cupboard. Usually in these cases an inert solvent such as ether or tetrahydrofuran is added to the flask before evaporation commences. If time is important the flask may be placed on a warm water bath (c. 45–50 °C) and the flask contents stirred; this should also be carried out in a fume cupboard. In either case a stream of nitrogen may be introduced into the flask if the product is sensitive to atmospheric oxidation. The subsequent treatment of the residue will depend upon the particular reaction and individual experiments should be consulted for typical isolation procedures.

With volatile products which may arise in reactions which do not lead to the initial formation of metal salts (i.e. dehydrohalogenations, alkylations leading to terminal acetylenes) the following procedure is recommended.[35]

The three-necked reaction flask is fitted with a stopcock in one side-neck, a stopper in the second side-neck and a wide-bore glass tube (4–5 mm internal diameter) fitted by means of a rubber bung or screw-capped adapter to the central neck. This glass tube, which reaches to within a few millimetres from the flask bottom, is fitted with a plastic tube which terminates below the surface of an ample quantity of crushed ice contained in a large conical flask. Some extraction solvent which is to be used in the work-up is added to the crushed ice. When the stopcock is turned off the pressure build-up forces the liquid ammonia solution into the ice–solvent mixture, the flow being controlled by periodically opening the stopcock. Additional ice is added to the conical flask as required until the transfer of liquid ammonia solution is complete. The reaction flask is rinsed with extraction solvent and this is added to the main bulk. If the reaction mixture contains large amonts of salts (e.g. sodium halides) it is necessary to swirl the flask in order to keep the salts in suspension and so prevent the tube becoming blocked – if this should happen the stopcock must be opened immediately. An alternative procedure is to allow the salts to settle to the bottom of the reaction flask and gradually lower the glass tube through the liquid as transfer is effected; when all the supernatant liquid has been transferred crushed ice and extraction solvent is added to the residue which is then combined with the main bulk.

2.17.8 REACTIONS INVOLVING AIR-SENSITIVE COMPOUNDS

It is often necessary to carry out reactions in an inert atmosphere or to handle starting materials, intermediates or products which are air-sensitive. Such reactions can be carried out successfully without specialised apparatus, such as Schlenk tubes and purpose-designed vacuum lines,[36] provided attention is given to the detail of the procedure. The procedures described in this section should be routinely within the capacity of advanced students and of the practising organic chemist. Suppliers of air-sensitive materials provide guidance on handling techniques which should always be followed carefully. Particularly useful is the pamphlet published by Aldrich Chemical Company.[37] Reactions involving organolithium reagents (e.g. Expts 5.10; 6.158; 7.3), organoboranes[38] (e.g. Expt 5.44) and Wittig reagents (Section 5.17) are among those which require these standard procedures. The yield from Grignard reactions (e.g. Expts 5.39–5.42) may well be improved if the reactions are carried out in this manner.

Even if reactions of this sort are carried out only relatively infrequently, it is advisable to set up a simple nitrogen (or argon) line which will facilitate many of the operations described in this section. The line leading from the gas cylinder is shown diagrammatically in Fig. 2.70.
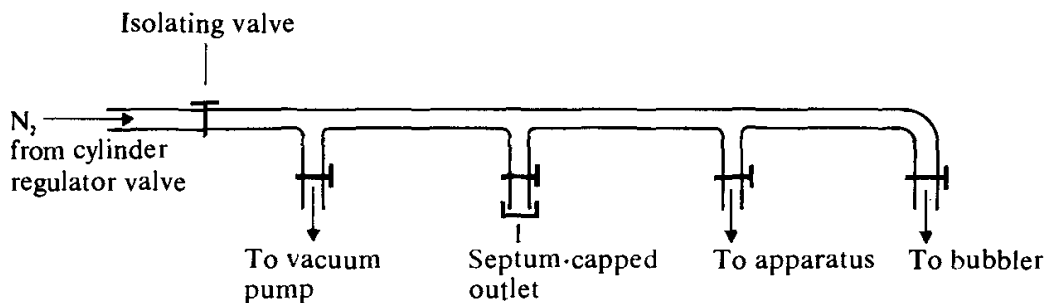
Isolating valve

N,
from cylinder
regulator valve

To vacuum   Septum-capped   To apparatus   To bubbler
pump   outlet

Fig. 2.70

It consists of a pressure reducing valve, a T-piece to allow flushing of syringes and cannulae, T-pieces to allow flow of inert gas to the apparatus and to allow evacuation of the apparatus, and a bubbler to indicate the flow of the inert gas and to allow a slight positive pressure of the inert gas to be maintained in the apparatus. Nitrogen can be led to the apparatus directly by rubber or preferably polythene tubing. It is important that this tubing is dry and flushed with nitrogen before attaching it to the apparatus. It is advisable to keep a selection of tubing specifically for this purpose and not to mix it with tubing used for water condensers and other purposes. An alternative and convenient method of leading nitrogen to the apparatus is to attach a syringe needle to the nitrogen line by means of a wired-in Luer lock fitting. Nitrogen can thus be fed easily into a reaction set-up via a rubber septum.

