cible, differing appreciably in polarity but little in vapour pressure. Suitable pairs can be chosen from solvents such as cyclohexane, ethyl acetate, carbon tetrachloride, acetone, chloroform and hexane. Bottles containing such mixtures in different proportions should be kept ready for use. Frequently a pair containing diethyl ether may give better resolution but cannot be kept for long (enrichment by the higher boiling partner, peroxide formation), and should be used only in a tightly closed vessel.

TLC of carboxylic acids and other highly polar compounds usually results in streaks and otherwise poorly resolved spots. What works well in such cases is a mixture of a non-polar solvent with a small amount of acetic or formic acid. For example, diisopropyl ether and acetic acid in ratios ranging from 99:1 to 90:10 on silica plates can give well defined spots with carboxylic acids of higher molecular weight. Such mixtures must be kept in tightly closed vessels, preferably under argon (danger of peroxide formation).

Multiple development is a technique which in effect increases the height of the TLC plate, although this does not mean that in practice the same effect is obtained by a plate 50 cm in height. Find out which solvent combination (say ethyl acetate–cyclohexane, 1:3) gives an R_F value of ca 0.4–0.5 after one development. Then use a combination which doubles the relative amount of the non-polar component (i.e. to 1:6), and develop the plate in this three or four times, drying lightly but not completely after each development. In this way greatly improved resolution will be obtained.

On the whole there is little sense in recording R_F values for future use unless with reference to a standard substance run on the same plate at the same time, because they can differ greatly from day to day depending on atmospheric conditions (temperature and humidity).

Visualisation

This depends very much on the chemical nature of the

substance(s) on the palte and, since this may differ a great deal between the components of a mixture, one should never rely on one method of visualisation alone. Fluorescence quenching observed on examination under UV light is restricted to substances with chromophoric groups, and the intensity of the spots observed will differ according to the nature of these—groups and of course components having no such groups will hardly show up at all. Staining by iodine double bonds and very strong with compounds containing isolated double bonds and very weak with those containing aromatic rings (which, of course, show strongly under UV light). Compounds that have only functional groups such as ester, carboxylic acid or nitrile can hardly be discerned by either method. Hence, in order to get a complete picture, the first examination should be under UV light, with a note made of the findings, then in an iodine vapour chamber, and, to make quite sure, another plate should be treated after drying with a desctructive agent such as sulphuric acid and/or acidic cerium(IV) sulphate (an exhaustive list is given in most books on the subject). Only then can you come to some conclusion regarding relative amounts of products.

Following a Reaction by TLC

This is one of the most useful applications of the technique and probably the mildest and most convenient tool available when trying to optimise reaction conditions (solvent, time, temperature, relative proportions of reactants) by trial experiments. Gas chromatography (GC) does have the advantage of giving a quantitative picture (although under the dubious assumption that on direct injection of a reaction mixture the course of the reaction is frozen), but it takes far less time to find a suitable TLC solvent and plate than to establish the right GC column filling, oven temperature and flow-rate. The third alternative, of using spectroscopic methods (IR, NMR) means having to allow for interference by solvent and other components of the mixture.

Indeed, when planning reaction conditions, TLC follow-up

should be one of the factors to be kept in mind. This means choosing a suitable concentration and taking into account the nature of the solvent. A high-boiling solvent will usually interfere in that it is difficult to dry off completely on the plate, and will drag spots along with it, resulting in a dreadful smear. Dimethylformamide, dimethyl sulphoxide and hexamethylphosphorotriamide are specific offenders in this regard. Sometimes this can be corrected for by changing the nature of the plate, for example from silica to alumina. This may be essential anyway when, for example, the course of an acid-catalysed reaction is being followed. Here only alumina plates which instantly neutralise the catalyst will give a true picture. On silica the reaction can proceed further on the plate itself, and at a rate significantly faster than in the reaction mixture. Other cases where one has to think ahead are where one or more components are present not in the free state but, say, as enolates. Sometimes instant protonation occurs on the (water-containing) silica plate which solves the problem; in others it may be necessary to submit a drop of the reaction mixture to a micro-work-up in a micro-centrifuge tube.

Above all, you should remember that the picture you actually get when trying to gauge the progress of a reaction is *that of the contents of the capillary at the moment of application to the TLC plate* (and of what happens on the plate subsequently). Statements such as 'the reaction mixture was kept at $-40\ ^{\circ}C$ until TLC showed reaction to be complete' are complete nonsense unless your laboratory is somewhere in Siberia in the middle of January in an open field. If you should follow such a procedure, naturally keeping the temperature as low as possible during work-up, you will most likely discover that nothing at all has happened. All that is even more likely when following such a reaction by GC.

Other Considerations

TLC can help you determine to what extent a product or product mixture is sufficiently stable to survive protracted

purification by column chromatography or high-performance liquid chromatography (HPLC). Instability is not sufficiently indicated by one TLC development or even two. What you should do, if instability is suspected, is to make one development, leave the plate overnight (best under argon in a desiccator), and then do another development the following morning. Compare the result with that of two developments done one after the other.

Always keep on hand TLC samples from every significant experimental run—starting material, intermediate stages and crude product—until your project has come to a conclusion either in the form of writing up for publication or by being irrevocably abandoned. You can be sure there will be a time when you will wish you had not thrown that sample down the sink .... Obviously that is what should be done with leftover or recovered sample solutions from spectroscopic examination. They are best kept for that purpose in 1 dram screw-capped vials which take up little space but are yet large enough to carry a legible label or serial number.

Preparative Thin-Layer Chromatography

In many places this technique is being superseded by either HPLC or by the 'Chromatotron' which is simply a clever, speeded-up (and expensive) version of preparative TLC. However, that brings to mind the very advantage of the older technique. The fact that a preparative plate can take up to 2 h for development and needs no attention whatever during that time means that you can kill two birds with one stone: separate a mixture and do something else of a constructive nature at the same time.

The problem, however, is that of visualisation. When the product has chromophoric groups there is no problem except if by any chance there are additional products not in that category. When the components are coloured in the visible region one is often tempted to preserve the plate for posterity as the *dernier cri* in post-impressionist painting. When there are no

chromophoric groups there are only two possible solutions. One is to run a single spot of the mixture on the plate alongside the streak of the bulk of the product (see Fig. 6, where there are two holes, one each side, for that purpose) and expose this to a spray or to iodine vapour while keeping the bulk portion of the plate covered. This is on the assumption that all the main zones will be parallel to the spots, which is true only if the plate is of the highest quality and the product main solution is applied with an automatic streaking or dropping device. The other way out of the dilemma is to divide the plate arbitrarily into a large number of sections, extract each separately and subject all extracts to analytical TLC systematically.

An important thing to remember is that adsorbed compounds are very sensitive to air oxidation and more so at higher temperature. Hence, when subjecting preparative plates to multiple development, in-between drying should be done as quickly as possible and never to complete dryness.

Elution of scraped-off sections is best done by Soxhlet extraction. The thimble should be as small as possible in order to economise on the amount of solvent needed; dead space can be filled up by clean glass beads. Many extraction solvents may slightly dissolve or otherwise carry over traces of the adsorbent; hence the solution after concentration should be filtered through a very small 'column' inside a capillary pipette (cf. Fig. 3).

COLUMN CHROMATOGRAPHY

Columns and Adsorbents

As is well known, for a given amount of adsorbent, columns of smaller diameter effect better separation but have lower capacity and are slower to develop. As the diameter of the column is increased these properties are reversed. A compromise solution that has received comparatively little attention is that of the multibore column[51] as shown in Fig. 7. None of these are available commercially, but construction by a glassblower is not much of a problem. In these the diameter of each portion is in the ratio of ca 1.4:1 to the adjoining one.

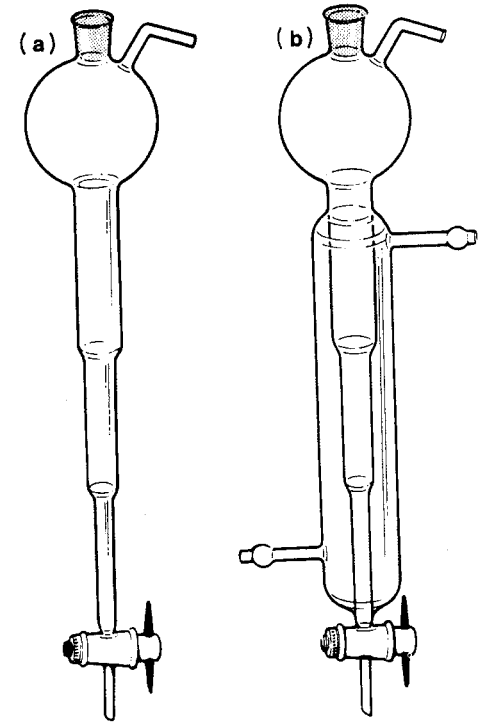


Fig. 7.

These columns are appreciably better at separation than the ordinary ones with uniform diameter. Moreover, there is surprisingly little difference in flow-rate with different amounts of adsorbent. A column such as those shown, with lengths of sections of 12, 12 and 13 cm and outer diameters of 1.2, 1.7 and 2.4 cm, respectively, can serve for quantities of between 5 and 40 g of silica; when using 'gradient elution' (see below), the amount of adsorbent necessary for an average good separation rarely has to be greater than 15 g per gram of substrate. This should be compared with the 50–100-fold quantity required in

'flash chromatography',[52] moreover, the claim advanced for the latter technique that the adsorbent can be used many times over is not often borne out by actual experience. When working in a hot climate the use of a water-jacketed column [Fig. 7(b)] may become imperative, and may be good policy in general, since exothermic adsorption of a substrate is the most common cause of 'cracking' of a column.

