PURIFICATION
OF
LABORATORY CHEMICALS

Second Edition

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Preface to First Edition

WE BELIEVE that a need exists for a book to help the chemist or bio-chemist who wishes to purify the reagents he uses. This need is emphasized by the previous lack of any satisfactory central source of references dealing with individual substances. Such a lack must undoubtedly have been a great deterrent to many busy research workers who have been left to decide whether to purify at all, to improvise possible methods, or to take a chance on finding, somewhere in the chemical literature, methods used by some previous investigators.

Although commercially available laboratory chemicals are usually satisfactory, as supplied, for most purposes in scientific and tech-nological work, it is also true that for many applications further purification is essential.

With this thought in mind, the present volume sets out, firstly, to tabulate methods, taken from the literature, for purifying some thousands of individual commercially available chemicals. To help in applying this information, two chapters describe the more common processes currently used for purification in chemical laboratories and give fuller details of new methods which appear likely to find increasing application for the same purpose. Finally, for dealing with substances not separately listed, a chapter is included setting out the usual methods for purifying specific classes of compounds.

To keep this book to a convenient size, and bearing in mind that its most likely users will be laboratory-trained, we have omitted manip-ulative details with which they can be assumed to be familiar, and also detailed theoretical discussion. Both are readily available elsewhere, for example in Vogel's very useful book Practical Organic Chemistry (Longmans, London, 3rd ed., 1956), or Fieser's Experiments in Organic Chemistry (Heath, Boston, 3rd ed., 1957).

For the same reason, only limited mention is made of the kinds of impurities likely to be present, and of tests for detecting them. In many cases, this information can be obtained readily from existing monographs.

By its nature, the present treatment is not exhaustive, nor do we claim that any of the methods taken from the literature are the best possible. Nevertheless, we feel that the information contained in this book is likely to be helpful to a wide range of laboratory workers, including physical and inorganic chemists, research students, bio-chemists, and biologists. We hope that it will also be of use, although perhaps to only a limited extent, to experienced organic chemists.

We are grateful to Professor A. Albert and Dr D.J. Brown for helpful comment on the manuscript.

Preface to Second Edition

SINCE the publication of the first edition of this book there have been major advances in purification procedures. Sensitive methods have been developed for the detection and elimination of progressively lower levels of impurities. Increasingly stringent requirements for reagent purity have gone hand-in-hand with developments in semiconductor technology, in the preparation of special alloys and in the isolation of highly biologically active substances. The need to eliminate trace impurities at the micro- and nanogram levels has placed greater emphasis on ultrapurification technique. To meet these demands the range of purities of laboratory chemicals has become correspondingly extended. Purification of individual chemicals thus depends more and more critically on the answers to two questions -- Purification from what, and to what permissible level of contamination. Where these questions can be specifically answered, suitable methods of purification can usually be devised.

Several periodicals devoted to ultrapurification and separations have been started. These include "Progress in Separation and Purification" Ed. (vol. 1) E. S. Perry, Wiley-Interscience, New York, vols. 1-4, 1968-1971, and "Separation and Purification Methods", Ed. E. S. Perry and C. J. van Oss, Marcel Dekker, New York, vol. 1 -, 1973 -. Nevertheless, there still remains a broad area in which a general improvement in the level of purity of many compounds can be achieved by applying more or less conventional procedures. The need for a convenient source of information on methods of purifying available laboratory chemicals was indicated by the continuing demand for copies of this book even though it had been out of print for several years.

We have sought to revise and update this volume, deleting sections that have become more familiar or less important, and incorporating more topical material. The number of compounds in Chapters 3 and 4 have been increased appreciably. Also, further details on purification and physical constants are given for many compounds that were listed in the first edition.

We take this opportunity to thank users of the first edition who pointed out errors and omissions, or otherwise suggested improvements or additional material that should be included. We are indebted to Mrs S. M. Schenk who emerged from retirement to type this manuscript.

