in the aqueous and the organic phase.
C_B and $C_{B\ org}$ = total concentrations in the aqueous and the organic phase.
$C_{HBX\ org}$ = total ion pair concentration in the organic phase.
C_B^0 = initial total concentration taken as being entirely in the aqueous phase.
$H_2A_2X_{2\ org}$ in the figures denotes the dimer, the concentration of which is calculated as monomer equivalents, *cf.* the construction of Fig 3b.
V_{org} = volume of organic phase.
V_{aq} = volume of aqueous phase.
$Q = V_{org}/V_{aq}$.
μ = ionic strength.

a_{H^+} = hydrogen ion activity.
$K'_{HB} = a_{H^+}[B]/[HB^+]$ = apparent acid dissociation constant.
$D_B = C_{B\,org}/C_B$ = partition ratio.
$k_{d(B)} = [B]_{org}/[B]$ = partition coefficient.
$E_{HBX} = [HBX]_{org}/[HB^+][X^-]$ = extraction constant.
$k_2 = [H_2B_2X_2]_{org}/[HBX]^2_{org}$ = dimerization constant.

For a base, B, in a medium where no extractable ion pairs are formed, we have the following relation between partition coefficient and partition ratio.

$$D_B = k_{d(B)}/[1 + (a_{H^+}/K'_{HB})]$$

In Fig. 2 log D_B is presented as a function of pH for alprenolol and noralprenolol. This type of graph has been used earlier for the separation of atropine and tropine.[8]

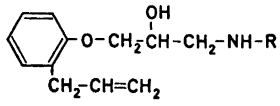

Fig. 1. Alprenolol: R=CH(CH$_3$)$_2$; noralprenolol: R=H.

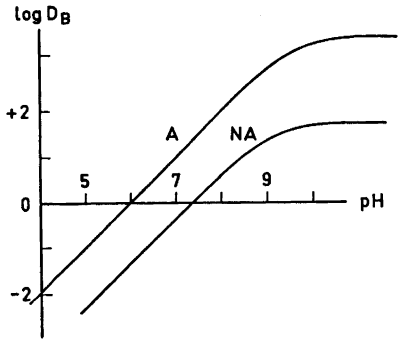

Fig. 2. Partition of alprenolol (A) and noralprenolol (NA) as bases. Organic solvent: chloroform.

It is obvious from the figure that there exists no pH-value where A and NA are separated unless a cumbersome fractionating process is used. The method of ion pair extraction gives a much better possibility of separating A from NA. A logarithmic plot is a useful tool for the calculations.

Compare the protolytic reaction with the ion pair extraction.

$$\frac{a_{H^+} \times [B]}{[HB^+]} = K'_{HB} \text{ and } \frac{[X^-] \times [HB^+]}{[HBX]_{org}} = \frac{1}{E_{HBX}}$$

In an ordinary logarithmic diagram [9] we thus have to replace pH with pX, [B] with [HB$^+$], [HB$^+$] with [HBX]$_{org}$, and pK'_{HB} with log E_{HBX}. Such a diagram is given in Fig. 3a for the hydrochlorides of A and NA using equal volumes of both layers and $C_A{}^0 = 1$ and $C_{NA}{}^0 = 0.1$. No dimerization has been considered and no simple separation seems possible. Diagrams of this type have been used earlier in studies of substoichiometric separations.[10] The extensive dimerization of HACl in the organic layer totally changes the situa-

