Theory, Scope, and Methods of Recrystallization

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Properly applied to appropriate mixtures, recrystallization is often the best method for the separation and purification of organic compounds. The conditions under which a single compound may be isolated, or two compounds may be "completely" separated, are discussed; attention is drawn to mixtures inseparable by recrystallization and to those which yield only one pure component. The applicability of simple batchwise and of continuous countercurrent recrystallization is considered. Schemes for batchwise, countercurrent fractional recrystallization are outlined, and the distribution of the components in the phases after each recrystallization cycle is investigated.

IN BIOCHEMISTRY and synthetic organic chemistry there is probably no greater thrill than that derived when a substance which has stubbornly defied crystallization is obtained in crystalline form. Why is the chemist so pleased to get crystals? Only incidentally does he delight in their beauty. Primarily, he is gratified because a way is opened up, first, for purification of the material by recrystallization, and secondly, for recognition of its purity and chemical identity by virtue of the special physical properties exhibited by crystals—e.g., melting point, crystallographic characteristics, and x-ray diffraction.

The process of recrystallization is one of the oldest methods known for the separation and purification of organic compounds. When properly applied to appropriate mixtures it is often the best method for sorting out the molecules. However, at one time it fell into disrepute, when certain mixtures not amenable to this treatment were encountered. Thus, the fact that a product has been repeatedly recrystallized and has a sharp melting point, unchanged by further recrystallization, does not prove that it is pure; it may be a eutectic composition or a special type of solid solution.

GENERAL PRINCIPLES OF RECRYSTALLIZATION

In order that a mixture may be recrystallized, it is obviously essential that the desired components shall first have been obtained crystalline. It will be assumed that crystallization has been effected, yielding a batch of crystals of compound A contaminated with compound B, substances which do not form a compound or compounds with each other. The problem is either (1) to separate A from B, possibly obtaining both A and B in pure condition, or (2) to purify either A or B. The discussion is limited to a consideration of the behavior of supersaturated solutions, including supercooled melts.

Let us first consider the simplest case, in which the mixture can be melted without decomposition of A or B. When the melt is cooled, in the presence of nuclei of A and B, solid solutions of A and B may or may not be deposited.

Solid Solutions Not Formed. If solid solutions are not formed we have a simple eutectogenic system as shown in Figure 1. If A is present in excess (relative to the eutectic composition, *C*) it will crystallize first and continue to crystallize with slow cooling until the eutectic temperature *D* is reached, when the eutectic composition of A and B will crystallize. On the other hand, if B is present in excess of composition *C*, compound B will crystallize until the eutectic temperature is reached. In the absence of secondary effects due to adsorption and inclusion, these crystals of A or B will be practically pure. If they are filtered off just before the eutectic temperature *D* is reached and recrystallized a few times in the same way, they are usually obtained very pure. Exceptions to the above are encountered if nucleating crystals of one component are unobtainable or deliberately withheld, or if one component crystallizes much more slowly than the other, when it may be possible to pass the eutectic temperature without deposition of the mixture having the eutectic composition.

It is therefore evident that, if A and B give a simple eutectic, it is possible to obtain the component present in excess in pure condition. It is not possible to obtain both A and B pure from the recrystallization of a given mixture under equilibrium conditions In order to obtain the other component pure, it is necessary to apply some other technique which will separate the eutectic composition. If the starting material already had the eutectic composition *C*, no separation by recrystallization is possible, except by overshooting the eutectic point. Thus, this kind of system gives an all-or-none effect as regards purification of one component. In a sense, it resembles distillation of two immiscible liquids.

In recrystallization from the melt, a series of fractions of crystals is obtained by stepwise cooling. If of comparable purity, the fractions are combined and recrystallized; if not, each fraction is remelted and again fractionated by stepwise cooling. Thus, the steps in one recrystallization cycle are: (1) melt the mixture, (2) supercool the melt, (3) nucleate, if necessary, (4) encourage growth of the crystals, and (5) separate the crystals from the melt. (Another method which is applicable involves stepwise partial melting of the crystals.) In certain cases such fractionations of an impure melt are highly effective, as in the purification of mobile, chemically stable liquids such as benzene, *p*-xylene, benzoic acid, and acetanilide. However, as a rule, they are not very practical because of such factors as high viscosity (which may retard crystallization), chemical instability, and difficulty of removal of crystals if the melt is viscous.

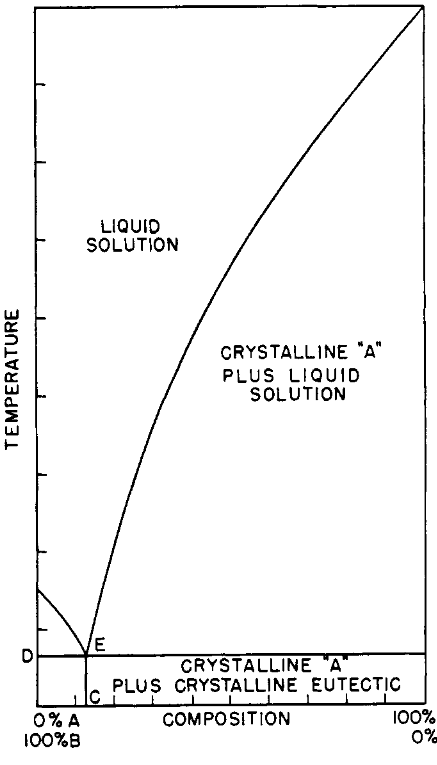

Figure 1. Relation between Composition and Freezing Temperature of Mixtures of Two Components Giving a Eutectic Only, Naphthalene-Benzene System (*13*)