Contents

CLASSES OF COMPOUNDS (continued)

CHAPTER 1

COMMON PHYSICAL TECHNIQUES
USED IN PURIFICATION

GENERAL REMARKS

Purity is a matter of degree. Quite apart from any adventitious con-
taminants such as dust, scraps of paper, wax, cork, etc., that may
have been incorporated into a sample during manufacture, all commer-
cially available chemical substances are in some measure impure. The
important question, then, is not whether a substance is pure but
whether a particular sample is sufficiently pure for some intended
purpose. That is, are its contaminants likely to interfere in the
process or measurement that is to be studied. By suitable manipulat-
ions it is often possible to reduce levels of impurities to acceptable
limits, but absolute purity is an ideal which, no matter how closely
approached, can never be shown to be attained. A "negative" physical
or chemical test indicates only that the amount of an impurity in a
substance lies below a certain level; no test can demonstrate that a
specified impurity is entirely absent.

When setting out to purify a laboratory chemical, it is desirable that
the starting material should be of the best grade commercially avail-
able. Particularly among organic solvents there is a range of qualit-
ies varying from "laboratory chemical" to "spectrophotometric",
"chromatographic" and "electronic" grades. Many of these are suitable
for use as received. With many of the commoner reagents it is possible
to obtain from current literature some indications of likely impurit-
ies, their probable concentrations and methods for detecting them.
See, for example, Reagent Chemicals (American Chemical Society Spec-
ifications, 5th edn., 1974), the American Society for Testing Mater-
ials D56-36, D92-46, and national pharmacopoeias. Other useful sources
include Analar Standards for Laboratory Chemicals, 7th edn., 1977
(The British Drug Houses Ltd., and Hopkin and Williams Ltd.), and
Reagent Chemicals and Standards, J. Rosin, 5th edn., 1967 (Van
Nostrand, New York). However, in many cases complete analyses are not
given so that significant concentrations of unspecified impurities may
be present.

Solvents and substances that are specified as "pure" for a particular
purpose may, in fact, be quite impure for other uses. Absolute ethanol
may contain traces of benzene, which makes it unsuitable for ultra-
violet spectroscopy, or plasticizers which make it unsuitable for use
in solvent extraction.

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Irrespective of the grade of material to be purified, it is essential that some criteria exist for assessing the degree of purity of the final product. The more common of these include:

1. Examination of physical properties such as

   (a) Melting point, freezing point, boiling point, and the freezing curve (i.e. the variation, with time, in the freezing point of a substance that is being slowly and continuously frozen).

   (b) Density.

   (c) Refractive index at a specified temperature and wavelength. The sodium D line, at 5892.6 Å (weighted mean of D_1 and D_2 lines) is the usual standard of wavelength but results from other wavelengths can often be interpolated from a plot of refractive index versus $1/(wavelength)^2$.

   (d) Absorption spectra (ultraviolet, visible, infrared, and nuclear magnetic resonance).

   (e) Specific conductivity. (This can be used to detect, for example, water, salts, inorganic and organic acids and bases, in non-electrolytes.)

   (f) Optical rotation and circular dichroism.

   (g) Mass spectra.

2. Empirical analysis, for C, H, N, ash, etc.

3. Chemical tests for particular types of impurities, e.g. for peroxides in aliphatic ethers (with acidified KI), or for water in solvents (quantitatively by the Karl Fischer method).

4. Physical tests for particular types of impurities.

   (a) Emission and atomic absorption spectroscopy for detecting and determining metal ions.

   (b) Chromatography, including paper, thin layer, liquid and vapour phase.

   (c) Electron spin resonance for detecting free radicals.

   (d) X-ray spectroscopy.

   (e) Mass spectroscopy.

   (f) Fluorimetry.