To carry out reactions successfully in an inert atmosphere it is necessary to ensure each of the following:

1. That the 'inert atmosphere' is in fact inert and does not react with any of the reagents or intermediates.
2. That before the reaction is started the apparatus is thoroughly dry and filled with the inert gas.
3. That all reagents and solvents are dry and oxygen free.
4. That solvents and reagents are transferred to the reaction vessel in such a way that they do not come into contact with air or moisture.
5. That the air-sensitive materials are handled in an inert atmosphere throughout.

How to achieve each of these requirements is described in the following sections.

INERT GAS

Nitrogen is commonly used as the inert gas and the commercially available material is satisfactory for most purposes without pretreatment. If there is any doubt about the purity of the nitrogen gas it may be purified as described in Section 4.2.52. An alternative inert gas to nitrogen may be required in cases where one or more of the reagents (e.g. lithium metal) reacts with nitrogen. In such cases argon may be used although it is considerably more expensive than nitrogen.

DRYING THE APPARATUS AND FILLING WITH INERT GAS

One of the following procedures should be used to ensure that the apparatus to be used is dry and filled with inert gas.

Method 1. Dry the apparatus in the oven (120 °C) for several hours, and

preferably overnight. Allow the apparatus to cool in a desiccator and then assemble with a stream of nitrogen flowing through it.

Method 2. After over-drying, assemble the apparatus hot and allow it to cool while nitrogen flows through it.

Method 3. Assemble the apparatus cold and flame it thoroughly with a Bunsen flame to drive out moisture while purging with nitrogen and allow to cool with continuing nitrogen flow.

Method 4. Evacuate the apparatus using a vacuum pump and refill it with inert gas. Repeat the evacuation and refilling process twice more. This procedure is described in more detail below.

DRYING SOLVENTS AND REAGENTS

Procedures for drying reagents and solvents are described in Chapter 4. Dry solvents which have not been redistilled under nitrogen should be de-oxygenated by bubbling a stream of nitrogen through them using the gas delivery tube shown in Fig. 2.59. This procedure can be carried out conveniently in a two-necked flask equipped with the gas inlet tube and a rubber septum into which a syringe needle is inserted to allow nitrogen to escape after bubbling through the solvent. Solvent may be removed using a syringe or cannula inserted into the septum as described below. An alternative method of ensuring that relatively small volumes of solvent are oxygen free is to use the repeated freeze/thaw cycle. In this procedure the liquid is placed in the reaction set-up and frozen with liquid nitrogen. The apparatus is then evacuated, isolated from the vacuum line and allowed to warm up. Gas absorbed in the liquid is released. The liquid is again frozen and the apparatus is evacuated to pump off the released gases. This process is repeated once more and finally the reaction apparatus is filled with nitrogen. Many dried and redistilled solvents absorb air and moisture very readily and it is therefore advisable to transfer them by the procedure described below using a syringe or cannula so that they are not exposed to the atmosphere.

TRANSFER OF SOLVENTS AND REAGENTS

Liquids. Routine transfer of air-sensitive liquids is carried out with a syringe or with a long flexible wide-bore, double-tipped needle (cannula), which is inserted into reaction vessels and storage containers via a rubber septum. A septum is simply a flexible rubber stopper with a sleeve which folds down over the neck of the container. The septum can be pierced by a syringe needle and reseals itself when the needle is removed. It is thus an essential piece of equipment for reactions in an inert atmosphere. They are available in a range of sizes to fit standard ground glass joints, stopcock arms and containers. Septa gradually deteriorate when exposed to organic solvents for a long period. Exposure to solvents should therefore be limited as far as possible, for example by separating them from refluxing solvent by attaching them to a flask via an interposed stopcock rather than directly into the neck of the flask. After repeated insertion of needles into the septum it will eventually cease to be gas-tight and will need to be discarded.

Glass syringes are available in a wide range of sizes and with a variety of fittings. Syringes for the transfer of small volumes of liquids are individually ground and calibrated and do not have interchangeable barrels and plungers. It is important that the barrels and plungers are used only as a matched pair, otherwise accuracy will be lost and there will be a danger of the plunger sticking in the barrel. Larger volume syringes have interchangeable plungers, although

in this case the accuracy with which the volume of liquid can be measured is reduced. Plastic syringes are also available and although they are suitable for transferring many aqueous solutions they are not recommended for general use in the organic laboratory.

