

Ion Pair Extraction in Preparative Organic Chemistry

A Convenient Method for the Preparation of Salts of Amines

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Salts of amines with different monobasic acids are often obtained by extracting a strong aqueous solution with methylene chloride or chloroform and evaporating the solvent. The yields are usually excellent. The importance of ion pair dimerization in the solvent is stressed.

In analytical and inorganic chemistry ion pair extraction has been given considerable interest in recent years.¹⁻³ In spite of this, the method is seldom used in preparative organic chemistry. Most chemists engaged in the preparation of organic amines, however, sometimes observe that a considerable quantity of the hydrochloride of an amine unexpectedly appears in the organic layer. This occurs especially when shaking a solution of the amine in strong hydrochloric acid with chloroform or methylene chloride. It is, however, not usually recognized that ion pair extraction can be used as a highly specific method for the purification of amines and, at the same time, as a fairly general method for the preparation of salts of the amines.

The standard method for the preparation of a salt (usually a hydrochloride) of an amine is by the addition of an anhydrous solution of the acid to a solution of the amine in an organic solvent. After chilling and scratching the salt may often be obtained in a crystalline form which can be purified by recrystallization. This method cannot be applied to the preparation of the nitrate or perchlorate as the anhydrous acid cannot safely be mixed with an organic solvent. Even for the preparation of the tetrafluoroborate, the thiocyanate, the iodide, and the bromide this method is impossible or highly unsatisfactory.

When an ammonium ion, HA^+ , is extracted as an ion pair with an anion, X^- , the extraction equilibrium can be expressed by the extraction constant, E , which is defined

$$E = [\text{HAX}]_{\text{org}} \times [\text{HA}^+]_{\text{aq}}^{-1} \times [\text{X}^-]_{\text{aq}}^{-1}$$

A number of extraction constants for simple ion pairs of some secondary and tertiary amines and of some quaternary ammonium ions are reported in the literature.⁴⁻⁶ The constants range within the interval $10^{-1.5}$ — 10^{10} . When the constants are high there are of course no difficulties involved in achieving quantitative extraction of the ion pair. But in the reverse case, however, it might be concluded that ion pair extraction of the salt from an acid solution would be an unsatisfactory and tedious method for the preparation of the salt. The situation is, however, highly improved by the fact that the ion pairs may be associated in the organic solvent. Consequently the degree of extraction increases with the concentration of the amine in the extraction system. An increase in concentration is thus very effective in forcing the ion pair into the organic layer. This is readily demonstrated in Fig. 1 which shows the per cent of an amine hydrochloride extracted from dilute phosphoric acid into an equal volume of chloroform. The values are calculated for an extraction constant (E) = 0.1 and different dimerization constants

$$k_2 = [\text{H}_2\text{A}_2\text{X}_2]_{\text{org}} \times [\text{HAX}]_{\text{org}}^{-2}$$

viz. 0, 10^2 , and 10^4 , resp. [For alprenolol, 1-(2-allylphenoxy)-3-isopropyl-amino-propanol-(2), trade name Aptin[®], at $\mu=0.15$ has been found $E=7 \times 10^{-2}$ and $k_2=10^{4.4}$].

The degree of extraction can be further increased by using an excess of anion. If, for instance, a 0.5 M solution of an amine hydrochloride ($E=0.1$, $k_2=10^4$) in dilute phosphoric acid is shaken with chloroform 60 % is extracted (Fig. 1), but with an aqueous phase of 1.5 M HCl the degree of extraction is increased to about 95 %.

It is readily seen that two portions of chloroform will very efficiently extract the amine salt from an acid solution as soon as the concentration of chloride is above 1 M.

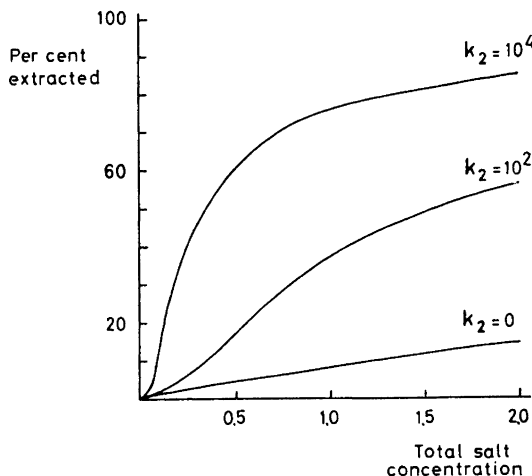


Fig. 1. Per cent amine hydrochloride extracted as a function of concentration, calculated for $E=0.1$ and different k_2 values.

The calculations are based on theories discussed in the references which are mentioned earlier.

From experience ^{4,5,7,8} it has been found that

1. tertiary amines are more easily extracted than secondary and primary amines,
2. salts of most monobasic acids are extracted as easily as or better than the hydrochloride,
3. high molecular weight as well as the absence of hydrophilic groups will support the extractability of the salt,
4. the choice of organic solvent is very important.

The degree of extraction of a solution, 0.5 M in alprenolol and 1.0 M in HCl, when shaken with an equal volume of an organic solvent is given in Table 1.

The following procedures can usually be applied for the preparation of salts of most secondary and tertiary amines with a molecular weight of 250 or higher.

Table 1. Degree of extraction of alprenolol hydrochloride by different solvents.

Solvent	Per cent extracted
CHCl ₃	100
CH ₂ ClCH ₂ Cl	92
CH ₂ Cl ₂	88
CCl ₄	0.6
CHCl=CCl ₂	1.5
CH ₃ COOC ₂ H ₅	16
C ₂ H ₅ OC ₂ H ₅	0.6

With benzene a three layer system was obtained.

EXPERIMENTAL

When an aqueous solution of the acid is available the following procedure A, demonstrated for alprenolol bromide, is convenient. 0.5 mole of the free amine dissolved in a mixture of 250 ml of 48 % hydrobromic acid and 250 ml of water is extracted with 200 + 50 ml of methylene chloride. The combined organic layers are dried with anhydrous magnesium sulphate and evaporated using reduced pressure at the end of the evaporation process. The hydrobromide crystallizes spontaneously and is obtained in quantitative yield; it is recrystallized from ethyl acetate.

When an inorganic salt is available the following procedure B is useful. 0.1 mole of the free amine and 35 g of NaClO₄ are dissolved in a mixture of 125 ml of 1 M H₃PO₄ and 125 ml of H₂O and extracted with 2 × 100 ml of methylene chloride. The combined organic layers are dried with anhydrous magnesium sulphate and evaporated under reduced pressure. On scratching the salt will crystallize in a quantitative yield. The product is dissolved in 100 ml of benzene, diluted with petroleum ether, and chilled. In this way the pure perchlorate will be obtained.

The salts prepared are listed in Table 2.

Table 2. Salts of alprenolol prepared by extraction with chloroform.

Salt	Procedure	Recrystallization solvent	Yield	M.p.	Equivalent found	weight calc.
HCl	A	Acetone	96	107.5	286	286
HBr	A	Ethyl acetate	97	108.5	331	330
HI	A	Ethyl acetate	97	109.9	381	377
HSCN	B	Benzene + petrol ether	93	54.3	306	308
HNO ₃	A	Acetone	87	93.8	308	312
HClO ₄	B	Benzene + petrol ether	97	88.4	347	350
HF ₄	A	Benzene + petrol ether	97	76.9	337	337

The melting points were taken with the Mettler FP1 melting point apparatus.

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