There is no practical alternative to Teflon stopcocks for chromatographic columns, certainly for your peace of mind when a separation has to be interrupted even for going to lunch. Glass stopcocks cannot be greased for obvious reasons, and even the use of spherical joints and interruption of flow by inclining the socket portion upward does not guarantee against leakage.

Adsorbents should be obtained only from well established firms who have a reputation to keep up—this is one of those items which you cannot 'purify'. When purchased they should be of activity I. A quick way to test for this[53] is the yellow colour which should appear on shaking with a 1% solution of chlorotriphenylmethane in benzene, which is absent if more than 0.5% water is present. However, for actual use in chromatography they have to be deactivated in a specific manner, by mixing with the specified amount of water. The best way to do this is a closed jar on a ball-mill (without the balls), or in a large flask attached firmly and in a nearly horizontal position to a rotary evaporator (without applying vacuum). In both cases a speed of not more than 1 rev. s^{-1} should be used, and 2 h is usually sufficient. A fluorescent indicator can be incorporated at the same time, and for adsorbents to be impregnated with silver nitrate[54] (for separation of olefins) the latter can be dissolved in the water used for deactivation.

The way to fill a column depends on the adsorbent. In the case of silica and Florisil these should be slurried in hexane in an amount sufficient to pour most if not all the suspension into the column in one go. For alumina it is best to add this in a fine stream from a separating funnel with a non-greased stopcock into the column containing at least 3 ml solvent per gram of adsorbent used. Only after that should the hexane be replaced

gradually by the initial solvent mixture (if more polar) used. In all cases the column should be perfectly vertical and vibrated by hand or with an electric vibrator to encourage even settling. The most critical portion of the column is the very top. Its homogeneity and levelness will predetermine whether the zones will elute in sequence or not. For this reason it is inadvisable to disturb this layer such as by adding another layer of sand. Everything depends on how carefully the substrate solution is added by capillary pipette down the sides while there is still a sufficient head of solvent. Any resinous material which might clog the top layer should have been removed by the preliminary purification.

Elution Order and Choice of Adsorbent

Roughly, and in general, functional groups in an organic compound contribute to its retention in the following order: halide < hydrocarbon < olefin < ether < nitro < ketone < carboxylic ester < aldehyde < amine < tertiary amide < secondary amide, lactone < alcohol, primary amide < phenol < carboxylic acid.

On silica amines may be more strongly retained than is indicated. Another general factor is the relative proportion of the functional and the non-functional part of the molecule. For example, a butyl ester is less strongly adsorbed than the corresponding methyl ester, and a neopentyl glycol acetal less than the dimethyl acetal. A mixture of olefinic alcohols is separated much better after conversion into the corresponding acetates or methoxymethyl ethers, in particular when using silver nitrate-impregnated adsorbent. Often, such functional modification can be planned both to facilitate separation and as part of the synthetic pathway, e.g. ketone → mixture of acetals with chiral glycol → chromatographic separation of diastereomers and resolution → halogenation of acetal. As a general principle, the functional group which is the most polar one should be modified to give a less retentive group.

Silica and to a lesser extent alumina are now the most com-

monly employed adsorbents; the last 10 years have seen a great improvement in the quality and variety (activity, mesh size, etc.) over those encountered in the past. However, one keeps coming across examples in the literature[55] of decomposition of compounds on these adsorbents, and of solving the problem by use of Florisil, a naturally occurring magnesium silicate, which, for example, is found not to cause epimerisation next to a carbonyl group, or opening of a sensitive epoxide ring. Indeed, specially prepared magnesium silicate for chromatography, although very expensive, can be greatly superior in the separation of difficult to separate compounds whether sensitive to decomposition or not.

Elution Solvents

Many books show a table of elutropic order of solvents,[56] with some differences apparent from one book to another. It must be remembered that this holds in any case only for absolutely pure solvents. Traces of ethanol (as stabiliser) in either diethyl ether or chloroform may strongly modify the position of these solvents in the elutropic series. Further, for accurate and reproducible work it may be necessary to use solvents which are 'isotonic' with regard to the adsorbent, i.e. which contain a requisite amount of water,[57] otherwise desorption of water from the adsorbent which had been used for deactivation may occur at certain eluent compositions and lead to a sudden and sometimes drastic change in activity.

The best course of action is to choose a mixture of two solvents which differ widely in boiling point (which also makes recovery easier) and differ fairly widely in polarity, with the less polar one preferably of higher boiling point. An excellent pair is dichloromethane–hexane with increasing proportions of the former, followed by dichloromethane–chloroform (containing ca 1% ethanol for stabilisation—the commercial grade). The procedure to follow is to start by dissolving the mixture of products in ca 2 ml/g^{-1} of dichloromethane, then add hexane up to beginning turbidity, and to use that combination as the starting

eluent. If the components to be separated are of relatively non-polar nature as evidenced by the TLC plate, then elution should be continued with a fairly large amount of the same solvent combination, or one can even go back to a less polar eluent, i.e. containing relatively more hexane; if not, then one can go over to gradually increasing the proportion of dichloromethane, with more graduality on approaching the 1:1 ratio. The gradual increase of the more polar solvent can be automated by devices ensuring 'gradient elution'[58] in which the proportion of solvents is made to vary continuously and not step-by-step. Hexane, in this connection, refers to what are commonly termed 'hexanes', or light petroleum of b.p. 50–70 °C. Acetone should be avoided because of its possible reactivity on the adsorbent, with itself and possibly with the substrate, and even ethyl acetate, which is an excellent component solvent for TLC, may cause complications in chromatography such as transesterification of esters.

Fraction Collection

The feast of gadgeteering in this connection has now ended, except in certain modifications of the chromatographic technique. This is because it is feasible only when fractions are collected in test-tubes, from which evaporation of solvent is difficult and necessitates transfer to a flask. This has meant that anyone religiously monitoring fractions by TLC has been wasting a lot of time and TLC plates on fractions containing nothing at all. It is better to see as soon as possible whether anything is coming off the column, and that means collecting in flasks. These should be of 50, 100 and 250 ml capacity, depending on the scale of material used; those without a standard joint cost only half to one third of the variety with such a joint. They should be wired, with a ring and/or hook so as to enable them to be hung on a wire (see Chapter 4, Fig. 1, item c), and evaporation on a rotary evaporator can be done by a suitable adapter which is attached to the flask by means of a section of thick rubber latex tubing (probably best as far as resistance to solvent attack is concerned) as shown in Fig. 8. When evapor-

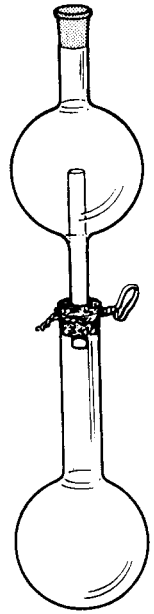


Fig. 8.

ation shows that material has been eluted, solvent is added (more if crystallisation indicates a more or less homogeneous fraction, less if a mixture of products is suspected), and a TLC sample can be taken by lowering the micropipette in its applicator using a long pair of forceps.

Carboxylic Acids

Column chromatography of carboxylic acids is a problem because they tend to smear with the usual eluents just as they do on a TLC plate unless a non-polar eluent containing 1–5% of either formic or acetic acid is used. That means that on evaporation of fractions these addends are left and would either have to be removed *in vacuo* or azeotropically with toluene. Another remedy would appear to be to use adsorbents previously treated with methanol.[59] There is, however, a different

method of 'fractionation' of carboxylic acids, that of fractional extraction:

> the crude mixture (e.g. 20 mmol) dissolved in a solvent such as *tert*-butyl methyl ether is shaken with small portions (say 4 ml) of 3% sodium hydrogencarbonate and each extract is back-extracted with more solvent. Each consecutive extract is acidified separately. When the amount of product obtained decreases, one should proceed to 6% sodium hydrogencarbonate, then to 10%, then to 3% sodium carbonate and so forth, up to reaching 5% sodium hydroxide. Each acidified fraction can be examined separately by TLC. This method has given excellent results with both highly coloured impure products which could not be purified by Kugelrohr distillation, and even with mixtures of different acids.

ON GETTING YOUR PRODUCT CRYSTALLINE

This is where the men are separated from the boys and where organic chemistry is not a science at all. It was said of Adolf von Baeyer that his success was in large measure due to his large beard harbouring seeds of every compound he ever made. Beards are indeed again in fashion—unfortunately that does not seem to have contributed to the experimental skill of the average young organic chemist. In fact, in many research groups there appears to prevail an attitude of disdain towards the crystalline compound—all that seems to matter is the 400 MHz NMR spectrum. The fact that both matter soon dawns on whoever emerges into the real world.

Which Solvent Should I Use?

At the outset a distinction must be made between getting a compound crystalline, and recrystallising it. Rarely is a given solvent suitable for both.

The former requires a good solvent (at any rate, to start with) for the gum or oil which you want to crystallise (assuming that

TLC and/or GC shows it to be a single compound), one which itself has a low freezing point and low viscosity right through its liquid range, and high volatility. A prime example is diethyl ether, followed closely by *tert*-butyl methyl ether. That is for active attempts at crystallisation, which means cooling the concentrated solution right down to -100 °C, and scratching all the time while the solution is warming up. The scratching should be done not with a glass rod but with a micro-spatula, because with that you can get around bends, and it is at the bend of a round-bottomed flask, where the round portion ends and the straight part begins, and where the glass is roughened by previous scratching, that crystallisation usually begins.

The passive approach to crystallisation is to dissolve the gum in a good solvent, add some 'bad' solvent, such as hexane, and leave the flask open during the weekend. That may sound shocking, but it usually works. Slow evaporation, together with nucleation by dust, can work hand in hand. Leaving the flask in the refrigerator not only prevents both, but leads to greater viscosity of the medium. Of course, these remarks apply only to compounds in which instability (to temperature and oxygen) is not suspected; if so, it would be best to leave the compound dissolved in the minimum amount of diethyl ether in the freezer.