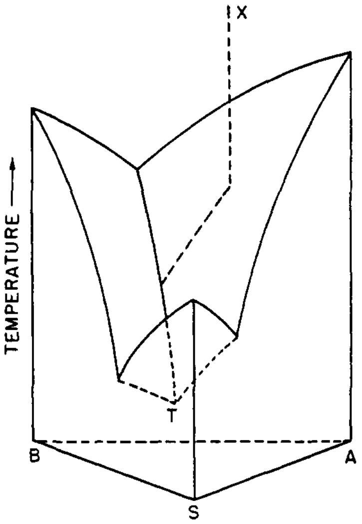

Figure 2. Relation between Composition and Freezing Temperature of Hypothetical Three-Component Solution Depositing No Solid Solutions

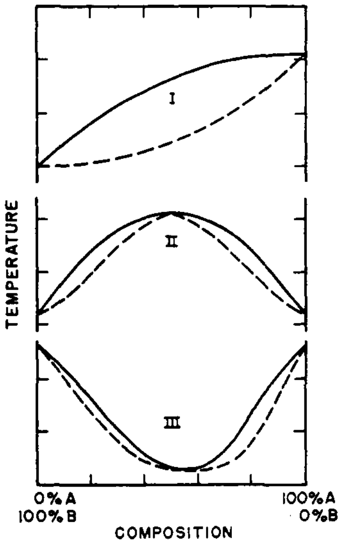

Figure 3. Freezing Points of Hypothetical Continuous Series of Solid Solutions

As a rule, it is preferable to recrystallize from a suitable solvent, *S*, which does not form solid solutions with the solutes (Figure 2). It must be borne in mind that, depending on the proportions of A, B, and *S* there is the possibility of deposition, on slow stepwise cooling—e.g., from *X*—of (1) any one component, if present in excess of its eutectic compositions; (2) any one binary eutectic composition, if present in excess of the ternary eutectic; and (3) the ternary eutectic, *T*. Apart from its polar effects, the solvent may be regarded as an inert medium which dilutes the system, lowering the viscosity so that crystallization may proceed at a reasonable rate, and providing a mother liquor in which the eutectic of A with B remains when the desired crystals are filtered off. One or two simple recrystallizations will usually suffice to give extremely pure crystals. In fact, in this event, the most complete purification possible by recrystallization then results.

The methods employed for the isolation of successive fractions of crystals are, of course, essentially those used for obtaining a supersaturated solution. Thus, by stepwise cooling to successively lower temperatures, a series of crops of crystals is obtained. It is sometimes possible to use differential crystallizability. Another method consists in stepwise introduction of a suitable third solute which may be a solid, a gas, or a poor solvent. Finally, controlled fractional evaporation may be employed. Combinations of these methods are often advisable.

Solid Solutions Formed. If A and B form solid solutions but no compound with each other, there are five possibilities. If A and B form a continuous series of solid solutions (see Figure 3) and the melting point of every possible composition lies between those of pure A and B (see curve I), the first crystals deposited are richer in one component than was the original melt. The melt naturally becomes correspondingly poorer in this component. Consequently, by repeated fractional recrystallization it is possible eventually to isolate pure A and pure B. This is the only two-component system which gives both components pure by fractional recrystallization of a given composition under equilibrium conditions. The diagram (I, Figure 3) resembles that for the fractional distillation of two liquids giving no azeotrope.

In other systems, there may be a composition of maximum (II) or minimum (III) melting point. In this event, purification proceeds only as far as pure A or pure B as one fraction, and the composition of maximum or minimum melting point as the other fraction. The result obtained thus depends on which side of this constant composition the original composition had been. If the starting material has the composition of maximum or minimum melting point, no separation is possible. The situation is precisely that encountered with azeotropes in distillation.

If there is a discontinuous series of solid solutions, there may be a eutectic of two types of solid solution, or there may be a system with a transition point. Similar principles apply to such systems.

Should a suitable solvent (which does not form solid solutions with the solutes) be added, in appropriate proportion, results similar to the above will be obtained. The possibility of deposition of the various eutectics with solvent must again be borne in mind—see, for example, Figure 4, which represents the only case in which both A and B can eventually be obtained pure from one starting composition, under equilibrium conditions.

SCHEMES FOR REPEATED RECRYSTALLIZATION

All fractionation procedures, whether involving distillation, extraction, diffusion, sublimation, or recrystallization, are schematically much the same, but the terms normally employed to describe the processes are different, as shown in Table I.

Subsequent discussion is confined to consideration of recrystallization from an added solvent, as a means of separation or purification. Such recrystallization is a repetitive process. After a suitable solvent has been chosen, the steps in one recrystallization cycle are as follows: (1) dissolution of the crude substance in the solvent (and removal of any insoluble impurity); (2) preparation of a supersaturated solution; (3) nucleating, if necessary; (4) growth of the crystals—i.e., usually, equilibration; (5) separation of these crystals from the mother liquor; (6) washing, if necessary; and (7) drying the crystals. When a supersaturated solution of compound A is caused to crystallize and is kept until equilibrated—i.e., until crystallization is complete at the chosen temperature—there is a distribution of A

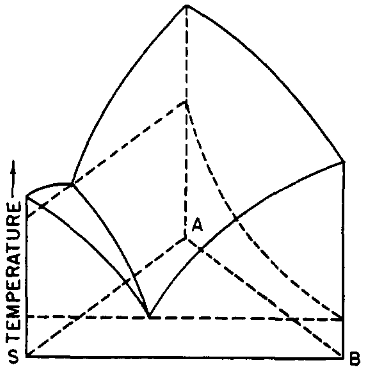

Figure 4. Relation between Freezing Temperature and Composition of Hypothetical Three-Component Solution

Continuous series of solid solutions of A and B with no maximum or minimum freezing point

Table I. Comparable Terms Employed in Three Fractionation Procedures

Recrystallization	Distillation	Liquid-Liquid Extraction
Crystallizand	Distilland	Extrahend
One recrystallization cycle	One simple distillation	One equilibration
Crystals	Distillate	Extract
Mother liquor	Still residue	Raffinate
Distribution constant = $\frac{\text{weight of A as crystals}}{\text{weight of A in mother liquor}}$		Partition coefficient = $\frac{\text{weight of A in extract}}{\text{weight of A in raffinate}}$

between crystals and mother liquor which is usually expressed as per cent yield (ratio of the weight of crystals to the original weight of A) but which can be expressed as a distribution constant relative to the two phases as shown in Table I. For pure A and a given solvent, this ratio will be a constant, provided that the proportion of solvent to solute is constant, the upper and lower temperature limits are accurately controlled, and equilibrium is reached in the recrystallization.