5. Electrochemical methods.

6. Nuclear methods.

A substance is usually taken to be of an acceptable purity when the
measured property is unchanged by further treatment (especially if it
agrees with a recorded value). In general, at least two different
methods, such as recrystallization and distillation, should be used
in order to ensure maximum purification. Crystallization may be rep-
eated until the substance has a constant melting point or absorption
spectrum, and a substance may be redistilled in a fractionating
column until it distils repeatedly within a narrow, specified,
temperature range.

With liquids, the refractive index at a specified temperature and
wavelength is a sensitive test of purity. Under favourable conditions,
freezing curve studies are sensitive to impurity levels of as little
as 0.001 moles per cent. (See, for example, Mair, Glasgow and
Rossini, J.Res.Nat.Bur.Stand. 26, 591 (1941).) Analogous fusion curve
or heat capacity measurements can be up to ten times as sensitive as
this. (See, for example, Aston and Fink, Anal.Chem. 19, 218 (1947).)
However, with these exceptions, most of the above methods are rather
insensitive, especially if the impurities and the substances in which
they occur are chemically similar. In some cases, even an impurity
comprising many parts per million of a sample may escape detection.

The common methods of purification, discussed below, comprise distill-
ation (including fractional distillation, distillation under reduced
pressure, sublimation and steam distillation), crystallization,
extraction and chromatographic adsorption. In some cases, volatile
impurities (including water) can be removed by heating. Impurities
can also sometimes be eliminated by the formation of derivatives from
which the purified material is recovered.

Safety in the Chemical Laboratory

Although most of the manipulations involved in purifying laboratory
chemicals are inherently safe, it remains true that care is necessary
if hazards are to be avoided in the chemical laboratory. In partic-
ular there are dangers inherent in the inhalation of vapours and
absorption of liquids through the skin. To the toxicity of solvents
must be added the risk of their flammability and the possibility of
eye damage. Chemicals, particularly in admixture, may be explosive.
Compounds may be carcinogenic or otherwise deleterious to health. The
use of radio-isotopic labelling poses problems of exposure and of
disposal of laboratory waste.

At the least the laboratory should be well ventilated and safety
glasses should be worn, particularly during distillation and manipul-
ations carried out under reduced pressure or elevated temperatures.
With this in mind we have endeavoured to warn users of this book
whenever greater than usual care is needed in handling chemicals. As
a general rule, however, all chemicals which are unfamiliar to the
user should be treated with great care and assumed to be highly
flammable and toxic.

Trace Impurities in Solvents

Some of the more obvious sources of contamination of solvents arise
from storage in metal drums and plastic containers and from contact
with grease. Many solvents contain water. Others have traces of acidic

materials such as hydrochloric acid in chloroform. In both cases this leads to corrosion of the drum and contamination of the solvent by traces of metal ions, especially Fe^{3+}. Grease, for example on the stopcocks of separating funnels and other apparatus is also likely to contaminate solvents during extractions and other chemical manipulation.

A much more general source of contamination that has not received the consideration it merits comes from the use of plastics for tubing and containers. Plasticizers can readily be extracted by organic solvents from PVC and other plastics, so that most solvents, irrespective of their grade (including spectrograde and ultrapure) have been reported to contain 0.1 to 5 p.p.m. of plasticizer (de Zeeuw, Jonkman and van Mansvelt, Anal.Biochem., 67, 339 (1975)). Where large quantities of solvent are used for extraction (particularly of small amounts of compounds), followed by evaporation, this can introduce significant amounts of impurity, even exceeding the weight of the genuine extract and giving rise to spurious peaks in gas chromatography (for example, of fatty acid methyl esters (Pascaud, Anal.Biochem., 18, 570 (1967)). Likely contaminants are di(2-ethylhexyl)phthalate and dibutyl phthalate, but upwards of 20 different phthalic acid esters are listed as plasticizers as well as adipates, azelates, phosphates, epoxides, polyesters, trimellitates, and various heterocyclic compounds. These plasticizers would enter the solvent during passage through plastic tubing or containers or from plastic coatings used on cap liners for bottles. Such contamination could arise at any point in the manufacture or distribution of a solvent. The trouble with cap liners is avoidable by using corks wrapped in aluminium foil.