Solvents for Recrystallisation

Here again there are two main categories: (1) Single-solvent recrystallisation and (2) recrystallisation by a solvent pair (and occasionally trio).

For (1), the single solvent must exhibit as steep a solubility–temperature gradient as possible. Of course this depends to a large extent on the solute, but there are many solvents which in principle are bad ones in that respect. Often it takes some time to find the right one for any given compound, which is the reason why most first attempts at recrystallisation are by approach (2), dissolving in a low-boiling solvent which is a good one (e.g. dichloromethane), and replacing it by a high-boiling bad solvent (e.g. hexane or cyclohexane).

Perhaps it might be best to give a brief overview, based on some years of the author's experience, of the most common solvents used for recrystallisation, and what kinds of compounds they are good for, in rough order of their polarity:

Hexane, cyclohexane, heptane: as single solvents for compounds of moderate polarity (alcohols, aldehydes, ketones, amines, esters, nitriles, acyl chlorides), of m.p. 50–80, 80–100 and 100–120 °C, respectively.

Diisopropyl ether: an excellent single solvent for the above and compounds of greater polarity (e.g. unsaturated ketones) of m.p. below 80 °C, where the use of hexane may cause 'oiling out'; may need cooling to 0 °C or even below to give maximum recovery. Must be tested frequently for peroxides!

Benzene: a bad solvent for single-solvent recrystallisation, mainly because crystallisation in it is slow and it is more viscous. Also suspected to be a carcinogen—it should be used as little as possible; it is banned in many laboratories.

Toluene: better than benzene because it is higher boiling and considered to be non-toxic (at time of writing this section!). Good as a single solvent for compounds of higher polarity (carboxylic acids, amides, lactones, polyfunctionals, e.g. hydroxyketones, ketonitriles) of higher m.p. (above 150 °C).

Carbon tetrachloride: often a surprisingly good single solvent for compounds of higher polarity (sulphonyl chlorides, unsaturated ketones and unsaturated aldehydes, alcohols) of m.p. below 100 °C; good for decolorisation by charcoal. Disadvantages: crystallisation may be slow, product swims on top and hence removal of mother liquor by pipette may be difficult. May need cooling and addition of hexane to ensure maximum recovery with low-melting solutes.

Diethyl ether, tert-*butyl methyl ether*: rarely suitable as single recrystallisation solvents, and then only by using the range -30 °C (freezer temperature) to $+30$ °C.

Dichloromethane, chloroform: too good solvents to be suitable for single-solvent recrystallisation, but the ideal first components for solvent-pair recrystallisation. A less good solvent but higher boiling is: 1,2-dichloroethane. Trichloroethylene is probably toxic.

Tetrahydrofuran: a special case. An excellent solvent in particular for polar polyfunctional compounds, particularly dicarboxylic acids, keto acids of m.p. above 150 °C (owing to solvation). Rarely good as a single solvent, but excellent as the first component in a solvent pair for such compounds, e.g. in THF–toluene or THF–cyclohexane.

Acetone: As for THF in many respects, but often unsuitable because of its reactivity. Much better as a solvent, although not for single-solvent recrystallisation, because it is higher boiling, is butan-2-one (ethyl methyl ketone).

Ethyl acetate: Often surprisingly good as single-solvent recrystallisation candidate for moderately polar compounds of m.p. 100–150 °C. Excellent as the first component in solvent pair such as ethyl acetate–cyclohexane, especially for fractional crystallisation. Has to be used with caution for recrystallising compounds containing ester groups because of possible transesterification.

Methanol: For non-polar compounds (hydrocarbons, olefins, aromatics, nitro compounds, halides) as a single solvent, sometimes the only one feasible for compounds in which the non-polar part is predominant (e.g. steroids). If necessary, and for higher-melting compounds of that type, as the second component in solvent-pair crystallisation (e.g. diethyl ether–methanol, dichloromethane–methanol). Good also for low-temperature recrystallisation of more polar compounds (ketones, aldehydes, enones) because it retains coloured and polar impurities; provided crystals formed are such that the mother liquor can be removed by pipette.

Ethanol, isopropanol: as for methanol, although less polar as solvents, particularly isopropanol. More viscous than methanol and hence crystallisation is slower. Isopropanol is a good compromise recrystallisation solvent for high-melting polar compounds containing coloured impurities.

Pyridine, dimethylformamide, nitromethane: often the solvents of last resort in cases of high-melting insoluble compounds of whatever intrinsic polarity.

Acetic acid: good as a single recrystallisation solvent for other carboxylic acids of high m.p. and also, surprisingly for relatively non-polar compounds of m.p. 100–150 °C.

Proper Tools and Technique for Recrystallisation

When finally collecting your product for recrystallisation, after chromatography or other methods of purification such as Kugelrohr distillation or sublimation, the size of the flask used should bear a reasonable relationship to the total amount. For instance, 25 mg should never be in a flask of over 10 ml capacity. And before recrystallisation, never forget to keep a seed crystal (e.g. from one of the chromatographic fractions).

From the list of solvents for recrystallisation given above it can be seen that the majority boil below 100 °C, i.e. can be used on a steam-bath, which is also the safest way of heating. The trouble with steam-baths is the concentric metal rings used. They are either too small or too large for the round-bottomed or Erlenmeyer flask. The best way to deal with this (and some other) problems is to use Neoprene rubber filter cones (Fig. 9) in a manner for which they were not originally intended (see Fig. 10). These are available with upper diameters from 70

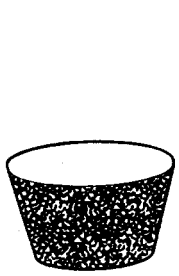


Fig. 9.

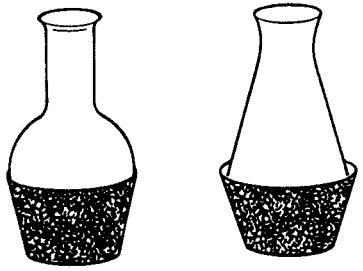


Fig. 10.

down to 22 mm, and are thus suitable for round-bottomed and Erlenmeyer flasks of up to 100 ml capacity. Their use provides not only for greater flexibility in the use of steam-bath rings but also a steady place for the flask to stand (or sit). Moreover, if you want to reduce the amount of steam heating (for reasons of excessive foaming, etc.), all you have to do is place another smaller filter cone inside the original one.

Recrystallisation of small amounts is most conveniently (and cheaply) done in jointless round-bottomed flasks of the type shown in Fig. 11 and of 10–25 ml capacity. These when ordered in bulk should cost no more than $2–3. Hot filtration is best done using small funnels whose angle is ca 45° and not the usual 'regulation' 60°, and the stem should be fairly wide (Fig. 12) to allow solvent vapour from the flask on the steam-bath to rise and dissolve material which has crystallised on the filter paper.

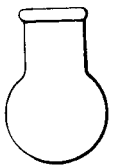


Fig. 11.

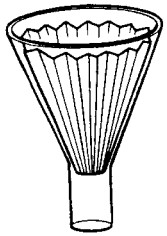


Fig. 12.

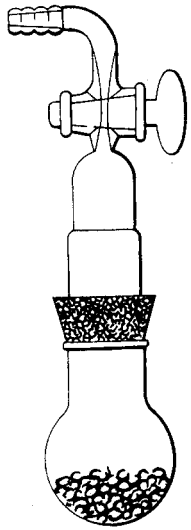


Fig. 13.

Incidentally, cotton-wool should never be used for filtration; it always contains some fat or grease.

Another consideration when choosing a crystallisation solvent, although one which cannot be planned in advance, is whether the crystals formed are sufficiently compact to allow removal of mother liquor with a capillary pipette. It is worth spending some effort on finding such a solvent, because filtration on a small scale always leads to losses. This is particularly true of low-temperature recrystallisation, when both solvent removal and washing with additional solvent must be done while the flask (after standing in the freezer compartment) is immersed in a dry-ice–carbon tetrachloride bath. On this point, a low-temperature recrystallisation should be done in stages, first at room temperature, then in the main refrigerator compartment (+4 °C), and only subsequently in the freezer compartment. This should also help in obtaining compact crystals.

Drying crystals in a flask can be done either as shown in Fig. 13 (illustrating another use for the rubber filter cones, this time the small sizes), or (and this applies to Erlenmeyer flasks which should *never* be thus evacuated) in a vacuum desiccator. In that case the neck should be covered with aluminium foil held in place with a rubber band and punctured by a needle in several places. That will prevent the crystals from jumping out as the last remaining traces of solvent come off.