There are three general ways of contacting phases in a separation process: (1) simple batchwise, (2) cascade or batchwise countercurrent, and (3) continuous or differential countercurrent treatment.

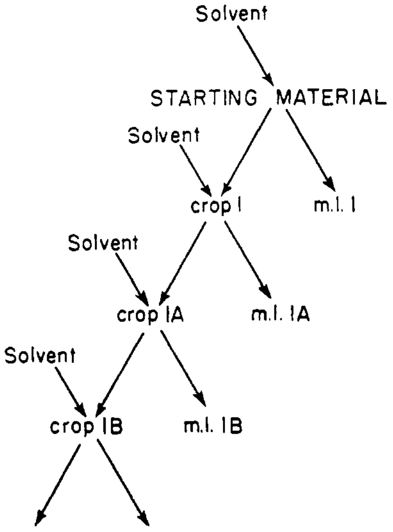

Figure 5. Simple Repeated Recrystallization

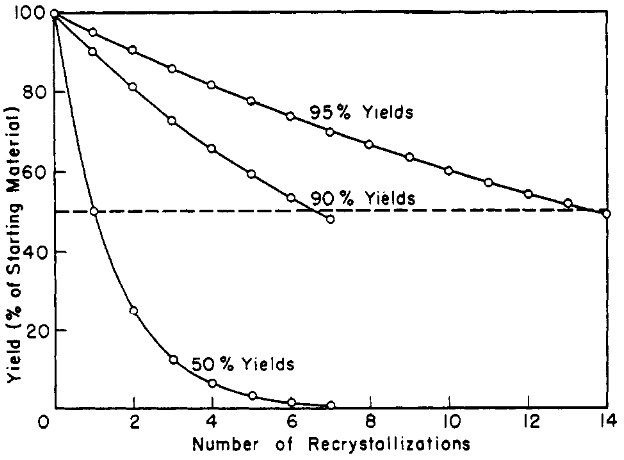

Figure 6. Typical Successive Yields for Repeated Simple Recrystallizations

Simple Batchwise Repeated Recrystallization. For purification involving removal of a small proportion of impurity, a number of simple recrystallizations may be performed as shown in Figure 5. After each recrystallization, an estimate of the degree of purification achieved is made. The mother liquors (m.l.) are discarded, reworked, or, if A and B are eutectogenic, they are pooled and their components are separated by some other method. Simple repeated recrystallization may be regarded as a multiple or successive contact process using fresh solvent at each stage. It is analogous to a one-stage batchwise extraction, which Hunter and Nash (*12*) call "multiple-contact extraction." In each recrystallization there is equilibration corresponding to that achieved by thorough shaking in multiple fractional extraction.

Two important points are the yield of crystals and the purification effected in each recrystallization cycle. Figure 6 compares the successive yields on repeatedly recrystallizing material, at yields of 95, 90, and 50% per cycle. Thirteen recrystallizations at 95% give about the same final yield (50%) as six at 90% yield per cycle. In this graph, and those which follow, the lines joining the points are drawn in as a visual aid the process is actually discontinuous.

Table II. Ways of Expressing Enrichment

(1)[a] $\dfrac{\text{Weight of A in crystals separated}}{\text{weight of A in mother liquor}}$

(2)[a, b] $\dfrac{\text{Concentration of A in crystals separated}}{\text{concentration of A in original crystals}}$

(3)[a] $\dfrac{\text{Concentration of A in crystals separated}}{\text{concentration of A in crystals next separated (from mother liquor)}}$

[a] (*23*).
[b] (*24*).

If A and B are eutectogenic there will not be a great deal of B as impurity in A (or vice versa) after the first recrystallization, and therefore we may be able so to choose the solvent, its amount, and the upper and lower temperature limits as to obtain a good yield—e.g., 95%—at each recrystallization cycle after the first. Because only a few recrystallizations will usually be necessary, the final yield may still be high and the product very pure.

However, if A and B give solid solutions—e.g., of the type shown in Figure 4, to which the ensuing discussion is mainly confined—the situation is different. In the first place, the procedure may entail great loss of material because many recrystallizations may be necessary. Secondly, if the proportion of impurity removed at each stage is constant, this series will constitute the first term of a binomial expansion. Thus, although it is usually fairly easy to raise the purity from 80 to 90%, it is more tedious to raise it from 90 to 99%, still more tedious to raise it to 99.9%, and usually extremely tedious to raise it to 99.99%. That is because 100% purity is approached asymptotically.

There are various ways of expressing enrichment (*23*), as shown in Table II. In the following discussion, the first is employed as being the ratio most intelligible to and convenient for the organic chemist.