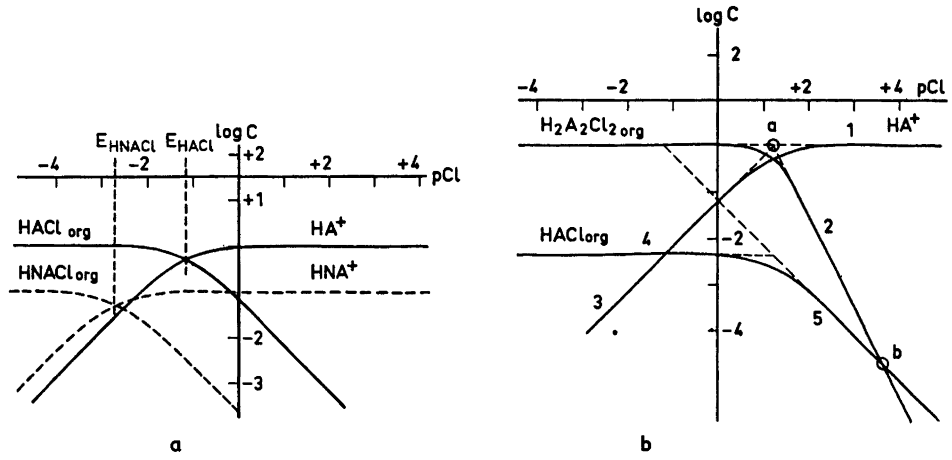

Fig. 3. Extraction of alprenolol (A) and noralprenolol (NA) as chloride ion pairs with chloroform. a. The dimerization of HACl neglected. b. The dimerization of HACl taken into account.

tion. The dimerization reaction removes $HACl_{org}$ from the extraction equilibrium so that HACl is forced into the organic layer. The extent of dimerization and in consequence the degree of extraction will increase with increasing ion pair concentration in the organic layer as can be seen from the following equations

$$k_2 = \frac{[H_2A_2Cl_2]_{org}}{[HACl]^2_{org}}$$

and $$C_{HACl\ org} = [HACl]_{org} + 2[H_2A_2Cl_2]_{org} = [HACl]_{org} + 2k_2[HACl]^2_{org}$$

The dimerization is accounted for in Fig. 3b.

The fundamental equations for construction of the diagram are obtained from the definitions of the extraction and dimerization constants given in the list of symbols. After logarithmization these equations take the form

1. $\log 2[H_2A_2Cl_2]_{org} = \log 2k_2 + 2\log E_{HACl} + 2\log [HA^+] + 2\log [Cl^-]$
2. $\log [HACl]_{org} = \log E_{HACl} + \log [HA^+] + \log [Cl^-]$
3. $\log 2[H_2A_2Cl_2]_{org} = \log 2k_2 + 2\log [HACl]_{org}$

The diagram is constructed as follows:

1. The horizontal line indicating $\log C_A^0$ is drawn (1). The left-hand part of this line represents $2[H_2A_2Cl_2]_{org}$ and the right-hand part $[HA^+]$.
2. The point on line (1) where $2[H_2A_2Cl_2]_{org} = [HA^+] = C_A^0$ is derived from eqn. (1) which gives

$$pCl = (\log 2k_2 + 2 \log E_{HACl} + \log C_A^0)/2$$

This value is marked on line (1) given above (point a).

3. A line (2) with the slope -2 down to the right is drawn through point (a). This line represents $\log 2[H_2A_2Cl_2]_{org}$ obtained from eqn. 1 when $[HA^+] \simeq C_A^0$.

4. A line (3) with the slope 1 down to the left is drawn through point (a). This line represents $\log[HA^+]$ obtained from eqn. 1 when $2[H_2A_2Cl_2]_{org} \simeq C_A^0$.
5. The line (4) representing $\log [HACl]_{org}$ when $2[H_2A_2Cl_2]_{org} \simeq C_A^0$ is derived from eqn. 3

$$\log [HACl]_{org} = (\log C_A^0 - \log 2k_2)/2$$

The slope of the line is zero and it is drawn in the figure.

6. In the right-hand part of the system there is one point where $[HACl]_{org} = 2[H_2A_2Cl_2]_{org}$ which is obtained from eqn. 3

$$\log [HACl]_{org} = -\log 2k_2$$

This value is marked on line (2) as point (b).

7. A line (5) with the slope -1 is drawn through point (b). This represents $\log [HACl]_{org}$ when $[HA^+] \simeq C_A^0$.
8. Check that the extension of line (5) intersects line (1) where $pCl = \log E_{HACl}$
9. Check that the lines (3) and (4) intersect where $pCl = \log E_{HACl}$
10. Connect lines in the left-hand part of the system with lines in the right-hand part in the usual way.

The lines representing the NA system are the same as in Fig. 3a, and are, for the sake of simplicity, not introduced in Fig. 3b.