Fractional Crystallisation

It would be a disaster if this were to become a forgotten art. Imagine getting a crystalline mixture, with a melting range of 10–20 °C, say of diastereomers as shown by the NMR spectrum, whose TLC behaviour shows that there is almost no hope of separation by chromatographic methods, or that if there is a slight hope it will only come about by a lengthy procedure, especially if quantities of 1 g or more are involved. Are you going to leave it at that ('an inseparable mixture was obtained'), or are you willing to have a go at another method, even if it is one practised for over 200 years? If the latter, then look at Fig. 14,

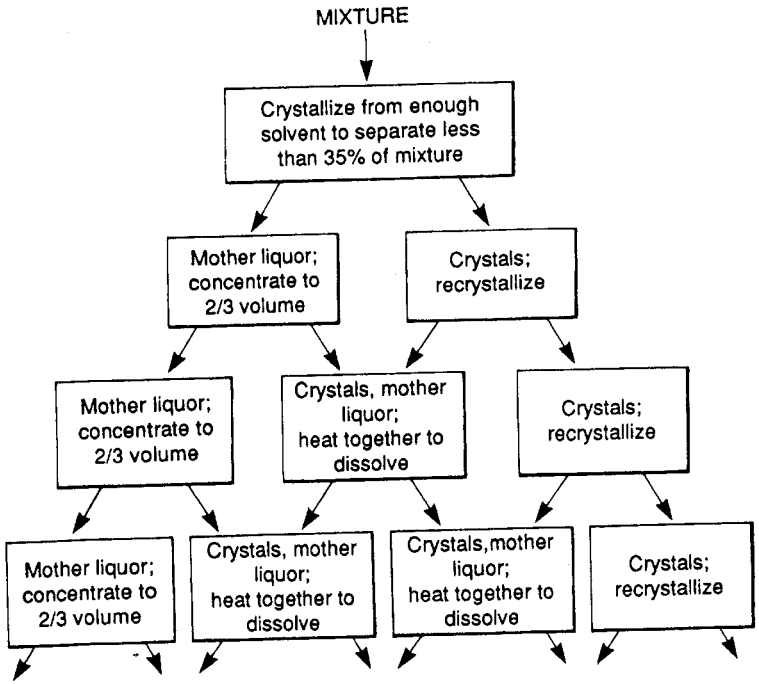


Fig. 14.

which shows the general scheme to be followed. It is a leisurely process, and one which rarely harms the product.

The sequence shown is interrupted at any stage where melting point determination or spectroscopic evidence shows that a pure product has been separated. Any 'unpartnered' mother liquors left as a result should then be combined to start the process afresh, with seeding where appropriate.

There are a few rules for this game which must be observed:

(a) Cleanliness must be ensured. Solvents must be absolutely pure. Mother liquor removal and washing of crystals by pipette only! No boiling stones!
(b) Use only a single solvent, or a pair with similar vapour pressures. No hygroscopic or peroxide-forming solvents!

(c) Careful judgment must be employed to decide when to proceed to the next stage. Close examination of crystals is of help.
(d) Resist the temptation to pick up the flask while crystallisation is progressing! Let forming crystals lie!

Beware of Explosive Crystallisation

Notwithstanding the last injunction, some attention must be drawn to the fact that the process of crystallisation can be very exothermic. This can cause a disaster, particularly when a solvent pair is used for recrystallisation—the mixture may boil right out of the flask. Hence: have an ice–water bath handy just in case, and once again: *Never leave unattended!*

Once melting point determination and spectroscopic evidence has established the purity of your compound, almost all of it can be transferred to a suitably sized vial. Whatever sticks to the side of the flask and cannot be scratched out can still be made use of as a TLC sample: simply add a few drops of a solvent such as 1,2-dichloroethane, place on a steam-bath, allow the rising and condensing vapour to dissolve and wash down the material and, after cooling, transfer to a small vial by capillary pipette.

6

Solvents

'Which solvent did you use?'
[Standard question, conveniently asked on waking up after (almost) any organic chemistry lecture]

ECONOMICS

Solvents as a group usually constitute the biggest single item in the budget of a research group, especially where much chromatographic work is done and even where provision for partial recovery is made.

The figures in Table 1 should be an eye-opener regarding the enormous difference in cost between solvents purchased in bulk and in individual glass bottles. They refer to the annual consumption of 11 common solvents by a department of a well known European university.

As to the obvious question of whether a difference such as this would not cover at least six times the annual salary of someone solely engaged on distilling bulk solvents, that is clearly not the direct concern of you, the individual researcher. It does, however, constitute one good reason why you should either distil solvents yourself or rely solely on locally distilled material. The other good reason is that you know what you are working with. On the matter of purity of solvents there can be no compromise. Any glass bottle from a manufacturer designated 'analytical grade' or 'puriss' is bound to pass through

Table 1. Cost of solvents purchased in bulk and in individual 2.5 litre bottles

Solvent	Annual consumption (litres)	Cost in bulk (SWF)	Cost in bottles (SWF)
Acetone	15 000	16 950	105 000
Diethyl ether	7 000	21 140	210 000
Ethanol	3 000	3 450	24 000
Benzene	100	247	2 000
Chloroform	400	2 048	32 000
Ethyl acetate	2 000	3 400	32 000
Hexane	4 600	7 360	82 800
Methanol	1 000	740	4 500
Light petroleum (b.p. 60–90 °C)	100	133	1 600
Tetrahydrofuran	10	142	200
Toluene	400	480	7 360
Total		65 190	509 460
Difference		442 270 (681.5%)	

some weak link in a chain, e.g. the man who cleaned the bottles that morning or the one who was in charge of the filling unit—*and you were not there at the time*. Of course, any reputable firm will apologise handsomely if there is any reason for complaint and will pay full compensation for the defective bottle, but that will not be any consolation for what may be weeks of work and other expensive reactants wasted.

SOLVENT DISTILLATION

Any arrangement for routine distillation of solvents should ideally answer to the following requirements:

(1) it should be one fixed in position and yet allow for the easy switch-over from one solvent to another;
(2) it should be in a safe location; and
(3) since that means usually a hood, and since hood space is always at a premium, it should be constructed so as to take up as little usable space as possible.

Figure 1 shows an apparatus, planned by Dr J. Schreiber (ETH, Zurich), which was designed with these criteria in mind. The dimensions are in millimetres. The condenser C is mounted high up on the wall in the centre of the hood. It is connected by linking tubes to the distillation flask A at one side of the hood, and to the receiving vessel B at the other end. The important point is that all connecting joints are spherical, allowing for maximum flexibility in both position and size of A and B and making disconnection of both these an easy matter. Position 1 is for distillation from A to B while position 2 is for reflux from the condenser back into A via the right-angled tube. If one forgets to change B in time it will simply fill up and solvent will reflux back into A. The little extension D serves to create an air cushion inside B which will prevent spillage on subsequent change of receiver in such a case. Naturally, all these dimensions, and in particular the lateral ones, should be adjusted in accord with your local ones—as you can see the ones given are

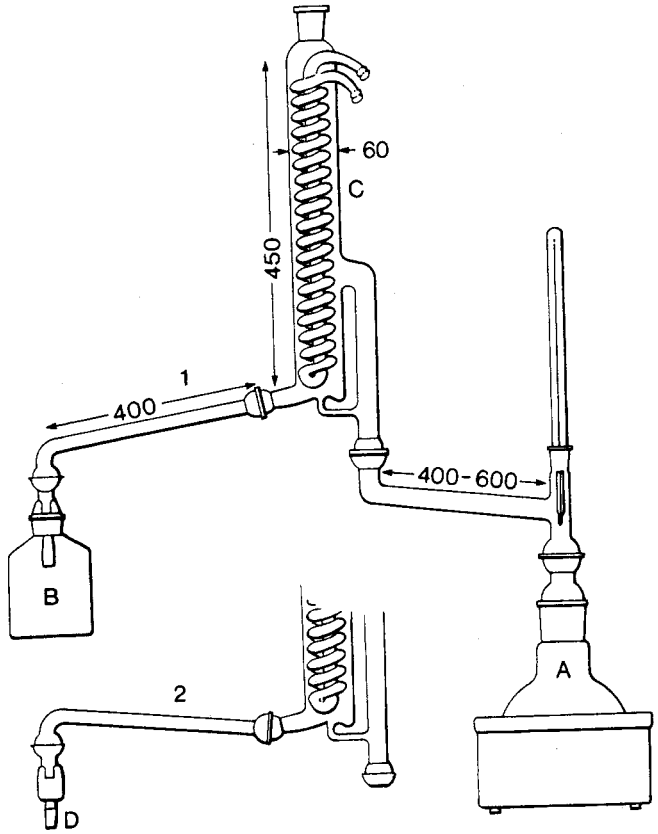


Fig. 1.

for a hood at least 1.5 m wide. The result is, of course, that the entire space between A and B is free for additional apparatus.

Anhydrous Solvent Distillation

In almost every research laboratory nowadays there is a need for an arrangement or device which will allow continuous refluxing over a drying agent, and at the same time withdrawal of such dried solvent in a desired amount and whenever needed,

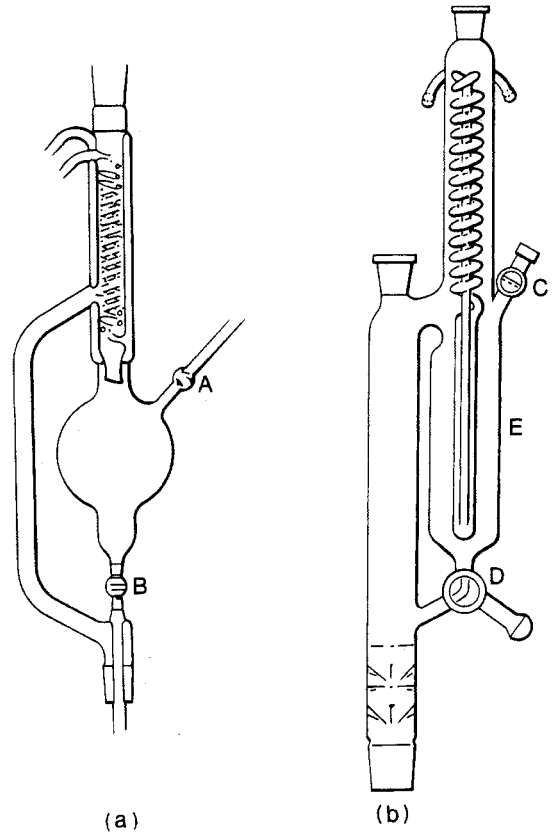


Fig. 2.

and all this preferably while under an inert atmosphere. Figure 2(a) and (b) show two such designs of apparatus.