Let us consider a simple, hypothetical, numerical example. Suppose that we start with 200 grams of a 50–50 mixture of A and B. The solvent, its amount, and the higher and lower operating temperatures are so chosen that, for B, half goes into the crystals and half remains in the mother liquor at each recrystallization stage. Hence, the distribution constant for

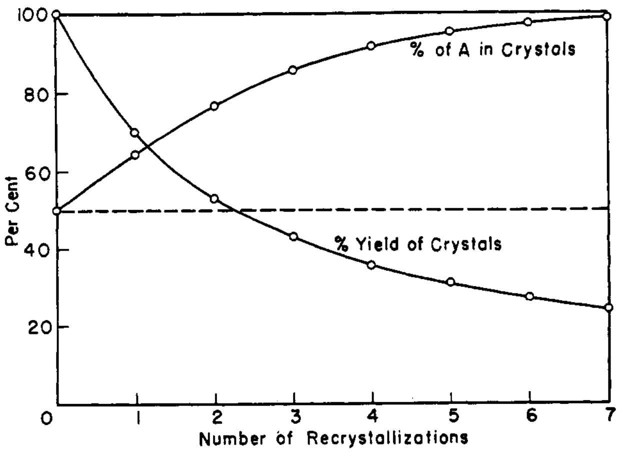

Figure 7. Yield and Purity of Successive Crops of Crystals in a Repeated Simple Recrystallization

In terms of % A:
$K_A = 9$; $K_B = 1$

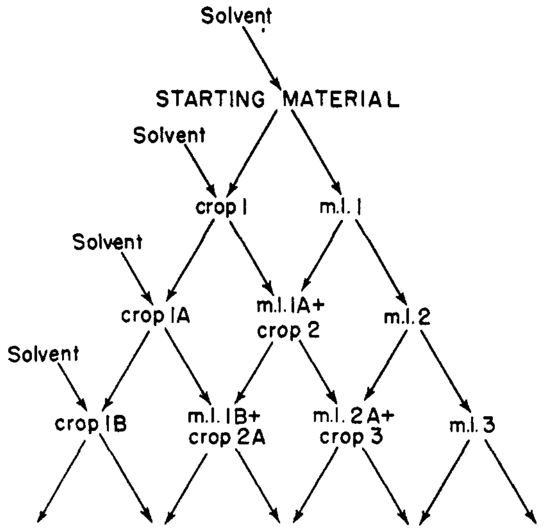

Figure 8. Triangular Fractional Recrystallization

$B = K_B = \frac{\text{weight of B in crystals}}{\text{weight of B in mother liquor}} = 1$. We shall suppose that, under these conditions, 90% of A crystallizes out in each step, and 10% stays in the mother liquor—i.e., $K_A = 9$. [It is assumed that conditions can be achieved such that K_A and K_B really are constants. If the solid solutions and liquid solution which are in equilibrium are not too concentrated, this can be accomplished with such systems as thiophene-benzene in bromoform (*2*), phenol-benzene or piperidine-benzene in benzil (*4*) and *p*-dichlorobenzene-*p*-dibromobenzene in alcohol (*17*). If K_A and K_B are not constants, the schematic principles involved will be similar, but the mathematics will be more complicated (*10, 15, 21*). An important factor is the speed of crystallization (*21*).]

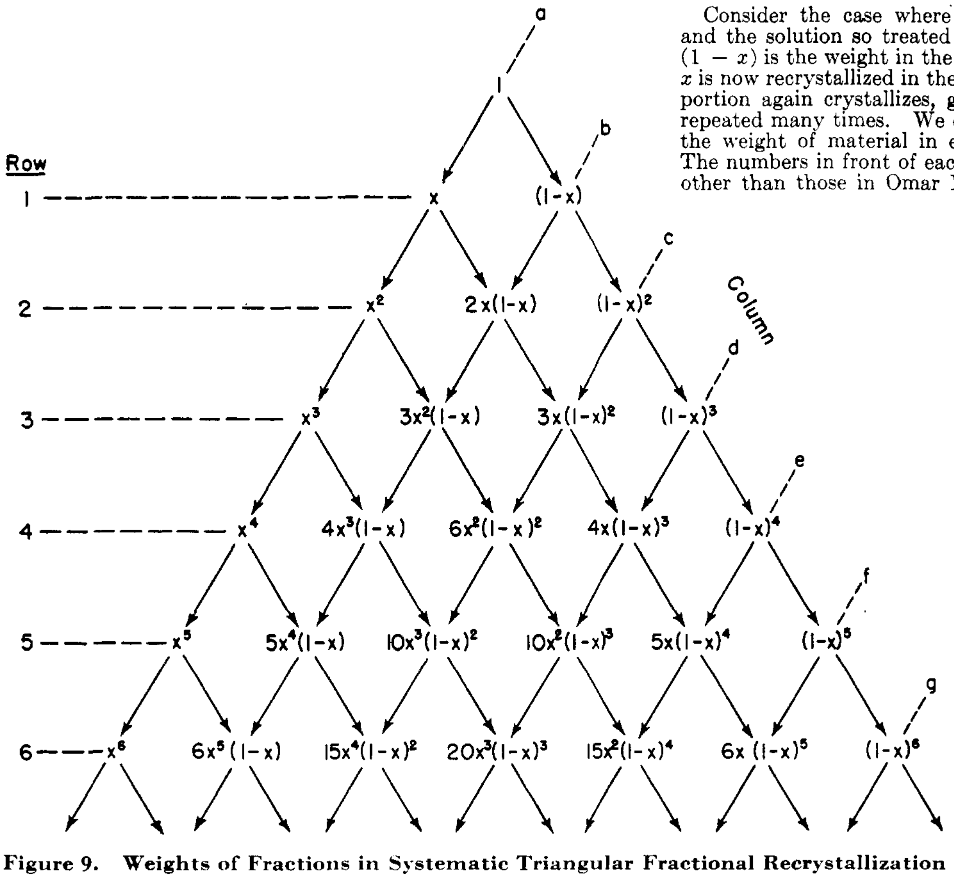

Figure 9. Weights of Fractions in Systematic Triangular Fractional Recrystallization

The results of several simple recrystallizations under these conditions are shown in Figure 7, from which it is seen that, after seven recrystallizations, crystals containing 98.4% of A are obtained, but in only a 24.3% yield. In this example, very favorable distribution constants of 9 and 1 were chosen. But if the constants were 1.5 and 1, many more recrystallizations would be necessary to give the same degree of purity, and the loss of product would be much greater.