From the figure it is easily seen that the degree of extraction and the separation of A from NA is very good for $[Cl^-] \geq 1$.

Some data are compiled in Table 2 which demonstrates the case when a solution 1 M in A and 1 M in NA is extracted from two aqueous solutions

Table 2. Extraction of alprenolol (A) and noralprenolol (NA) as ion pairs with chloride. Initial concentration: $C_A^0 = C_{NA}^0 = 1$ M.

Cl^-	Per cent extracted in			
	1st extr.		2nd extr.	
	A	NA	A	NA
1	93	0.2	5	0.2
5	98	1	2	1

Organic solvent: chloroform.

which contain 1 and 5 M chloride, respectively. It is seen that when the equilibrium chloride concentration is increased from 1 to 5 M, only a small increase in the yield of A is obtained, while the yield of NA is increased five times.

By tradition it is considered that repeated extractions are very useful to increase the yield. That is, however, not the whole truth when dimerization is the factor giving the high degree of extraction. In the actual case the low gain in yield of alprenolol is obtained at the expense of a higher degree of impurity.

When the demands for both yield and purity are high, the chloroform solution can be washed with a strong solution of sodium chloride. If the extraction is performed at $[Cl^-]=5$ and the chloroform layer is washed with an equal volume of a 5 M solution of NaCl, the chloroform layer contains 96 % of the initial concentration of A but only 0.01 % of that of NA.

All these calculations of separations, where advantage is taken of the dimerization of A in contrast to NA, are based on the assumption that no cross dimerization occurs between one molecule of A and one molecule of NA. To test this, a solution 1 M in A and 0.2 M in NA, and 5 M in Cl^- was extracted with an equal volume of chloroform. The chloroform layer should now contain HACl contaminated with 0.2 % of HNACl. This low degree of contamination was confirmed by quantitative determination after separation by thin-layer chromatography.

The practical example discussed above clearly demonstrates that excellent separations are possible for compounds which differ in the dimerization constants.

The unusual possibilities for separation by means of ion pair dimerization can be further demonstrated by theoretical cases, in which the dimerization constants are the same for both compounds. As an example, let us consider a case where the cations A^+ and B^+ are to be separated with the anion X^-.

The constants are as follows $E_{AX}=10^{-1}$, $E_{BX}=10^{-2}$ and $k_2=5\times10^3$ for both compounds which may be true when we have two closely related compounds differing by two carbon atoms in a side chain. Furthermore the cations are assumed to be present as AX and BX in equal concentrations (1 M).

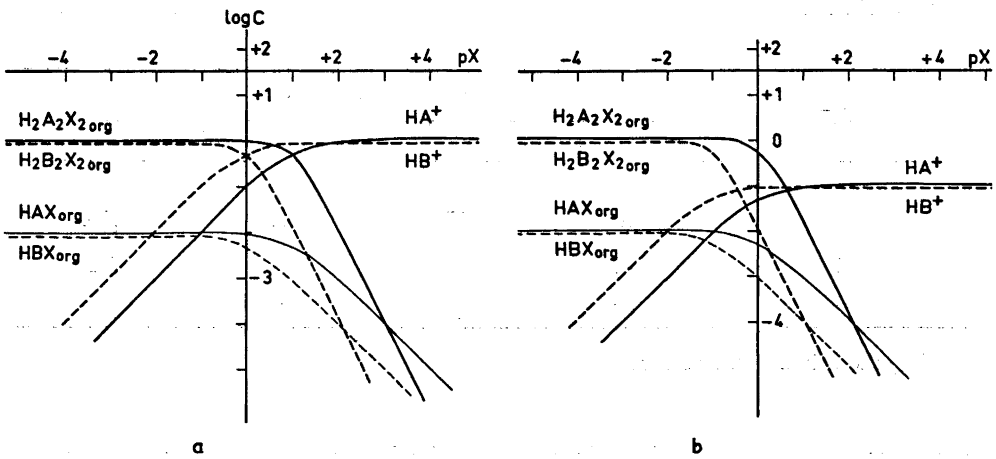

Fig. 4. Separation diagram for the substances HAX and HBX. $E_{HAX}=10^{-1}$, $E_{HBX}=10^{-2}$. $k_{3(HAX)}=k_{3(HBX)}=5\times10^3$. $C_{HAX}^0=C_{HBX}^0=1$. a. $V_{org}=V_{aq}$. b. $V_{org}=0.1\ V_{aq}$.