A degree of care is necessary when handling syringes if expensive damage is to be avoided and accurate delivery of volumes of liquid ensured. Care is also needed to ensure that the needle is firmly fitted to the syringe. If it should become detached with the syringe full of air-sensitive or pyrophoric compound the consequences could be disastrous. Two further commonly encountered problems are the attachment of the needle to the barrel of the syringe, and plungers sticking in the barrel of the syringe. With the simple syringe design a tight seal between the syringe and the needle is best obtained by attaching the needle to the barrel when both are hot after drying in the oven, and allowing them to cool together. The greater contraction of the metal needle ensures a good fit. In order to remove the needle subsequently it may be necessary to warm its neck gently in the Bunsen flame. This should not be done until all organic material has been removed by flushing with a suitable low-boiling solvent and 'pumping' to evaporate the remaining traces of liquid. Syringes with Luer lock fittings should not present any difficulty in attaching the needle to the syringe. In order to ensure that the plunger moves freely in the barrel and to minimise the dangers of sticking, the plunger on interchangeable syringes can be lubricated with a small amount of silicone grease. Normally syringe needles have bevelled tips in order to penetrate the rubber septum easily. In some cases it is desirable to have a needle with a flat tip, for example in the flask-to-flask transfer of liquids described below when it is desired to remove the last drops of liquid from a container. These are available commercially, but it is necessary to puncture the septum initially with a normal bevel-tipped needle before attempting to pass the flat-tipped needle through.

A typical procedure for transferring a liquid (5–100 ml) from one septum-capped vessel to another with a syringe is as follows. Select a syringe with a capacity of the same order as the volume of liquid to be transferred. The needle should be long enough to reach below the surface of the liquid to be transferred and also sufficiently long and flexible to allow the syringe to be inverted while still inserted in the septum. Ensure that the syringe and needle are clean. Dry them in an oven at 120 °C for 3–4 hours and allow them to cool in a desiccator. The needle can be attached to the barrel of the syringe while it is hot so that as it cools a tight fit is assured. Flush the syringe with nitrogen as follows. Push the plunger to the bottom of the barrel of the syringe and insert the needle through the septum on the nitrogen line (see Fig. 2.70). Slowly withdraw the plunger to the maximum graduation on the barrel to fill it with nitrogen and then withdraw the needle from the septum. Expel the nitrogen from the syringe and repeat the process of filling with nitrogen and emptying twice more. The syringe is now ready for use in transferring air-sensitive liquids. Ensure that the vessel from which the liquid is to be removed is connected to the nitrogen line and that there is a slight positive pressure of nitrogen. This can be achieved most easily by inserting a syringe needle attached to the nitrogen line through the rubber septum. Now hold the needle of the prepared syringe close to its tip and insert it through the septum into the vessel containing the liquid to be transferred. It should be inserted sufficiently far for the tip of the needle to be below the surface of the liquid in the vessel. Slowly withdraw the plunger until slightly more than

the required volume has been taken up into the syringe. It is quite likely that in this process bubbles of gas will be generated in the liquid and accumulate at the surface of the liquid in the syringe. This gas can be expelled, assuming a sufficiently long and flexible needle has been attached to the syringe initially, by raising the tip of the needle above the surface of the liquid in the flask, carefully inverting the syringe and then expelling the gas into the vessel (Fig. 2.71). The syringe should now contain only liquid and can be returned to the vertical position. The required volume of liquid can be obtained by depressing the plunger appropriately. The needle can now be withdrawn from the septum and the liquid transferred via a septum to the reaction vessel or dropping funnel. The plunger should be depressed gradually to the bottom of the barrel.

If the transfer of an accurately measured volume is required the liquid remaining in the needle should not be expelled by pumping the plunger of the syringe. Syringes are calibrated to deliver a given volume when the plunger is fully depressed. In any event, the volume of liquid in the needle will obviously vary significantly depending on the length and diameter of the needle. Care should be taken in disposing of any reactive material remaining in the syringe needle by carefully drawing into the syringe suitable clean, dry solvent and then expelling the syringe contents into a container for treatment or disposal. The accuracy with which a volume of liquid can be measured with a syringe is limited. With a syringe up to 1 ml an accuracy of 1–2% may be achievable with practice and this should be satisfactory, for example, for the removal of aliquot portions in the estimation of solutions of alkyllithiums (Section 4.2.47, p. 442). With larger volumes the accuracy of measurement decreases. If a precisely measured volume of liquid is required for addition to a reaction it is advisable to pre-calibrate a dropping funnel specifically for this purpose or to transfer an accurately measured volume or weighed amount, rather than rely on the accuracy of a syringe or a graduated dropping funnel.