In both the top of the condenser is connected to an inert gas manifold such as Chapter 4, Fig. 5. In the first, simpler version, solvent can be withdrawn by syringe, through the wide Teflon stopcock A, from the 500 ml capacity intermediate collector with stopcock B closed. When the latter is open the dry solvent will circulate continuously from the distilling flask at the

bottom. In the second, more sophisticated apparatus, solvent withdrawal is possible either through the stopcock C or by direct run-out from the three-way stopcock D. The cylindrical form of the collector E allows for easy calibration of volume in terms of ml cm^{-1}; for example, when the outer diameter of the cooling finger is 12 mm and the inner diameter of E is 52 mm, then the scale is 20 ml cm^{-1}. Use of the thermometer socket is, of course, optional.

TREATMENT OF INDIVIDUAL SOLVENTS

Table 2, based on the author's experience, has withstood the test of time. It is meant to reconcile some of the conflicting advice encountered on the subject of solvent purification, drying and storage, and it takes into account the comparatively high state of purity now shown by many commercially supplied solvents even when purchased in bulk and described as being of 'practical' or even 'technical' grade.

A number of points must be stressed. First, most hydrocarbon (and halocarbon) solvents can be dried as thoroughly as by any other means by azeotropic water removal, which means distilling off between 5% and 25% of the total and thus drying not just the solvent but also the containing vessel (the author's own criterion is the lack of reaction with sodium hydride suspension). It follows that in many reactions where anhydrous conditions are essential the inclusion of an inert hydrocarbon—preferably toluene or cyclohexane—as part of the solvent system should be considered.

Second, the use of extruded sodium wire for drying solvents, especially diethyl ether, is a still persisting pernicious practice which should be stamped out once and for all. Its drying capacity is limited to start with and ceases immediately on formation of the adhering layer of sodium hydroxide. Wherever this is still practised it is a major cause of fires.

Third, a few comments on molecular sieves. Their use is now routinely advocated and is probably most generally effective.

However, it is often not sufficiently realised that this type of material must be freshly activated, usually by heating to 300–350 °C (metal bath) in a high vacuum. Either this is done immediately before use, or else the activated material should be stored under totally anhydrous conditions (e.g. like activated alumina in bottles with a very narrow opening stoppered by a rubber stopper). Many suppliers do not trouble to supply this in the proper kind of container, and thus newly supplied material must nearly always be subjected to this activation.

Now to the special problems posed by solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane. Tetrahydrofuran as now supplied by reputable suppliers is good enough as is for direct drying, either by passing through activated alumina (Chapter 4, p. 97) or, for larger amounts in an apparatus such as illustrated in Fig. 2. If of more doubtful origin, it must be treated with the same amount of suspicion as the other two solvents. That means first testing for the presence of peroxides and taking steps for their removal; in this connection you should be warned that the potassium iodide–starch test strips are not absolutely reliable. After that, pre-drying is usually required (see Table 2).

A few special remarks should be devoted to *tert*-butyl methyl ether. This is now the cheapest available organic solvent, a secret reasonably well kept by firms not especially keen to lose on sales of other solvents. The reasons for the low price is that it is now made on a relatively enormous scale as a gasoline additive in place of the banned tetraethyllead. For that reason, the cheapest supply is directly from one of the large petroleum processing firms. For the organic chemist, in considering it as a solvent for general extraction and chromatographic purposes there are other considerable advantages: (i) the negligible tendency for peroxide formation, (ii) its boiling point (55–56 °C), which is higher than that of diethyl ether yet still low enough for easy removal by distillation, a special advantage in summer or in warm climates, and (iii) its lower mutual miscibility with water. It is possibly inferior to diethyl ether and tetrahydrofuran for use with Grignard or other organometallic reagents,

Table 2. Purification, drying and storage of common solvents

Solvent	Boiling point (acceptable range, °C)	Preliminary purification	Further drying and purification	Recommended storage
Pentane Hexane Cyclohexane Other alkanes	36 (2–3) 69 (2–5*) 80.7 (1)	Wash several times with conc. sulphuric acid to remove olefins if necessary, wash with water, dry over $CaCl_2$, collect after wet forerun	Rarely necessary; if so by azeotropic water removal	Up to 500 ml in glass-stoppered bottles; above that and for long periods in dark screw-capped bottles. No sense in keeping over molecular sieves
Benzene† Toluene† Xylenes	80.1 (0.5) 110.6 (1) 144.5 (*ortho*) 139 (*meta*) 138.3 (*para*) (I)	Dry over $CaCl_2$, refractionate, reject first 5–10% of wet forerun	Boil off from or redistil into reaction flask, rejecting first 5% (see text)	
Dichloromethane Chloroform Carbon tetrachloride 1,2-Dichloroethane	40 (1) 61.2 (0.5) 76.8 (0.5) 83.5 (1)	Wash with water, dry over $CaCl_2$, redistil, collect after 5% wet forerun	Redistil from P_2O_5; on small scale and in special cases pass through alumina (basic, act. I) directly into reaction flask	As above, but chloroform for longer periods in tightly closed full bottles and in darkness.
Diethyl ether Diisopropyl ether *tert*-Butyl methyl ether	34.5 (1) 68.5 (1) 55 (1)	Test for peroxide; if positive wash with 5% metabisulphite soln, then with sat. NaCl; dry over $CaCl_2$; distil (but not over conc. H_2SO_4)	Small amounts: pass through up to 10 wt % alumina (basic act. I); with larger amounts best to use absolute diethyl ether from cans	Best in cool, dark place in nearly full screw-lidded metal cans. For long periods seal with Parafilm‡
Tetrahydrofuran 1,2-Dimethoxy ethane (glyme)	65.5 (0.5) 84 (1)§	Stand overnight over KOH, decant, test for peroxide; if positive stir with up to 0.4% wt % $NaBH_4$ overnight, add CaH_2, fractionate but not to dryness	Distil from potassium under argon (see text), small amounts pass directly into flamed-out reaction flask through alumina (basic act. I)	In dry plastic-insert screw-capped 100 ml bottles over basic active alumina under argon. For long periods seal with Parafilm; dioxane best kept frozen in refrigerator (but watch out for burst bottles!)
Dioxane	101.5 (1)§ (m.p. 11–12)		Distil from sodium under argon (see text)	
Carbon disulphide	46.5 (1)	Redistil in hood from small amount of phosphorus pentoxide; use only water bath heated by steam	Shake with small amount of mercury, redistil from phosphorus pentoxide	Don't! Avoid leaving around laboratory
Ethyl acetate Methyl acetate	77.1 (0.5) 57 (1)	Dry over active $CaSO_4$ (Sikkon) and/or anhydr. K_2CO_3, decant, distil carefully	Fractionate from up to 5 wt % of acetic anhydride	Over activated molecular sieves 5A in tightly closed bottles
Other esters boiling below 100 °C			Refractionate	

(*continued*)

Table 2. *(continued)*

Solvent	Boiling point (acceptable range, °C)	Preliminary purification	Further drying and purification	Recommended storage
Acetonitrile	81.5 (0.5)§	Predry over $MgSO_4$,‖ then over anhydr. K_2CO_3, decant, distil from CaH_2	Fractionate from P_2O_5. Small amounts: pass through alumina (basic act. I) directly into reaction vessel	Over activated molecular sieves 3A, best in 100 ml dated bottles
Acetone	56.2 (0.5)	Distil over 2 °C range, dry over anhydr. $CaSO_4$, decant, redistil	If used for oxidation reactions reflux over sufficient $KMnO_4$ to retain violet colour, distil, dry, fractionate. Very pure via NaI addition compound	Over freshly activated molecular sieves 3A
Butan-2-one	79.5 (0.5)	Fractionate off water azeotrope (b.p. 73.5 °C), dry this and remainder separately as for acetone		Over freshly activated molecular sieves 5A
Methanol	64.5 (0.5)	Simple fractionation now usually sufficient even with bulk grade	Predried material redistilled from CaH_2, best directly into reaction vessel	In small bottles over freshly activated molecular sieves 3A
Ethanol	78.3 (0.5)	From 'rectified spirit' (95%) most economically by reflux and distillation from CaO (at least 1.5 times amount needed to bind water present)		

Isopropanol	82.5 (0.5)	Fractionate, collect after water azeotrope (b.p. 80.3 °C), dry latter as for ethanol	Predried material redistilled from CaH_2, best directly into reaction vessel	In small bottles over freshly activated molecular sieves 3A
n-Propanol and higher alcohols	97.2 (0.5)	Fractionate, collect after aqueous azeotrope forerun		
tert-Butanol	82.5 (0.5) (m.p. 25.8)	Water azeotrope, b.p. 79.9 °C. Treat as for isopropanol	As for previous alcohols but care needed in distillation—solid may block condenser!	As for previous alcohols; bottles best kept in warm place during cool season to save bother of 'thawing out'
Ethylene glycol, higher glycols	198, 68–70/4 mmHg 108–110/28 mmHg (2)	Fractionate *in vacuo*, collect after 5–10% forerun. High latent heat of vaporisation!	Refractionate after dissolving up to 1 wt-% of sodium	Best in 100 ml plastic insert screw-capped bottles (very hygroscopic!), larger amounts only over large excess of molecular sieves
Nitromethane Nitroethane	101.3 (1)‖ 115	Dry over $CaCl_2$, decant, fractionate	Refractionate from molecular sieves 4A	Over molecular sieves 4A

(continued)