Cascade or Batchwise Countercurrent Recrystallization. In order to avoid the losses entailed in discarding the mother liquors, the principle of cascade fractional recrystallization was introduced. The schematic principles involved resemble those of cascade fractionation by extraction (*6*), precipitation (*9*), or distillation in a bubblecap still.

Cascade recrystallization differs from simple repeated recrystallization in that both the crystals and the mother liquor (m.l.) are repeatedly fractionated. In separation of A from B, to obtain both A and B, use of this process (or of continuous recrystallization) is essential. The procedure is normally performed batchwise and is an example of countercurrent distribution—that is, if one solute moves to the right, the other moves to the left. Such a scheme, often referred to as "triangular" fractional recrystallization, is shown in Figure 8. As a rule it is, like Craig's countercurrent liquid-liquid distribution (*7*), a discontinuous process operating at complete equilibrium in each cycle.

Separations depend upon the difference in the partition (between crystals and mother liquor) for A and B, respectively (*7, 16, 26*). It is assumed that, at equilibrium, the distribution ratio of one solute between the two phases is independent both of the absolute value of the concentrations and of the presence of other solutes; this is not necessarily true at high concentrations. The degree of separation achieved also depends on the number of recrystallizations applied; compounds A and(or) B may be isolated in any desired degree of purity by repeating the recrystallizations enough times (*25*).

Consider the case where unit mass of a solute is dissolved and the solution so treated that fraction x crystallizes out and $(1 - x)$ is the weight in the mother liquor. This crop of weight x is now recrystallized in the same manner, so that the same proportion again crystallizes, giving a crop of weight x^2. This is repeated many times. We can then draw up the table, showing the weight of material in each fraction, depicted in Figure 9. The numbers in front of each term in these expressions are none other than those in Omar Khayyam's mystical triangle, which led to his discovery of the binomial theorem. We see that the quantity in each row is a term in the binomial expansion

$$[x + (1 - x)]^n = 1$$

where n is the number of the row. [The same principle applies in systematic liquid-liquid extraction (*5*).]

Thus, when applied to the separation of two solutes, the over-all process can be set up to follow the binomial theorem. It is most efficient when a constant numerical fraction of the preceding weight is present as the crystals collected in each recrystallization step. The optimum value of this fraction will depend on the shape of the temperature-composition diagram of the original mixture.

In 1886, Crookes (*9*) came to the conclusion that, for an approximately 1 to 1 binary mixture (presumably having a fairly symmetrical temperature-composition diagram), the best separation (in terms of labor, and yield of both components) requires that x and $(1 - x)$ be equal—i.e., that half the material is crystallized out and half remains in the mother liquor—in each recrystallization cycle (*11*, *14*). The same principle has been discussed in relation to the separation of gases by diffusion (*18*, *19*). [Of course, if we wished to obtain very pure A in small amount in a few steps, it would pay to crystallize out a small percentage of A in each step. Similarly, the most rapid purification of B may result when the crystal crops are large. Consequently, it is sometimes desirable to produce a variable crop size in the recrystallization scheme—e.g., by slight additional evaporation during each fractionation—thus giving more rapid purification of small amounts of both A and B.]