An alternative to the syringe technique for the transfer of liquids uses the double-ended needle and is suitable when it is not necessary to know precisely the volume of liquid being transferred, or when the volume is being measured in some other way, e.g. by transfer from a septum-capped measuring cylinder. This
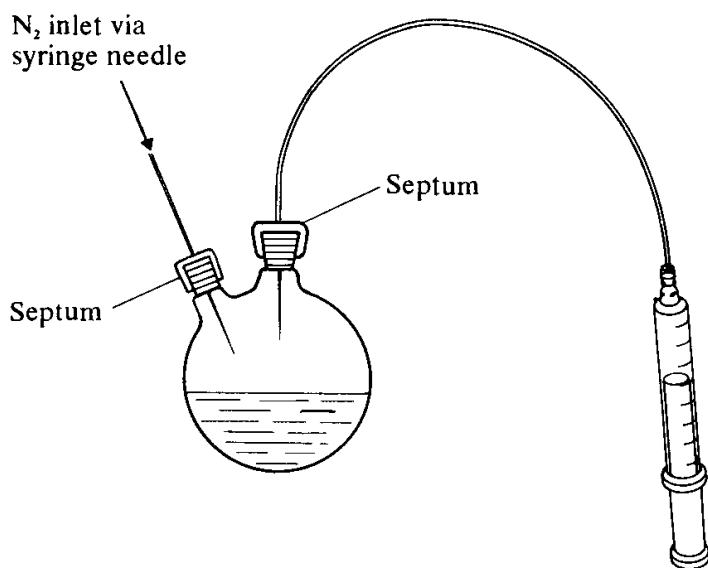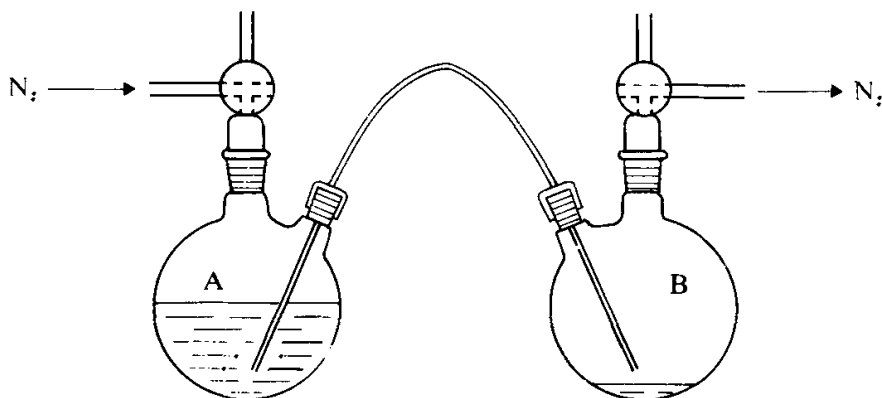
Fig. 2.71

124

Fig. 2.72

method is particularly useful for the transfer of an air-sensitive intermediate from the flask in which it has been prepared into a second reaction set-up, or for the transfer of commercially available air-sensitive material supplied in an airtight container. The procedure is illustrated in Fig. 2.72. The cannula (double-ended needle) is inserted just through the septum of flask A which contains the liquid to be transferred, through which nitrogen is flowing, and purged by allowing nitrogen to flow through it for a minute or two. The other end of the needle is then inserted through the septum of flask B, previously flushed with nitrogen. The tip of the needle in the delivery flask A is then lowered below the level of the liquid. The rate of transfer of liquid can then be controlled by adjusting the flow of nitrogen into the delivery flask with the three-way stopcock. If it is desired to transfer the total contents of the delivery flask a cannula with a flat end rather than the normal bevelled end should be used. The liquid could be transferred if required via a septum to the dropping funnel of the second reaction set-up rather than directly into the flask. On occasions it is necessary to transfer intermediates which have been prepared at low temperature and which would deteriorate if allowed to warm up. This problem may be solved in one of two ways depending on the temperature sensitivity of the intermediate. The first method is to transfer the solution in small batches to the dropping funnel (which could if necessary be jacketed) with the majority of the solution remaining in the cooled delivery flask. Alternatively the cannula itself can be looped and passed through a cooling bath held at the required temperature.

Solids. Some solids can be added to the reaction flask at the start of the reaction before the apparatus is filled with inert gas and therefore present little problem. Examples include magnesium for Grignard reactions and metal hydrides. In the latter case it may be necessary to remove oil in which the hydride is suspended (Section 4.2.*49*, p. 445) and this can be achieved using the procedures described below for separating solids and liquids in an inert atmosphere. If it is necessary to add a solid to the reaction mixture during the course of a reaction, a modification of the apparatus shown in Fig. 2.57 can be used in which a flask with a ground glass neck is linked to the reaction flask by an adapter with two male ground glass joints. Addition of the solid is achieved by rotation of the adapter in the neck of the flask. If the solid is to be added under reflux, the apparatus shown in Fig. 2.58 can be used.