Solutions in contact with polyvinyl chloride may become contaminated with trace amounts of lead, titanium, tin, zinc, iron, magnesium or cadmium from additives used in the manufacture and moulding of PVC.

N-Phenyl-2-naphthylamine is a contaminant of solvents and biological materials that have been in contact with black rubber or neoprene (in which it is used as an antioxidant). Although it was only an artefact of the separation procedure it has been isolated as an apparent component of vitamin K preparations, extracts of plant lipids, algae, livers, butter, eye tissue and kidney tissue (Brown, Chem.Brit. 3, 524 (1967)).

Most of the above impurities can be removed by prior distillation of the solvent, but care should be taken to avoid plastic or black rubber as much as possible.

On Cleaning Apparatus

Laboratory glassware and Teflon equipment can be cleaned satisfactorily for most purposes by treating initially with a solution of sodium dichromate in concentrated sulphuric acid, draining, and rinsing copiously with distilled water. Where traces of chromium (adsorbed on the glass) must be avoided, a 1:1 mixture of concentrated sulphuric and nitric acid is a useful alternative. (Used in a fumehood to remove vapour and with adequate face protection. Acid washing is also suitable for polyethylene ware but prolonged contact (some weeks) leads to severe deterioration of the plastic.) For much glassware, washing with hot detergent solution, using tap water, followed by rinsing with distilled water and acetone, and heating to 200-300°

overnight, is adequate. (Volumetric apparatus should not be heated: after washing it is rinsed with acetone, then hexane, and air-dried. Prior to use, equipment can be rinsed with acetone, then with petroleum ether or hexane, to remove the last traces of contaminants.) Teflon equipment should be soaked, first in acetone, then in petroleum ether or hexane for 10 minutes prior to use.

For trace metal analyses, prolonged soaking of equipment in 1M nitric acid may be needed to remove adsorbed metal ions.

Soxhlet thimbles and filter papers contain traces of lipid-like material; for manipulations with highly pure materials, as in trace-pesticide analysis, they should be extracted before use using hexane.

Trace impurities in silica gel for TLC can be removed by heating at 300° for 16 hours or by Soxhlet extraction for 3 hours with redistilled chloroform, followed by 4 hours extraction with redistilled hexane.

DISTILLATION

One of the most widely applicable and most commonly used methods of purification (especially of organic chemicals) is fractional distillation at atmospheric, or some lower, pressure. Almost without exception, this method can be assumed to be suitable for all organic liquids and most of the low-melting organic solids. For this reason it has been possible in Chapter 3 to omit procedures for purification of organic chemicals when only a simple fractional distillation is involved—the suitability of such a procedure is implied from the boiling point.

The boiling point of a liquid varies with the atmospheric pressure to which it is exposed. A liquid boils when its vapour pressure is the same as the external pressure on its surface, its normal boiling point being the temperature at which its vapour pressure is equal to that of a standard atmosphere (760 mm Hg). Lowering the external pressure lowers the boiling point. For most substances, boiling point and vapour pressure are related by an equation of the form,

$$\log \underline{p} = A + B/(\underline{t} + 273),$$

where p is the pressure, $\underline{t}$ is in ^{o}C, and A and B are constants. Hence, if the boiling points at two different pressures are known the boiling point at another pressure can be calculated from a simple plot of log p versus $1/(\underline{t} + 273)$. For organic molecules that are not strongly associated, this equation can be written in the form,

$$\log \underline{p} = 8.586 - 5.703 \ (\underline{T} + 273)/(\underline{t} + 273)$$

where $\underline{T}$ is the b.pt. in ^{o}C at 760 mm Hg. Table 1 gives computed b.pts over a range of pressures. Some examples illustrate its application. Ethyl acetoacetate, b.pt 180° (with decomposition) at 760 mmHg has a predicted b.pt. of 79° at 8 mm; the experimental value is 78°. Similarly, 2,4-diamino-toluene, b.pt. 292° at 760 mm Hg, has a predicted b.pt. of 147° at 8 mm.; the experimental value is 148-50°. For self-associated molecules the predicted b.pts. are lower than the experimental values. Thus, glycerol, b.pt. 290° at 760 mm Hg, has a predicted b.pt. of 168° at 20 mm Hg: the experimental value is 182°.