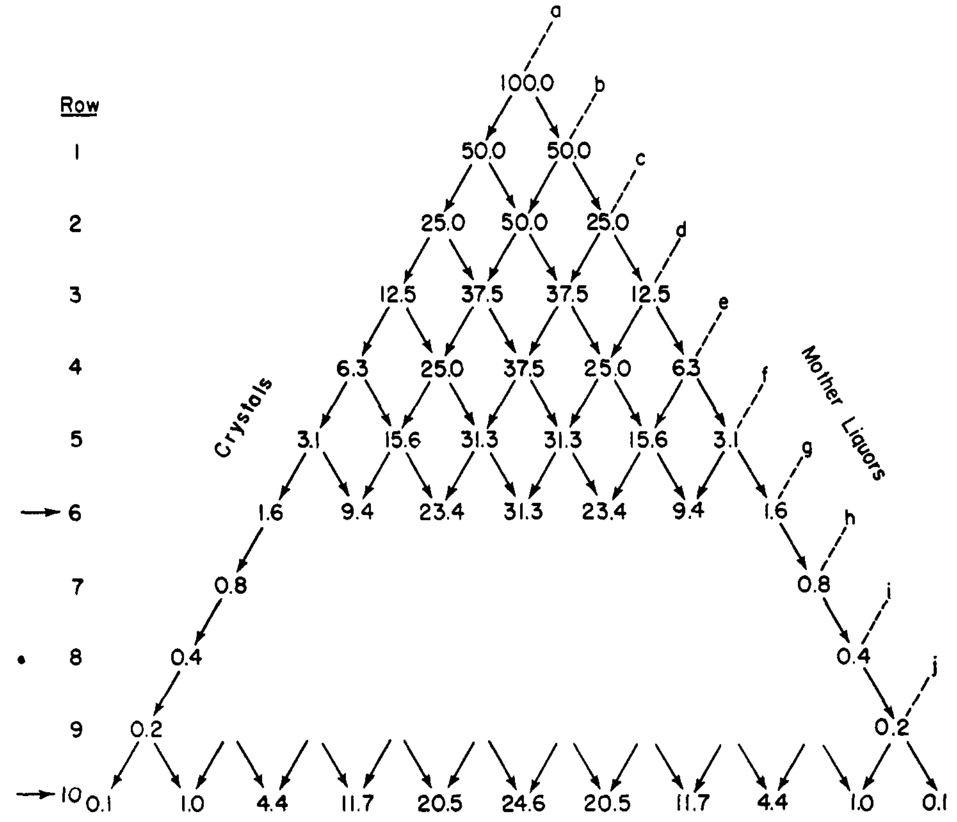

Figure 10. Actual Yields in Triangular Fractional Recrystallization

To nearest 0.1 gram
100 grams of material at 50% yield per recrystallization

First of all, let us examine the yields of each fraction in a "triangular" recrystallization of 100 grams of starting material, with a 50% yield per recrystallization. The weights of each fraction are shown in Figure 10. If we now plot the column letter against the weight of the fraction—e.g., at the sixth and tenth rows—symmetrical distribution curves are obtained for a single solute crystallizing from a solution at $K = 1$. It is found that the weights of the different fractions gradually decrease from the middle out toward the two ends, following the bell-shaped distribution curve or normal curve of error and becoming identical with it when n is infinite. In Craig's countercurrent extraction apparatus, this distribution occurs in a set of tubes arranged consecutively (*7*). Secondly, we find that the maximum of this distribution curve migrates along the row according to the row number. Thirdly, if we now plot the distribution curves when one third of the solute crystallizes out in each step—i.e., when $K = 0.5$—it will be seen that the rate of migration of the peak is related to the distribution constant. Furthermore, it is noted that, in this instance, there is a skew distribution.

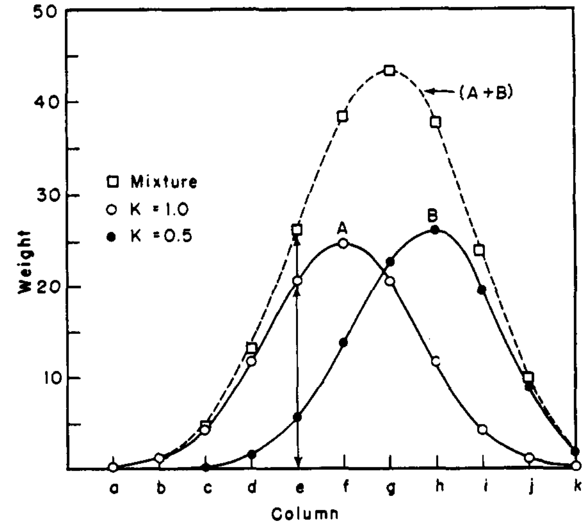

Figure 11. Tenth Row of Hypothetical Triangular Fractional Recrystallization

50–50 mixture of A and B
$K_A = 1.0$; $K_B = 0.5$

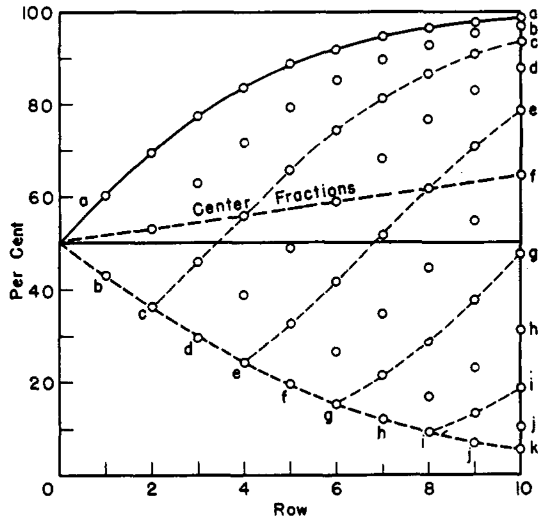

Figure 12. Purity of Every Fraction in Hypothetical Triangular Fractional Crystallization

In terms of % A
50–50 mixture of A and B
$K_A = 1.0$; $K_B = 0.5$

If we have two solutes, A and B, of different distribution constants, which migrate independently of each other, the resultant curve may be directly additive—i.e., it may be a summation of two such distribution curves, with regard to content of A and B, and may therefore be skew, as shown in Figure 11. This is precisely analogous to what happens in Craig's countercurrent scheme of liquid-liquid extraction (*6*, *7*, *27*). If the ratio of the distribution constants of A and B is large, separation is not too difficult. If K_A/K_B is greater than 2, many fewer recrystallizations are needed than if K_A/K_B is less than 2. The nearer the ratio approaches unity, the greater the number of recrystallizations necessary; and when it equals unity A and B are impossible to separate. It is therefore advisable to search for a solvent which gives a large ratio, or else to operate with derivatives of A and B with a more desirable ratio in the chosen solvent.

Let us now consider the purity of each fraction, with respect to A or B. After a few points have been established, we can obviously read off the per cent purity of any fraction from the curves (Figure 11), without extensive calculation. It is only necessary to divide the ordinate for A or B by the ordinate on the summation curve at any particular column. We then obtain the purity curves in terms of % A and % B—that is, a combination of the terms of two binomial series expresses the per cent purity of each fraction. Thus, if the weight of A equals 1 and the weight of B equals 1 in the original mixture, and if in row 1, the weight of A in the crystals equals x and the weight of B in the crystals equals p, then the weight of A in the mother liquor equals $(1 - x)$ and the weight of B in the mother liquor equals $(1 - p)$. Therefore, at equilibrium, $K_A = x/(1 - x)$ or $x = K_A/(1 + K_A)$ and $K_B = p/(1 - p)$ or $p = K_B/(1 + K_B)$. The per cent of A in every fraction (every row and every column) may then be expressed as shown in Table III, where $(1 - x) = y$ and $(1 - p) = q$.