Gases. Gases can be added to reactions in an inert atmosphere by an extension of the standard procedures noted in Section 2.15. If the quantity of gas does not
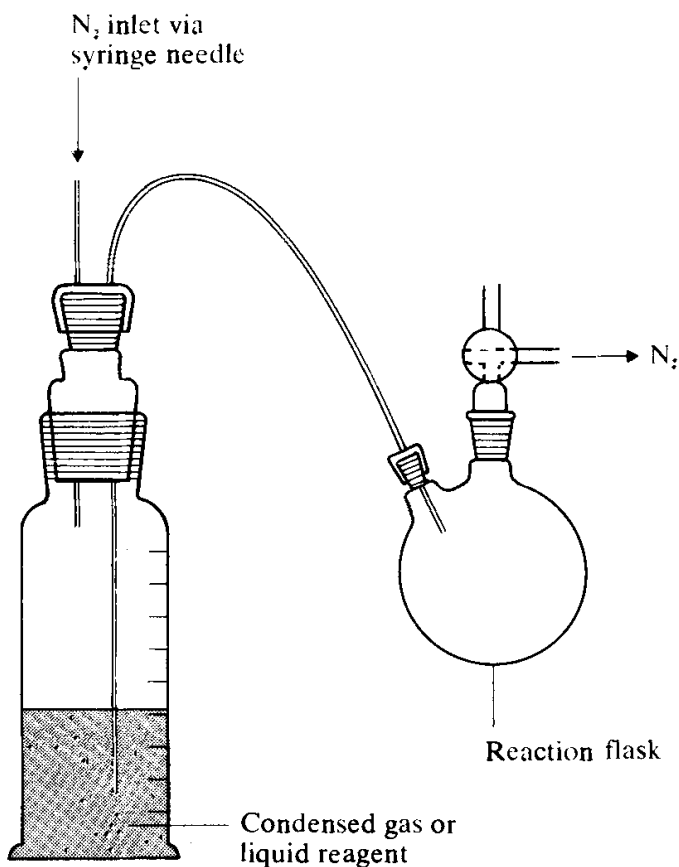
Fig. 2.73

have to be measured (i.e. it is simply required to produce a saturated solution), the gas can be bubbled into the liquid in the normal way as shown in Fig. 2.59, with the appropriate precautions being taken to ensure that the inert atmosphere is maintained. Alternatively a balloon inflated with the required gas and attached to the reaction flask can be used. If it is necessary to add a known quantity of gas the method to be used will depend on the boiling point of the gas. For gases which can be condensed relatively easily, e.g. with a dry-ice condenser, a given volume of gas can be condensed into a measuring cylinder and then allowed to boil off gradually via a cannula into the reaction flask, Fig. 2.73.

For precise determination of the amount of the condensed gas, the container should be weighed before and after the gas is condensed. For gases which are not easily condensed, the volume can be measured using a calibrated gas burette of the type shown in Fig. 2.63(a) and the gas then allowed to pass gradually into the flask after suitable drying or other purification.

MAINTAINING AN INERT ATMOSPHERE IN THE APPARATUS

Normally it is not necessary to have a continuous flow of the inert gas through the apparatus. If the reaction lasts for several hours this can be very expensive in the amount of gas used. It is sufficient to ensure that no air is allowed to enter the apparatus. This is usually achieved by maintaining a slight positive pressure of inert gas in the apparatus by means of a bubbler. It is important that all the ground glass joints are properly secured with spring clips, elastic bands or by being wired on, in order to ensure that they do not leak under the small positive pressure of the inert gas or, more importantly, come apart during the course of
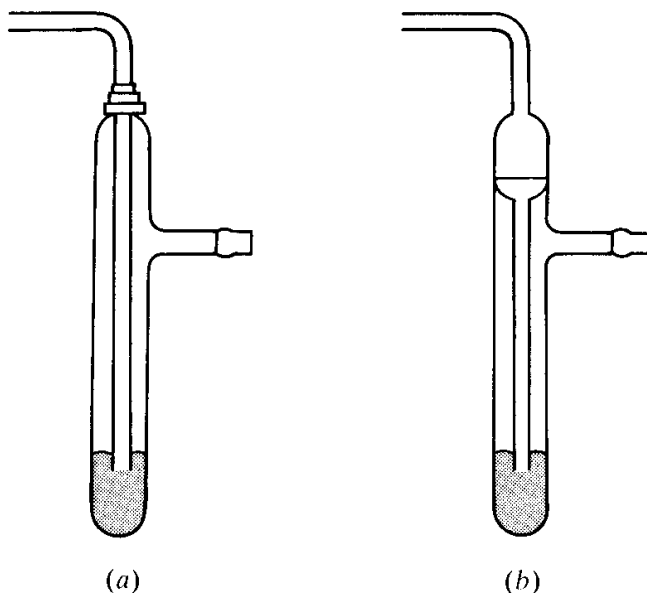
(a)   (b)

Fig. 2.74

the reaction. An alternative and simpler way of maintaining the inert atmosphere is to use the balloon technique in which a rubber balloon is inflated with the inert gas and wired to the reaction flask.* A number of different types of bubblers is available. The simplest type is shown in Fig. 2.74(a) and has been noted in Fig. 2.60.

The positive pressure of inert gas is determined by the height of the liquid (mineral oil or mercury) in the tube. There is a danger in this type of bubbler that a sudden reduction in the pressure in the reaction flask will cause a suck-back of the liquid from the bubbler into the reaction flask. This can be avoided by using a bubbler with an internal reservoir (Fig. 2.74(b)). Although this type of bubbler will prevent suck-back of the liquid in the bubbler into the reaction vessel, it will not prevent the ingress of air. This can be prevented by using a bubbler with a valve which closes when the pressure differential is reversed.