For pressures near to 760 mm, the change in boiling point is given approximately by (Crafts, Ber. 20, 709 (1887))

$$\Delta t = a(760 - p)(t + 273)$$

where a = 0.00012 for most substances, but a = 0.00010 for water, alcohols, carboxylic acids and other associated ligands, and a = 0.00014 for very low-boiling substances such as nitrogen or ammonia.

When all the impurities are non-volatile, simple distillation is an adequate purification. The observed boiling point remains almost constant and approximately equal to that of the pure material. Usually, however, some of the impurities are appreciably volatile, so that the boiling point progressively rises during the distillation because of the progressive enrichment of the higher-boiling components in the distilling flask. In such cases, separation is effected by fractional distillation using an efficient column.

The principle involved in fractional distillation can be seen by considering a system which approximately obeys Raoult's law. (This law states that the vapour pressure of a solution at any given temperature is the sum of the vapour pressures of each substance multiplied by its mole fraction in the solution.) If two substances, A and B, having vapour pressures of 600 mm Hg and 360 mm Hg, respectively, were mixed in a mole ratio of 2:1, the mixture would have (ideally) a vapour pressure of 520 mm Hg and the vapour phase would contain 77% of A and 23% of B. If this phase was now condensed, the new liquid phase would, therefore, be richer in the volatile component A. Similarly, the vapour in equilibrium with this phase is still further enriched in A. Each such liquid-vapour equilibrium constitutes a "theoretical plate". The efficiency of a fractionating column is commonly expressed as the number of such plates to which it corresponds in operation. (Alternatively, this information may be given in the form of the height equivalent to a theoretical plate, or HETP.)

In most cases, systems deviate to a greater or less extent from Raoult's law, and vapour pressures may be greater or less than those calculated from it. In extreme cases, vapour pressure-composition curves pass through maxima or minima, so that attempts at fractional distillation lead finally to the separation of a constant-boiling (azeotropic) mixture and one (but not both) of the pure species if either of the latter is present in excess.

Technique.

Distillation apparatus consists basically of a distilling flask, usually fitted with a vertical fractionating column (which may be empty or packed with suitable materials such as glass helices or stainless-steel wool) to which is attached a condenser leading to a receiving flask. The bulb of a thermometer projects into the vapour phase just below the region where the condenser joins the column. The distilling flask is heated so that its contents are steadily vaporized by boiling. The vapour passes up into the column where, initially, it condenses and runs back. The resulting heat transfer gradually warms the column so that there is a progressive movement of the vapour phase-liquid boundary up the column, with increasing

enrichment of the more volatile component. Because of this fraction-ation, the vapour finally passing into the condenser (where it con-denses and flows into the receiver) is commonly that of the lowest-boiling material in the system. The conditions apply until all of the low-boiling material has been distilled, whereupon distillation ceases until the column temperature is high enough to permit the next comp-onent to distil. This usually results in a temporary fall in the temperature indicated by the thermometer.

The efficiency of a distillation apparatus used for purification of liquids depends on the difference in boiling points of the pure material and its impurities. For example, if two components of an ideal mixture have vapour pressures in the ratio 2:1, it would be necessary to have a still with an efficiency of at least seven plates (giving an enrichment of $2^7 = 128$) if the concentration of the higher-boiling component in the distillate was to be reduced to less than 1% of its initial value. For a vapour pressure ratio of 5:1, three plates would achieve as much separation.