Table 2. *(continued)*

Solvent	Boiling point (acceptable range, °C)	Preliminary purification	Further drying and purification	Recommended storage
Formic acid	101 (1) (m.p. 8.3)	Fractionate, best under reduced pressure. Can be dried further by reflux and distillation from phthalic anhydride. Water azeotrope has b.p. 107 °C (22.5% water)	On prepurified material freeze completely, allow to thaw to extent of 10–20%, decant (all while protected from moisture), use remainder	In screw-capped bottles
Acetic acid	118 (0.5) (m.p. 16.6)	Refractionate after adding up to 5% acetic anhydride and up to 2% CrO_3		
Pyridine Methylpyridines	115.5 (0.5)	If very crude dry over KOH, decant, fractionate	Reflux with CaO, BaO or very active basic alumina, refractionate	In tightly closed dated bottles over molecular sieves 5A
N,N-Dimethyl-formamide¶ *N,N*-Dimethyl-acetamide *N*-Methyl-pyrrolidone	153, 42/10 mmHg, 55/20 mmHg; (1) 166, 58–59/11 mmHg, 63/18 mmHg; (1) 202, 78–79/10 mmHg; 96–97/24 mmHg; (1)	Fractionate *in vacuo*, rejecting first and last 10%. Avoid distilling at atmospheric pressure	Stir overnight with CaO, BaO or alumina (basic act. I), then refractionate *in vacuo*	Best over freshly activated molecular sieves in small dated bottles. With larger amounts (above 500 ml) the amount of sieves should be large to take up moisture introduced on frequent opening
Dimethyl sulphoxide	190, 50/3 mmHg, 72/12 mmHg, 84–85/22 mmHg; (1), m.p. 18.5	Fractionate *in vacuo*, rejecting first and last 10%. Avoid distilling at atmospheric pressure	Stir with CaH_2 overnight, then fractionate from CaH_2 *in vacuo*. Can be further purified by partial freezing if dry	Best over freshly activated molecular sieves in small dated bottles. With larger amounts (above 500 ml) the amount of sieves should be large to take up moisture introduced on frequent opening
Hexamethyl phosphoric-triamide	235, 68–70/1 mmHg, 115/15 mmHg; 126/30 mmHg; (1), m.p. 7		Stir for 1 h with CaH_2 at 100 °C under reduced pressure, then refractionate *in vacuo*	In small (50 ml) plastic insert screw-capped bottles under argon and over activated molecular sieves 13X or over oil-free NaH if available.

* Cheaper 'hexane fraction'.
† Assumed free of sulphur compounds such as thiophene.
‡ Can be stabilised or restabilised by adding up to 0.001% of a dihydric phenol.
§ May frequently be supplied in state of purity inferior to that claimed; purification calls for extra care.
‖ May be encountered in part as low-boiling azeotrope with water.
¶ Reported to be light-sensitive; probably best kept in dark bottles at all times.

although there are indications of its superiority to these two in heteroatom-facilitated metallation. Recently, there have been signs that at least in part, its place as a gasoline additive may be taken by *tert*-butyl ethyl ether, a solvent with probably the same advantages but with a higher boiling point. The one great disadvantage of both is, of course, their instability to strong acids.

Tetrahydrofuran now clearly holds pride of place as the best solvent for nucleophilic reactions, so much so that deciding to use it has become something of a kneejerk reaction. It is advisable, however, that where its solvation power is inherently of no importance or possibly even detrimental, other ethereal or even non-polar hydrocarbons should be tried. Much the same pre-eminence is occupied now by dichloromethane for electrophilic reactions. This is entirely understandable, in view of its stability, its excellent solvent power for Lewis acids of all kinds, simple and complex, and its low boiling point. It has also become fashionable for certain types of nucleophilic reactions, although here its reputation has suffered recently.[59a]

Dipolar Aprotic Solvents

These have undoubtedly advanced synthetic organic chemistry a great deal.[60] Table 3 summarises some useful information on the most important of these, much of it available only in brochures and other commercial literature.

Their chief drawback is the difficulty of getting rid of them once they have served their purpose. This applies particularly to hexamethylphosphorictriamide (HMPTA) and to the same extent to various substitutes for this that have been suggested recently, in view of the presumed toxicity of that solvent. Practically every month sees the publication of yet another example of how various reactions proceed under milder conditions, or in better yield, or proceed at all when using this or a similar solvent, but on closer examination one often finds that the substrates have been carefully chosen so as to make isolation of the product a simple matter, e.g. the product is non-polar and

Table 3. Dipolar aprotic solvents—some useful data

Property	*N,N*-Dimethylformamide[61]	*N,N*-Dimethylacetamide[61]	*N*-Methylpyrrolidone[62]	Dimethyl sulphoxide[63,64]	Hexamethylphosphorictriamide[65,66]
Melting point (°C)	−61	−20	−24.5	18.6	7
Dielectric constant	36.7	37.8	32.3	48.9	30
Basicity, as $\Delta\delta^{\infty}$ ($CHCl_3$)*	1.30			1.34	2.03
Some selected solubilities	(in g per 100 ml at 25 °C): $AgCl > 16.5$, $CuCl_2.2H_2O > 14.7$, $CuSO_4$ 1.7, KCN 0.2, KCNO 0.11, KCNS 17, $K_3Fe(CN)_6 < 0.05$, $KI > 23.6$, $KMnO_4 > 16.5$		More than 10% at 25 °C: $(NH_4)_2S$, $Pb(OAC)_2$, $PbCl_2$, S, $KMnO_4$, KCNS, $ZnCl_2$. KF: 3% at 190–200 °C	(in g per 100 ml at 25 °C): KI 20, KNO_3 10, KNO_2 2, $AgNO_3$ 130, NaI 30, $NaNO_3$ 20, $NaNO_2$ 20, $ZnCl_2$ 30, CuI 1, $CuBr_2$ 1, LiBr 31.4, $LiNO_3$ 10, $LiClO_4$ 31.5	(in g per 100 ml at 25 °C): NH_4Cl 4.4, $AgNO_3$ 33.3, $CuSO_4$ 13.7, NaCl 0.78, KCl 0.2, $NaNO_3$ 8.8, Na_2SO_4 0.1

* $\Delta\delta^{\infty} = \delta^{\infty} - \delta$, where δ^{∞} is the chemical shift of chloroform in the solvent at infinite dilution and δ is that of chloroform in an inert solvent (cyclohexane).

Table 4. Some important azeotropes

	Hexane 69*	Heptane 98.4	Benzene 80.1	Cyclohexane 81.4	Methylcyclo-hexane 100.3	Toluene 110.6	Carbon tetrachloride 76.8
Methanol 64.65*	50 (30)†	59.1 (51.5)	57.5 (39.1)	54 (38)	59.3 (54)	63.8 (69)	55.7 (21.6)
Ethanol 78.5	58.7 (21)	70.9 (49)	68.2 (32.4)	64.8 (31.3)	72.1 (47)	76.7 (68)	65 (16)
n-Propanol 97.2	65.6 (4)	87.5 (36)	77.1 (17)	74.3 (20)	86.3 (35)	92.6 (50)	73.4 (18)
Isopropanol 82.3	62.7 (23)	76.4 (50)	71.9 (33)	69.4 (32)	77.6 (53)	80.6 (69)	68.6 (28)
n-Butanol 117.7	—	94 (18)	—	79.8 (9)	95 (20)	105.5 (32)	76.55 (2.5)
sec-Butanol 99.5	67.2 (8)	88.1 (37)	78.5 (15)	76 (18)	89.9 (41)	95.3 (55)	74 (8)
tert-Butanol 82.8	63.7 (22)	78 (62)	74 (36.6)	71.3 (37)	78.8 (66)	—	71.1 (17)
tert-Amyl alcohol 101.8	—	—	80 (15)	78.5 (16)	92 (40)	100.5 (56)	—
Acetone 56.5	50 (59)	56 (89.5)	—	53 (67)	—	—	56 (88.5)
Butan-2-one 79.6	64 (29)	77 (73)	78.2 (45)	71.0 (52.5)	77.7 (80)	—	73.8 (29)
Tetrahydro-furan 65.5	63 (53)	—	—	—	—	—	—
Acetonitrile 81.6	57 (25)	69.4 (44)	73 (34)	62.2 (33)	71.1 (51)	81.1 (78)	65 (44)
Nitromethane 101	62 (18)	80 (35)	79.1 (14)	70.2 (28)	81 (39.5)	96.5 (55)	71 (17)
Dioxane 101.5	—	92 (44)	—	79.5 (25)	93.7 (45)	—	—
Pyridine 115.3	—	—	—	—	—	110.1 (20)	—
Methyl acetate 57.1	51.7 (60)	57 (96)	—	55 (83)	—	—	—
Ethyl acetate 77.1	65 (38)	—	—	72.8 (54)	—	—	74.8 (43)
Dimethyl carbonate 90.5	67 (20)	82.3 (61)	—	—	—	—	75.75 (12)
Acetic acid 118.1	68.2 (6)	95 (17)	79.6 (2)	79.7 (2)	96.3 (31)	104 (32)	76 (1.5)
Formic acid 100.7	60.6 (28)	78.2 (56.5)	71 (31)	70.7 (30)	80.2 (46.5)	86 (50)	66.65 (8.5)
Water 100.0	61.6 (5.6)	79.2 (12.9)	69.2 (8.83)	69.56 (8.4)	81	84.1 (13.5)	66 (4)

* Figures not in parentheses refer to boiling point in °C.
† Figures in parentheses refer to approximate percentage by weight of polar solvent in each azeotrope.

hence isolable with a hydrocarbon solvent such as pentane, not to speak of cases where on looking just a little closer one discovers that the product was not actually isolated at all but that results and yields were arrived at by GC or spectroscopic examination alone. When the method is applied to more complex cases one usually finds that product isolation is a lot more difficult.