Apparatus for reactions in an inert atmosphere. The experimental set-up will be determined by the nature of the reaction, but in all cases it will be necessary to meet the requirements set out above for the conduct of any reaction in an inert atmosphere. For the majority of purposes commercially available glassware with ground glass joints is adequate. A number of adapters are particularly useful for the addition of reagents via a septum. Several of these are illustrated in Fig. 2.75(a)-(e).The use of some of these adaptors is illustrated in the experimental set-ups which are described below. Either (a) or (b) can be fitted directly to the reaction flask to allow direct addition of reagents to the reaction vessel thus avoiding any undesired contamination which might arise from the use of a dropping funnel. Adapters (a) and (b) also allow removal and transfer of air-sensitive liquids. Adapter (c) can be used to accommodate a thermometer and to allow direct addition to the reaction flask via the septum side-arm. The range of adapters available allows considerable flexibility in arranging experimental set-

---

* The balloon technique is often recommended in suitable reactions to maintain an inert and dry atmosphere within the reaction flask. It should be noted however that air and moisture infuse rather rapidly and that this atmosphere may only be maintained for half-an-hour or so.
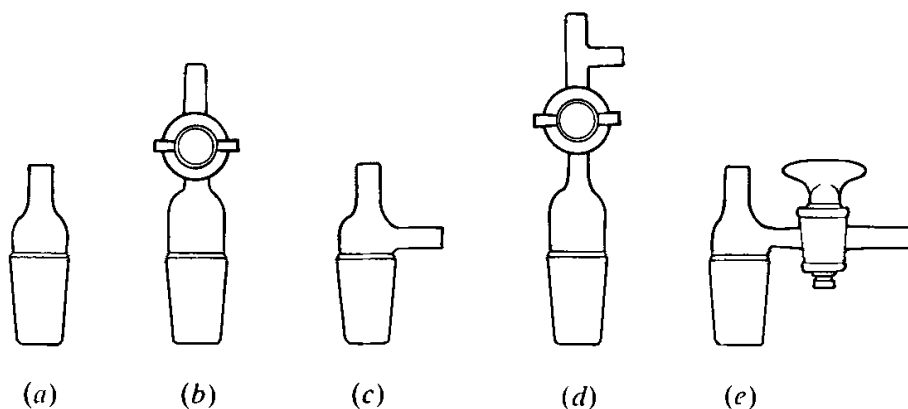
(a)   (b)   (c)   (d)   (e)

Fig. 2.75

ups for reactions in an inert atmosphere. The three-way stopcock which can be equipped with a rubber septum on one of its arms is particularly useful.

Stirring. The most convenient method of stirring, particularly in small-scale reactions, is to use a Teflon-coated magnetic stirring bar (Section 2.14). However, care must be taken to avoid over-rapid stirring which may cause the stirrer bar to fly free from the guiding magnet and penetrate the wall of the flask, with potentially disastrous results. A mechanical stirrer (such as that shown in Fig. 2.51(a) is to be preferred in any of the following circumstances: (i) large volumes of liquids are used; (ii) the reaction mixture is likely to become viscous; (iii) there are large amounts of suspended solids; (iv) very rapid stirring is required.

A very simple apparatus for reaction in an inert atmosphere is a one-necked flask equipped with a magnetic stirrer and three-way stopcock (Fig. 2.76). The vertical arm of the stopcock is fitted with a rubber septum and the horizontal arm leads to a second three-way stopcock giving access to the nitrogen supply and to the vacuum line. This apparatus is suitable for reactions which take place at or below room temperature, do not require addition of solid reagent once the
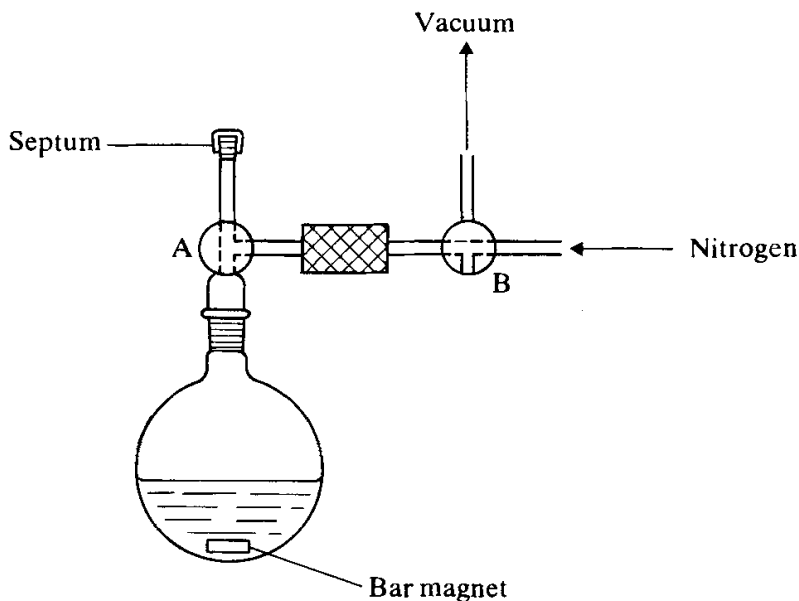

Fig. 2.76

reaction is under way and usually where no excessive gaseous by-products are formed, and where stirring can be accomplished satisfactorily with a magnetic stirrer. The use of this set-up is relatively limited, but the procedures described for filling the apparatus with inert gas and for adding liquids via the septum are of general applicability.