By means of Table III, let us now draw the curves expressing the per cent purity of every fraction for the hypothetical case when $K_A = 1$ and $K_B = 0.5$—i.e., $K_A/K_B = 2$. Two ways of doing this are shown in Figures 12 and 13. It is seen that the center fractions show gradual enrichment with regard to A and

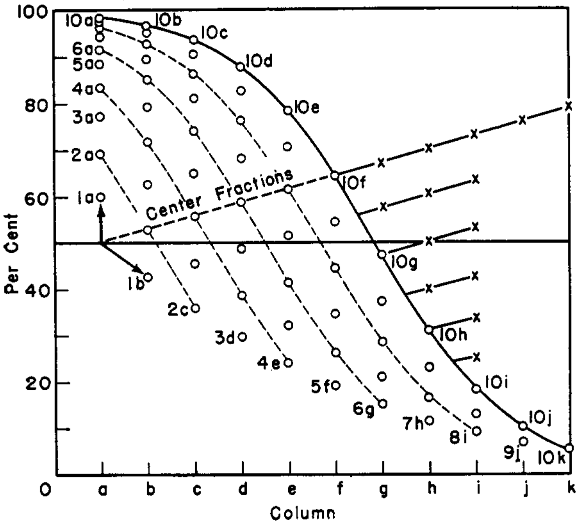

Figure 13. Purity of Every Fraction in a Hypothetical Triangular Fractional Recrystallization

In terms of % A
50–50 mixture of A and B
$K_A = 1.0$; $K_B = 0.5$

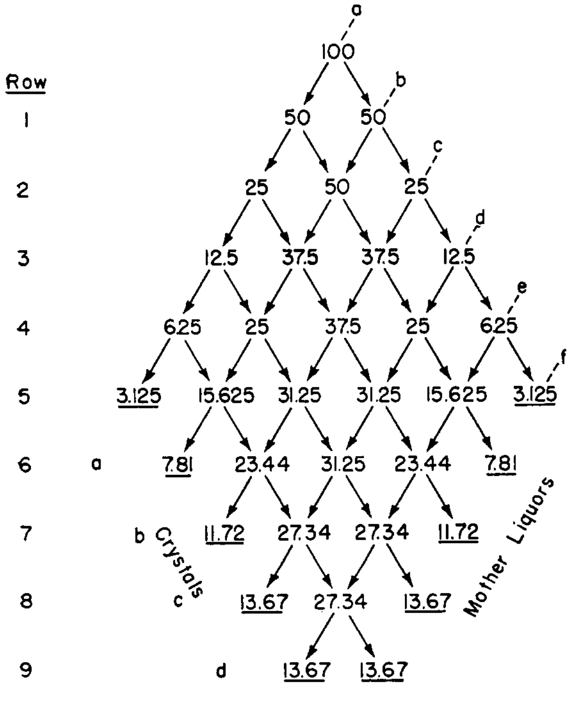

Figure 14. Weights of Fractions in Diamond Fractional Recrystallization

100 grams of material at 50% yield per recrystallization

Table III. "Purity" of Every Fraction (% of A) in a "Triangular" Recrystallization

Column Row	*a*	*b*	*c*	*d*	*e*	*f*
1	$\frac{x}{x + p}$	$\frac{y}{y + q}$				
2	$\frac{x^2}{x^2 + p^2}$	$\frac{xy}{xy + pq}$	$\frac{y^2}{y^2 + q^2}$			
3	$\frac{x^3}{x^3 + p^3}$	$\frac{x^2y}{x^2y + p^2q}$	$\frac{xy^2}{xy^2 + pq^2}$	$\frac{y^3}{y^3 + q^3}$		
4	$\frac{x^4}{x^4 + p^4}$	$\frac{x^3y}{x^3y + p^3q}$	$\frac{x^2y^2}{x^2y^2 + p^2q^2}$	$\frac{xy^3}{xy^3 + pq^3}$	$\frac{y^4}{y^4 + q^4}$	
5	$\frac{x^5}{x^5 + p^5}$	$\frac{x^4y}{x^4y + p^4q}$	$\frac{x^3y^2}{x^3y^2 + p^3q^2}$	$\frac{x^2y^3}{x^2y^3 + p^2q^3}$	$\frac{xy^4}{xy^4 + pq^4}$	$\frac{y^5}{y^5 + q}$
n	$\frac{x^n}{x^n + p^n}$	etc.				

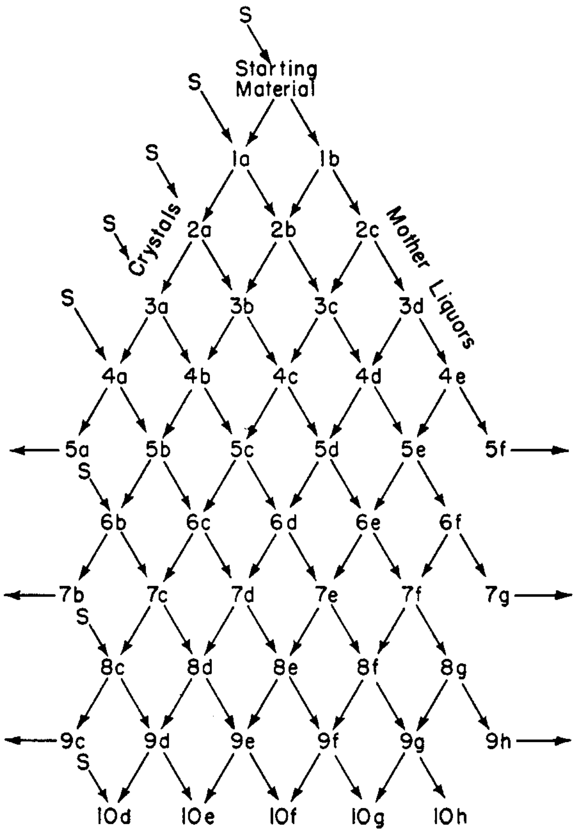

Figure 15. Double Withdrawal Scheme of Fractional Recrystallization

the "outer" fractions are asymptotic to 100% A and 100% B. The purity of fractions still to be obtained can then be read off, as at points X in Figure 13. It is seen that the crystal fractions are progressively enriched in compound A, while the mother liquor fractions are progressively impoverished in A as the number of recrystallizations increases. We see that the enrichment tends toward infinity, but that the purer the fraction the less its weight. Hence, unless the object is to prepare a small sample of very pure material, the simple triangular scheme is not of much use.