Another solvent in that category which deserves more attention than it currently enjoys is sulpholane (tetrahydrothiophene 1,1-dioxide) and its 3-methyl homologue, both commercially available. These have been found to be superior in reactions such as S_N2 displacement with fluoride ion,[67] palladium-catalysed oxidation of olefins[68] and the formation of sulphonyl chlorides from sulphonates.[69]

With all these solvents one should first investigate whether the use of a very minimum say (2–3 mmol per mmole of substrate), together with a more easily removable solvent (diethyl ether, tetrahydrofuran, toluene) will not give just as good results. Often there is no need even for enough to give a homogeneous mixture. When the product is acidic, HMPTA can be removed almost quantitatively by extraction of the alkaline solution with a chlorinated solvent such as chloroform,[66] and where the product is neutral it should be extracted with, e.g., toluene, and the HMPTA removed destructively by several washes with 3 M hydrochloric acid. In any case, the best policy when using dipolar aprotic solvents is to work the product up using only hydrocarbons (toluene if not hexane or cyclohexane) for extraction.

The Importance of Azeotropes

Many organic reactions are equilibrium reactions in which the yield of the desired product can be enhanced by removing one of the products (water, an alcohol or some other low-boiling material) from the system, and this is best achieved by the use of an inert reaction solvent which can do so as an azeotrope. This principle is likewise important when freeing a product from

traces of a high-boiling contaminant, and when recrystallising from a mixture of solvents. A reference book such as the ACS Monograph on the subject[70] should be available to every research group; for the sake of convenience, Table 4 lists azeotropes formed by inert solvents with the most commonly encountered polar solvents or reactants.

From this it is easy to see, for instance, that the only way to remove traces of pyridine is with toluene, that formic acid is removed azeotropically much more easily than acetic acid and that ethyl acetate–cyclohexane or ethyl acetate–carbon tetrachloride are suitable solvent pairs for TLC and fractional crystallisation.

7

Which Base Should I Use?

BRØNSTED BASES—DEPROTONATION AT CARBON

So much of synthetic organic chemistry nowadays involves deprotonation that it is not surprising that this is one of the questions most frequently asked by the perplexed organic experimentalist.

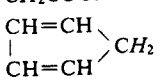
When you need a base it means usually that you have to remove a proton, most frequently from a carbon atom, but the question can be just as pertinent if it has to be removed from oxygen, nitrogen or sulphur. The major, although not the only, factor is the acidity of the substrate. Table 1[71] constitutes a rough guide, adapted to the most common types of carbon substrates, and the most frequently used Brønsted bases.

Put in a nutshell, the base appearing on the right should be able to deprotonate to an appreciable extent the type of substrate above it on the left, and the higher above the better. The fact that often this is not the case, and also need not be the case, can be due to a number of reasons.

Possibilities of Shifting the Equilibrium

All deprotonations are fundamentally equilibrium reactions, and an unfavourable equilibrium (i.e. one established between a base on the right and a substrate on the same level or below it) can be shifted to a favourable one, if by some means one of

Table 1. C—H and N—H acidities and commonly used bases (in dimethyl sulphoxide solution) (protons affected in italics)

Typical substrates for deprotonation	pK*	Commonly used bases
Cyano ester NC—*C*H*R*—CO_2R'	9	
3-Keto esters R″CO—*C*H*R*—CO_2R'	11	
Dinitriles R—*C*H(CN)$_2$		
1,3-Diketones R—CO—*C*H*R*′—COR″		
Malonic esters R—*C*H(CO_2R')$_2$	13	
Acid halides R—CH_2COCl	16	
Cyclopentadiene 		
Aldehydes R—R′*C*H—CHO	19	
Esters R—*C*H*R*′—CO_2R″	25	
Nitriles R—*C*H*R*′—CN		Sodium methoxide
Ketones R—*C*H*R*′—COR″		Sodium isopropoxide
Amides, primary R—CHR′—COH_2	27	Potassium *tert*-butoxide Lithium hexamethyldisilylazide
Amides R—*C*H*R*′—CONR″$_2$	28	
Acetylenes R—C≡*C*H		
Sulphones R—*C*H*R*′—SO_2R″		
Triarylalkanes Ar_3CH	31	Triphenylmethylsodium
Sulphoxides R—*C*H*R*′—SOR″	32	Sodium dimethylsulphoxide
Thioacetals RS—*C*H*R*′—SR″		
Diarylalkanes Ar_2CHR		
Dialkylamines R_2NH		Lithium diisopropylamide
(Hydrogen *H*—H)	36	Sodium hydride Potassium hydride
Arylalkanes Ar—*C*H*R*′R″	40	
Vinylalkanes —CH=CH—*C*H*R*		
Alkenes —CH=*C*H—	44	Phenyllithium
Thioethers RS—*C*H*R*′R″	48	
Alkanes, primary R—CH_3	50	n-Butyllithium
Alkanes, secondary R—CH_2—R′		*sec*-Butyllithium

* pK values of conjugate base (left column) or conjugate acid (right column).

the primary products is removed from the system. For example, sodium methoxide is a bad base, equilibrium-wise, for efficiently removing a proton from methyl acetate; but if the resulting enolate reacts with the carbonyl group of a non-deprotonated ester molecule and as a result a much less basic 3-oxo ester enolate is formed, the overall reaction will go to completion, especially if the solvent is diethyl ether, in which the enolate salt formed is insoluble and thus leaves the equilibrium system. Another example is how such a weak base as 5% sodium carbonate (not even mentioned in Table 1) can deprotonate at the α-carbon next to one of the carbonyls in a 1,5-diketone, even though this can proceed only to a minute extent at equilibrium, for the reason that the subsequent aldol cyclisation gives a very stable product (a cyclopentenone).

Another approach of considerable practical importance is through removal of one of the primary products by distillation, such as, again using sodium methoxide, removal of methanol formed in the form of an azeotrope (see Chapter 6, Table 4) with a co-solvent such as benzene or toluene. The same can apply to the stronger base potassium *tert*-butoxide. This works particularly well when the first-formed enolate is expected to react *in situ* with the carbonyl of a non-enolisable second reactant. An example of this is the reaction between a ketone and dimethyl carbonate to form a 3-keto ester. Dimethyl carbonate, incidentally, itself forms an azeotrope with methanol, so it can serve well as both solvent and reactant.

Actually for many such reactants sodium or potassium hydride is used. Theoretically these are much stronger bases and also the ideal 'irreversible' ones since here equilibrium is shifted by the irrevocable exit of hydrogen from the system. However, in most cases, because of their insolubility, they do not start to react until a trace of alcohol is present. In effect this means that one is actually using an alkoxide base, albeit one continuously generated as reaction proceeds and in effect under irreversible conditions.

Choice of Base to Avoid Side Reactions on the Substrate

Many of the common strong bases cannot be used under all circumstances, for the simple reason that they can also act as nucleophiles. This means most alkyllithium reagents, and even more so other organometallics such as Grignard reagents, and other types of bases such as sodium or lithium amides. In many cases this can be circumvented by increasing the steric bulk of the anionic part of the base, e.g. lithium diisopropylamide and hexamethyldisilylazide instead of unsubstituted amides or those substituted by less hindered alkyl groups. Another example is the use of isopropylmagnesium halides, which can act as efficient bases in many instances[72,73] where a less-hindered Grignard reagent would function exclusively as a nucleophile. Added advantages here are that this reagent is stable in tetrahydrofuran and available commercially and that the magnesium can act as additional driving force by chelating with the product.[74] Among organolithium compounds there is the example of mesityllithium[75,76] instead of phenyllithium as a non-nucleophilic base; this is also probably stronger than the ubiquitous lithium diisopropylamide with the added advantage of avoiding a problem generally overlooked with the latter, namely the formation of an amine as byproduct. Such introduction of hindrance may actually increase basicity to some extent; for example, whereas sodium phenoxide is an ineffective base, the 2,6-di-*tert*-butyl[77] and the 2,4,6-trimethyl[78] homologues are not only highly non-nucleophilic but also stronger as bases.

Choice of Base and Conditions to Avoid Side Reactions of the Substrate

Here are meant instances where a partially deprotonated substrate may as a nucleophile react with still protonated material, for example the undesirable self-condensation of an aldehyde, ketone or ester. The way to avoid this is three-fold: (a) doing the deprotonation at as low a temperature as possible, *and* (b) using as strong and as non-nucleophilic a base as possible *and* (c) adding the substrate to the base and not the other way around as is customary.

An important requirement is therefore that the base be soluble at that low temperature, which accounts for the popularity of lithium diisopropylamide and other amide bases of both high molecular weight and degree of hindrance. It is possible that if one goes down to $-100\,^{\circ}C$ (and can find a solvent system suitable at that temperature), then by following the above principles a strong and ordinarily nucleophilic base such as n-butyllithium could be used as base alone.

Incidentally, this may well be another instance where adding a substrate as a solid in small portions, i.e. with none ever in solution in excess, could be of advantage.

The Role of the Solvent and of Chelating Agents; Making Strong Bases as Strong as They Should Be

The advent of the polar aprotic solvents *N,N*-dimethylformamide (DMF), dimethyl sulphoxide (DMSO) and hexamethylphosphorictriamide (HMPTA) has made a considerable impact on carbanion and other anion chemistry and such solvents are described in detail elsewhere (see Chapter 6, p. 168). Briefly, their function is in solvating the cation and/or non-solvating the anion, thus making this and also the deprotonated intermediate more soluble and more reactive. Compared with hydroxylic solvents, reaction rate differences of up to 10^{14} are known; with the common ethereal solvents they are of the order of 'only' 10^2–10^3, which is still impressive, however.