In Fig. 4a the logarithmic diagram for this case is constructed using equal volumes of both layers. From the figure it can be seen that the separation factor, $C_{AX\ org}/C_{BX\ org}$, is 100 for pX = 1.5, and that this is rapidly decreased when pX is decreased below 1.0. If the organic layer is shaken with pure water $[HA^+]+[HB^+]=[Cl^-]$, and a pX of about 0.25 is obtained. This represents the lowest pX value obtainable with equal phase volumes. At this pX the ratio $C_{AX\ org}/C_{BX\ org}$ is only about 3. We have two possibilities to increase this ratio. The first is to change to another anion X^- with lower E-values for both compounds. In the diagram this is equivalent to moving the log C axis towards the right. The second possibility is to increase the volume of the aqueous layer. A diagram is given in Fig. 4b representing the concentrations when the volume of the aqueous layer is 10 times that of the organic one. We can see that at pX = 0, which means that 10 vol of 1 M NaX were used in the washing of the organic layer, 50 % of AX is left in the organic layer together with 1 % of BX. We have thus a separation factor of 50, and the two compounds are readily separated by a fractionating procedure.

The diagram in Fig. 4b can be constructed as demonstrated for Fig. 3b with the following modifications.

The total concentration equation will take the form

$$C_A^0=[HA^+]+Q[HACl]_{org}+Q2[H_2A_2Cl_2]_{org}$$

The equations (1) – (3) for construction of the diagram are the same as in Fig. 3b.

1. In the left-hand part of the system a total concentration line indicating $2[H_2A_2Cl_2]_{org}=C_A^0/Q$ is drawn.
   In the right-hand part the line $[HA^+]=C_A^0$ is drawn.
2. The pCl value where $Q2[H_2A_2Cl_2]_{org}=[HA^+]=C_A^0$ is calculated from eqn. 1

$$pCl=(\log 2k_2+2\log E_{HACl}+\log C_A^0+\log Q)/2$$

This value is marked on the lines above.

3 – 4. As in Fig. 3b.

5. The line representing log $[HACl]_{org}$ when $Q2[H_2A_2Cl_2]_{org}\simeq C_A^0$ is derived from eqn. 3

$$\log [HACl]_{org}=(\log C_A^0-\log 2k_2-\log Q)/2$$

6 – 10. As in Fig. 3b.

Another interesting feature of the dimerization is that separation of two substances with identical extraction as well as dimerization constants is possible, provided that their total concentrations in the system are different.

It might appear that the extraction constants in these examples are somewhat arbitrarily chosen. It must, however, be remembered that by proper choice of X^- it is possible to select almost any value of E within a region covering more than 10 powers of 10.

Rules are already available to estimate approximative values of E for many compounds, and within a near future this possibility will be rapidly increasing. If some doubts exist in the choice of the proper anion, a small one, which is not easy to extract, should be tried first. If this fails, a more extractable anion can be used with practically no disturbance from the first one.

After some practice ion pair extraction will appear as a very efficient, simple and rapid method to separate amines. In contrast to many other methods of separation this method usually operates excellently in very concentrated solutions and is well adapted to both analytical and large-scale operations.

EXPERIMENTAL

Apparatus. The spectrophotometric determinations were performed with a Zeiss Spektralphotometer PMQ 11. The pH measurements were made with Radiometer pH meter, using glass and calomel electrodes.

Chemicals and reagents. The amines or their hydrochlorides were prepared by our laboratory as described before.[11] They were recrystallized several times and assayed by a variety of methods. *Chloroform p.a.* was shaken with water several times to remove ethanol. *The buffers* used were prepared from phosphoric acid and sodium hydroxide.

Determination of constants. The acid dissociation constants were determined with ordinary potentiometric titrations. *The partition coefficients* of the bases and the *extraction constants* and *the dimerization constants* of the ion pairs were determined according to principles given in the literature.[12,13] *The ionic strength* of the aqueous phase was 0.15 unless otherwise stated.

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