A typical procedure for the use of the apparatus is as follows. Dry the flask in an oven at 120 °C for four hours or overnight and allow it to cool in a desiccator. The stopcocks should be dry and the barrels lightly greased. Charge the flask with any dry solid reagent required at the start of the reaction and with a Teflon-coated magnetic stirring bar. Insert into the neck of the flask the three-way stopcock A fitted with a rubber septum on the vertical arm. Attach the horizontal arm of the stopcock to a second three-way stopcock B, one arm of which is attached to the nitrogen line and one to the vacuum line. Care must be taken in adjusting the stopcocks to ensure that the vacuum is never applied directly to the nitrogen line. Turn stopcock B so that the apparatus is connected to the vacuum line and gradually open stopcock A so that the flask is evacuated. The small volume of air between the barrel of stopcock A and the rubber septum should also be evacuated and replaced by nitrogen by appropriate manipulation of the stopcock. Carefully adjust stopcock B so that the apparatus is connected to the nitrogen line and gradually fill the flask with nitrogen. CAUTION: *The nitrogen flow through the bubbler should be increased and the stopcock turned very slowly in order to avoid any suck-back through the bubbler.*

Once the flask has been filled with nitrogen turn the stopcock B so that the apparatus is connected to the vacuum line and evacuated once more. The process of evacuation and filling with nitrogen should be carried out three times. Adjust stopcock B so that the apparatus is connected to the nitrogen line and reduce the flow of nitrogen to a level sufficient to maintain a slight positive pressure in the system with the occasional bubble of nitrogen passing through the bubbler. Turn stopcock A so that the flask is open to the septum arm and to the nitrogen line, and introduce solvents or liquid reagents into the flask via the septum with a syringe or cannula which passes through the orifice of the stopcock and into the flask. It is advisable to isolate the septum arm from the reaction flask by appropriate adjustment of stopcock A, except when additions are being made, in order to avoid any possibility of leakage through the septum. The reaction flask should however always be connected to the nitrogen line. If the reaction flask should require cooling during the course of the reaction care should be taken to increase the flow of nitrogen through the bubbler to avoid the possibility of suck-back. If any gases are evolved during the course of the reaction they will escape from the exit tube of the bubbler. If these gases present any hazard the exit tube should be passed to a gas absorption trap (Section 2.15) or passed into a fume cupboard extraction vent.

An alternative to the use of the one-necked flask described above is to use the apparatus shown in Fig. 2.77. In this case a two-necked flask is used, with the septum which is used for the addition or removal of liquids fitted to one arm of the flask and a three-way stopcock to the other. With this arrangement it is not possible to isolate the septum from the reaction flask. Should this be required the septum is fitted to a stopcock in the second arm of the flask. Flasks with an integral stopcock are available commercially.

An experiment set-up which is more generally useful is shown in Fig. 2.78. It incorporates a reflux condenser, a pressure-equalising dropping funnel, a ther-
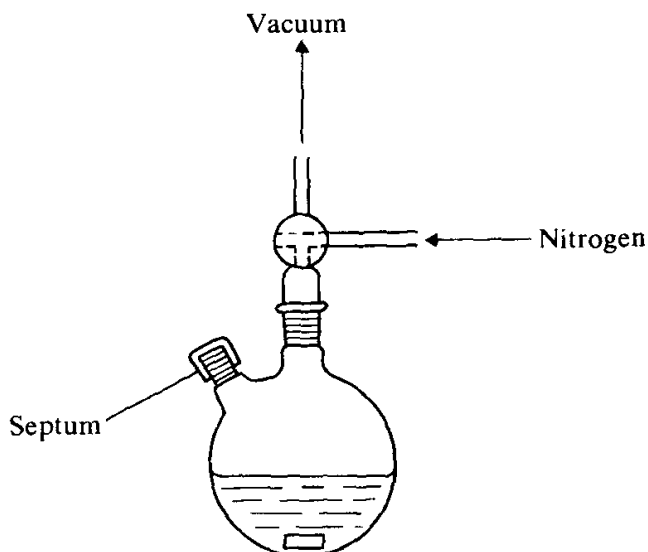
Fig. 2.77