Nonetheless, there are snags when using such solvents with strong bases. DMSO is itself acidic and will form the 'dimsyl' anion, which is both a weaker base and also a nucleophilic one compared with the initial deprotonator; DMF has a carbonyl group subsceptible to nucleophiles; HMPTA is attacked similarly and moreover has to live down its notoriety as a strongly suspected carcinogen. Hence the usefulness of these solvents is restricted to weaker bases, such as potassium *tert*-butoxide in DMSO, or to completely non-nucleophilic ones, such as sodium

hydride in DMF. In the latter there is the added advantage that alkyl halides are practically inert to that base even in that solvent, hence deprotonation can be done in their presence with *in situ* alkylation of the substrate as formed.

To a certain though lesser extent, this effect is observed with ethereal solvents, and there are differences between different compounds, although not to the same extent. Thus, the increasing order of effectiveness appears to be diethyl ether < tetrahydrofuran < dimethoxyethane (glyme) < (2,2′-bismethoxy)diethyl ether (diglyme), i.e. following the increasing number of oxygen atoms in the molecule. Unfortunately, this is also the order of increasing sensitivity to attack of strong base on the solvent itself.[79] As a result, tetrahydrofuran is the compromise solvent of choice for many such reactions, and substituted tetrahydrofurans appear to be more stable to strong bases.[80]

More recently, advantage is increasingly being taken of another development which allows us to have the best of both worlds: the use of chelating addends such as tetramethylethylenediamine (TMEDA) and of crown ethers. These can effect cation solvation on a more or less stoichiometric and even catalytic level, and thus make it possible to use strong bases in solvents which are completely inert but also completely non-solvating and thus ordinarily useless (e.g. saturated hydrocarbons). Thus, n-butyllithium with one equivalent of TMEDA in cyclohexane can deprotonate anything with a pK_a of less than 50, including hydrogen itself (a good way of making highly reactive lithium hydride![81]). What happens here in addition to cation solvation is the breaking-up of aggregation of molecules of the organometallic. It is this kind of factor that ordinarily makes them less strong bases than they ought to be on a pK_a basis. Thus, n-butyllithium in hydrocarbons cannot deprotonate the methyl group in toluene, although it should according to Table 1; it will do so after adding TMEDA.

It must be kept in mind that the n-butyllithium–TMEDA combination will attack a solvent such as tetrahydrofuran even more readily than the organometallic alone, hence it should be

prepared, and the substrate added, at as low a temperature as possible (below $-70\,^{\circ}C$ at any rate).[82]

These addends can show considerable specificity for the cation used. TMEDA and 14-crown-4 are mainly for lithium,[83] 15-crown-5 for sodium[84,85] and 18-crown-6 for potassium.[86] Their enhancing effect applies even to the insoluble hydrides of sodium and potassium, for example when extremely hindered alcohols have to be converted into the alkoxides.

Effect of Changing the Cation

This can have a marked effect but may introduce practical difficulties. On going from lithium to sodium and then potassium, the ionic character and hence reactivity generally increase, but at the same time solubility decreases. Thus butylsodium is more difficult to produce and use, but more reactive than butyllithium. This difficulty can apparently be overcome by adding potassium or sodium butoxide to either an alkyllithium[87] or a lithium dialkylamide,[88] although there is still controversy as to whether the resulting extremely strong and non-nucleophilic bases formed are in fact the alkylpotassium or -sodium. Striking differences have been found not only in the base strength but also the direction of deprotonation of the different hexamethylsilylazides,[89] which can be prepared directly by displacement from the corresponding unsubstituted amides or hydrides.[90] In the case of the metal hydrides, where solubility being non-existent is not an issue, reactivity differences are extreme.[90]

Double Deprotonation—Dianions and Polyanions

This is a greatly expanding subject, a fuller discussion of which is outside the scope of this chapter, and in any case there are a number of reviews.[91] From a practical point of view, it has been found desirable in most cases where a proton can be detached at two or more sites with a view to reaction at the most basic site, to use different bases for each site in sequence. This will

reduce the chances that the stronger base used for the less acidic site will complicate matters by acting as a nucleophile.

Thus, with ethyl acetoacetate the C-3 anion is formed with non-nucleophilic sodium hydride, followed by deprotonation at C-5 with n-butyllithium.[92] The same applies to dianions from carboxylic acids,[93] olefinic non-conjugated ketones,[94] phosphonates[95] and imides.[96] The use of an addend such as TMEDA in such cases appears to be beneficial or even essential.[97]

SOME PRACTICAL COMMENTS ON INDIVIDUAL BASES

n-Butyllithium

This is now undoubtedly the most widely used organometallic reagent, and one of the most frequently used strong bases. It is usually available in hexane solution in concentrations ranging from 1.0 to 2.5 M. However, in the author's experience it appears that for this and other alkyllithium reagents cyclohexane is the preferred hydrocarbon solvent. n-Butyllithium is also available at a lower price per gram-mole in high concentration, 9–10 M in hexane. Such solutions are far too viscous for dispensing, for example, by syringe and, after some investment in the necessary safety precautions (liberal blanketing of the entire operation with dry argon), it is a good idea to transfer each bottle under argon pressure into a flask large enough to allow dilution with high-quality cyclohexane to a concentration of 2–2.5 M. It can then be transferred to small (50 ml capacity) bottles. For both these operations the devices shown in Fig. 1 can be used: in Fig. 1(a) the stopper has a third hole, closing of which with one's finger creates the internal pressure for transfer; in Fig. 1(b) there is a small hole in the T-tube for the same purpose. At the above concentration, and provided the bottles are of the screw-cap closure variety and additionally sealed with Parafilm and kept in the refrigerator in a closed metal tin, such solutions can be kept for a prolonged period (1–2 years) without deterioration. Each bottle, after removal from the refrigerator, should be allowed first to reach room temperature, otherwise moisture will enter on opening. The precipitate formed on longer standing is lithium hydride, owing to attack on the solvent. This may take a long time to settle, particularly in solutions of still high concentration. It is probably responsible for anomalous results reported in certain cases (e.g. formation of lithium organocuprates) even where the titre of the solution (see below) was satisfactory. Misgivings regarding possible crystallising-out of cyclohexane at low temperatures have not been borne out.

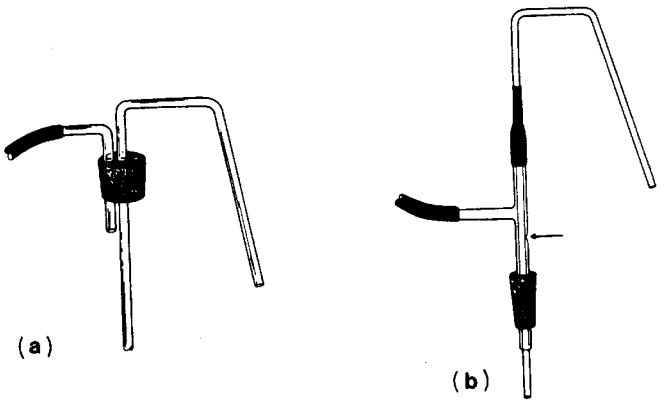


Fig. 1.

sec-Butyllithium

This presents a stability problem. It should be bought only in cyclohexane or isopentane–cyclohexane solution and if possible during the winter months. Even at 5 °C the rate of decomposition (as shown by formation of lithium hydride) is by no means negligible. However, there is little doubt that it is an even stronger base than n-butyllithium. Similar problems are met with in *tert*-butyllithium, exacerbated by the fact that it is commercially available only in pentane solution, is much more

spontaneously flammable on contact with air, and much more difficult to handle in a warm climate.

Methyllithium

Here is one organometallic that is indefinitely stable at room temperature in a particular solvent. The trouble is that the solvent is diethyl ether. Like n-butyllithium it is not stable in tetrahydrofuran, and it is insoluble in hydrocarbon solvents. Were it not for these facts, being much less nucleophilic it would have taken the place of butyllithium a long time ago. Once again, dispensing this reagent accurately is difficult except in a cold climate.

Recently it has been offered commercially as a tetrahydrofuran complex in cumene,[98] which looks like going to another extreme solvent-wise.

Other Organolithium Compounds. Preparation

There are not too many other organolithium reagents generally available commercially, and you might find it worthwhile to prepare some which look promising, such as cyclohexyl- or cyclopentyllithium. When doing so, and in any reaction involving Group I and II metals, it has been found advantageous to immerse in the upper part of the reaction mixture half of a razor blade of the old-fashioned variety tied by copper wire to a Teflon rod (see Fig. 2), in such a way that the cutting edge faces against the direction of stirring, thus scratching the metal particles and exposing fresh surfaces continuously. The suggestion has been made that pieces of broken glass be added for that purpose. That does not appear to be good advice, for two reasons: it does not do the flask and in particular the thermometer much good, and since lithium always swims on the top and the broken glass sits at the bottom one would have to stir really hard—and that will really chew up everything! The lithium should be of the kind containing ca 2% of sodium; if this is not specified it should not be used for that purpose. Incidentally, whereas sodium and potassium can be purified by cautious melting under an inert solvent, when the globules of the metal will separate from impurities such as the hydroxide,[99,100] this unfortunately does not apply to lithium. It needs a much higher temperature for melting and when it does there is no such separation from impurities. It can, however, be purified by subjection to ultrasound whilst in (or rather on) toluene; surface dross will separate then and sink to the bottom.

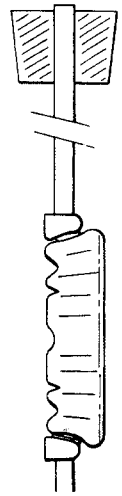


Fig. 2.

Lithium Diisopropylamide

This widely used base is generally prepared by adding the calculated amount of n-butyllithium to a solution of diisopropylamine (distilled from calcium hydride) in tetrahydrofuran or diethyl ether. It is difficult nowadays to find an issue of a journal devoted to organic chemistry where this is not mentioned at least half-a-dozen times. It is natural to look for some way of making a stock solution, but there are problems here. This base also decomposes ethereal solvents at room tempera-