In a fractional distillation, it is usual to reject the initial and final fractions, which are likely to be richer in lower-boiling and higher-boiling impurities. The centre fraction can be further purified by repeated fractional distillation.

To achieve maximum separation by fractional distillation:

1. The column must be flooded initially to wet the packing. For this reason it is customary to operate a still at reflux for some time before beginning the distillation.

2. The reflux ratio should be high, so that the distillation proceeds slowly and with minimum disturbance of the equilibria in the column.

3. The hold-up of the column should not exceed one-tenth of the volume of any one component to be separated.

4. Heat loss from the column should be prevented but, if the column is heated to offset this, its temperature must not exceed that of the distillate in the column.

5. Heat input to the still-pot should remain constant.

6. For distillations under reduced pressure there must be careful control of the pressure to avoid flooding or cessation of reflux.

Distillation at Atmospheric Pressure

The distilling flask. To minimize superheating of the liquid (due to the absence of minute air bubbles or other suitable nuclei for forming bubbles of vapour), and to prevent bumping, one or more of the following precautions should be taken:

(a) The flask is heated uniformly over a large part of its surface, either by using an electrical heating mantle or, much better, by partial immersion in a bath heated somewhat above the boiling point of the liquid to be distilled.

(b) Before heating begins, small pieces of unglazed fireclay
    or porcelain ("porous pot", "boiling chips"), pumice,
    carborundum, Teflon, diatomaceous earth, or platinum wire
    are added to the flask. (They act as sources of air bubbles.)

(c) The flask may contain glass siphons or boiling tubes. The
    former are inverted J-shaped tubes, the end of the shorter
    arm being just above the surface of the liquid. The latter
    comprise long capillary tubes sealed above the open lower end.

(d) A steady slow stream of gas is passed through the liquid.

(e) In some cases zinc dust can also be used. It reacts
    chemically with acidic or strongly alkaline solutions
    to liberate fine bubbles of hydrogen.

(f) The liquid in the flask is stirred mechanically. This is
    especially necessary when suspended insoluble material is
    present.

For simple distillations a Claisen flask (see, for example, Quickfit
and Quartz Ltd. catalogue of interchangeable laboratory glassware, or
Kontes Glass Co., Vineland, New Jersey, cat.no. TG-15) is often used.
This flask is, essentially, a round-bottomed flask to the neck of
which is joined another neck carrying a side arm. This second neck is
sometimes extended so as to form a Vigreux column.

For heating baths, see Table 2. For distillation on a semi-micro
scale, see Linstead, Elvidge and Whalley, 1955.

   Types of columns and packings. A slow distillation rate is necessary
to ensure that equilibrium conditions operate and also that the vapour
does not become superheated so that the temperature rises above the
boiling point. Efficiency is improved if the column is heat insulated
(either by vacuum jacketing or by lagging) and, if necessary, heated
to just below the boiling point of the most volatile component.
(Electrical heating tape is convenient for this purpose.) Efficiency
of separation also improves with increase in the heat of vaporization
of the liquids concerned (because fractionation depends on heat
equilibration at multiple liquid-gas boundaries). Water and alcohols
are more easily purified by distillation for this reason.

Columns used in distillation vary in their shapes and types of
packing. Packed columns are intended to give efficient separations by
maintaining a large surface of contact between liquid and vapour.
Efficiency of separation is further increased by operating under con-
ditions approaching total reflux. (That is, under a high reflux ratio.
The reflux ratio is the volume of the condensate that is returned
(as reflux) to the distilling flask divided by the volume of liquid
that is allowed to distil over.) Better control of reflux ratio is
achieved by fitting a total condensation, variable take-off, still-
head (see, for example, catalogues by Quickfit and Quartz, or Kontes)
to the top of the fractionating column. However, great care must be
taken to avoid flooding of the column during distillation. The
minimum number of theoretical plates for satisfactory separation of
two liquids differing in boiling point by Δt is approximately $(273 + t)$
$/3\Delta t$, where t is the average boiling point in $^{\circ}C$.