mometer and a magnetic stirrer. If a mechanical stirrer is required the thermometer and reflux condenser can be accommodated in one side-arm using an adapter (Fig. 2.15). This set-up can be flushed with nitrogen at the start of the reaction procedure by opening the stopcock on the dropping funnel and inserting a syringe needle in the septum to allow outflow of nitrogen. On occasions it may be found convenient to use a flask with four necks. Variations in these set-ups can be achieved using the adapters and the reflux condensers described in Section 2.7. Thus, for example, a Dewar condenser (Fig. 2.23) is used for reactions involving liquids with low boiling points.
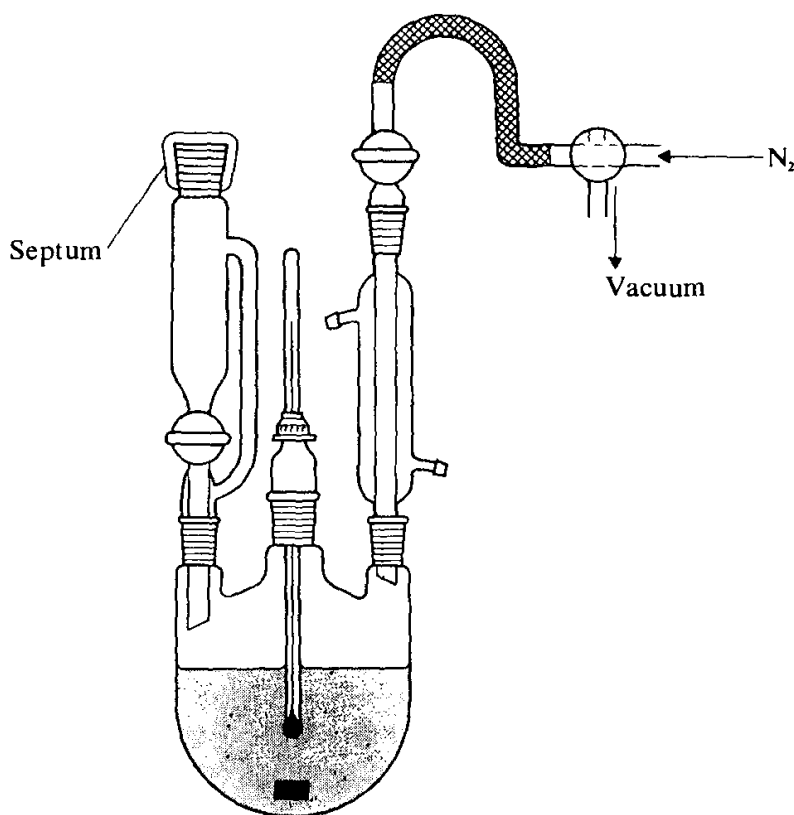

Fig. 2.78

SEPARATION OF LIQUIDS AND SOLIDS

On occasions it is necessary to separate a liquid and a solid in an inert atmosphere. If the liquid and solid separate easily and distinctly with the solid settling to the bottom of the flask, the process of separation can be accomplished by careful use of a syringe or cannula to remove the supernatant liquid. The liquid may be discarded, stored or transferred to another reaction set-up for further reaction as appropriate. The solid remaining in the flask can be washed if necessary by the addition and subsequent removal of further quantities of dry, oxygen-free solvent through the septum. If the solid is desired solvent-free, residual solvent can be removed by connecting the flask to the vacuum line and condensing the solvent in a suitable trap. If the solid and liquid do not separate easily and the solid remains in suspension, filtration will be necessary. The simplest way of achieving this is with the gas dispersion or filter tube with a sintered glass end (Fig. 2.59). The technique is simlar to that described in Section 2.20 (Fig. 2.81) for recrystallisation at low temperature. The filter tube can be fitted to the flask at the start of the reaction or subsequently inserted (after thorough drying) with a rapid stream of nitrogen flowing through the neck of the flask into which the tube is to be inserted. If the solid is required it remains in the flask after further washing. If the liquid is required for further reaction it can be led directly to a second reaction flask.

ISOLATION AND PURIFICATION TECHNIQUES

2.18 GENERAL CONSIDERATIONS

At the conclusion of a reaction the pure product must be isolated from the reaction mixture by a sequence of operations collectively termed the 'work-up'. As well as the required product the reaction mixture may contain, for example, solvent which has been used as the reaction medium, excess reactants or reagents, unwanted reaction products (by-products) arising from alternative reaction pathways and so on. The planning of the isolation operations and application to such complex mixtures is therefore an exacting test of the expertise of the chemist. Frequently a student fails to bring a successful reaction to a fruitful conclusion by using an ill-considered work-up procedure, which results in loss of the required product either by decomposition during attempted isolation, or from a premature discard of product because of lack of appreciation of its physical or chemical properties. It should be emphasised that even when a detailed published procedure is being followed it is unwise to discard any liquid or solid fractions separated during work-up until the final product has been isolated and adequately characterised.

Because of the length of time that a complete isolation process often takes, it is wise practice, particularly with new syntheses carried out for the first time, to monitor the progress of the reaction. Thus the disappearance from a reaction mixture of one of the reactants or the build-up of the reaction product, measured on small aliquot portions removed at convenient time intervals from the bulk reaction mixture, can yield valuable information on the progress of a reaction. Usually the former is to be preferred since the physical properties (e.g. spectroscopic information, Chapter 3), chemical reactivity (e.g. characteristic tests of functional groups, Section 9.5) and chromatographic behaviour (Section 2.31) of