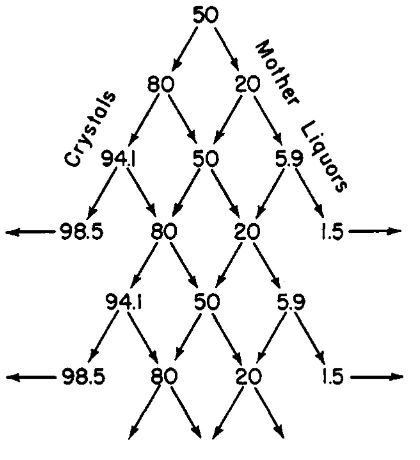

Figure 16. Purity of Fractions in Hypothetical Double Withdrawal Fractional Recrystallization

In terms of % A
50–50 mixture of A and B
$K_A = 4.00$; $K_B = 0.25$

Consequently, in order to improve the yield, the "diamond" scheme of fractionation was introduced. When the outermost fractions have reached the desired degree of purity, at the nth row, they are set aside and fractionation is continued as shown in Figure 14. A further row of recrystallizations is made, and the outer fractions are again removed. This is repeated until all the material is obtained as crystals or final mother liquor. It is useful to combine enriched fractions and again fractionally recrystallize *(20)*. Except in special cases, this system is not very good because fractions of different purities are recombined. In those instances where K_A is the reciprocal of K_B, each fraction has the same composition as the fraction "vertically" above it in the triangular scheme; and in even-numbered rows, the largest part, corresponding to the middle term, has the original composition.

A better method is therefore the double-withdrawal scheme depicted in Figure 15. For example, fractions 5a and 5f are withdrawn. The recrystallization is continued to row 7, and then fractions 7b and 7g are withdrawn. After many such withdrawals all the crystal fractions 5a, 7b, etc., are united and recrystallized. The mother liquor fractions 5f, 7g, etc., are also united, crystallized, and recrystallized. This same scheme is used in liquid-liquid countercurrent distribution. Hunter and Nash *(12)* call it "fractional distribution by multiple contact." The system is profitably employed when the ratio of the distribution constants is large, so that an effective separation can be obtained in a few rows. It is most satisfactory when K_A is the reciprocal of K_B. Thus if, in a hypothetical case, $K_A = 4.00$ and $K_B = 0.25$, and we start with 50 grams of A plus 50 grams of B, multiple fractional distribution gives fractions having the purities shown in Figure 16, in yields shown in Figure 17.

An alternative method is fractional recrystallization of aliquots, shown in Figure 18. It is useful when the main component is fairly soluble in the hot but only sparingly soluble in the cold solvent and when it is desired to use as little solvent as possible. The same portion of solvent is, up to a point, repeatedly used. The starting material is divided into several equal parts, 1, 2, 3, etc. Part 1 is recrystallized from the minimum volume of hot solvent, giving crop 1A and mother liquor 1A. Part 2 is then recrystallized from mother liquor 1A, yielding crop 2A and mother liquor 2A, which is, in turn, used for the recrystallization of part 3, to give crop 3A. Crop 1A is now recrystallized from pure solvent, giving crop 1B and mother liquor 1B. The latter is used for the recrystallization of crop 2A, and so on. The procedure is repeated until crop 1 (A or B or C, etc.) is pure. Then attention is concentrated on the purification of crop 2 (A, B, C, etc.).

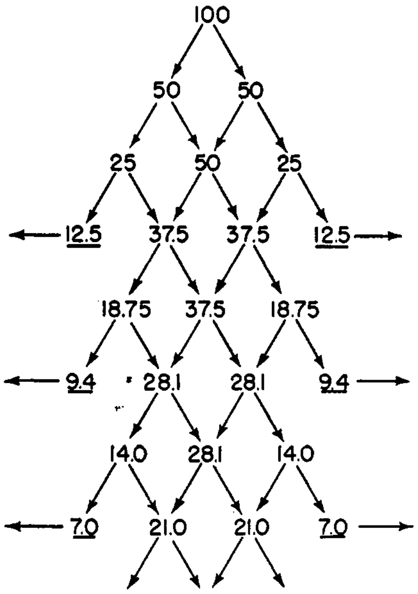

Figure 17. Weights of Fractions in Double Withdrawal Fractional Recrystallization

100 grams of material at 50% yield per recrystallization

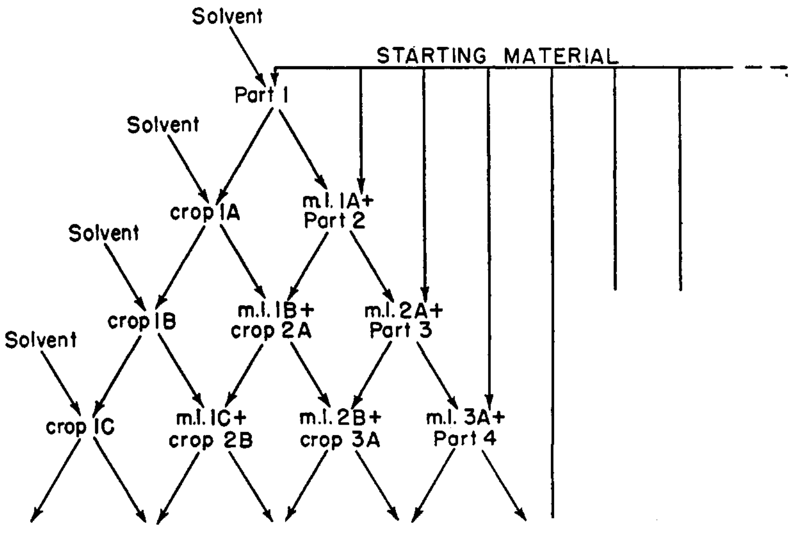

Figure 18. Fractional Recrystallization of Aliquots

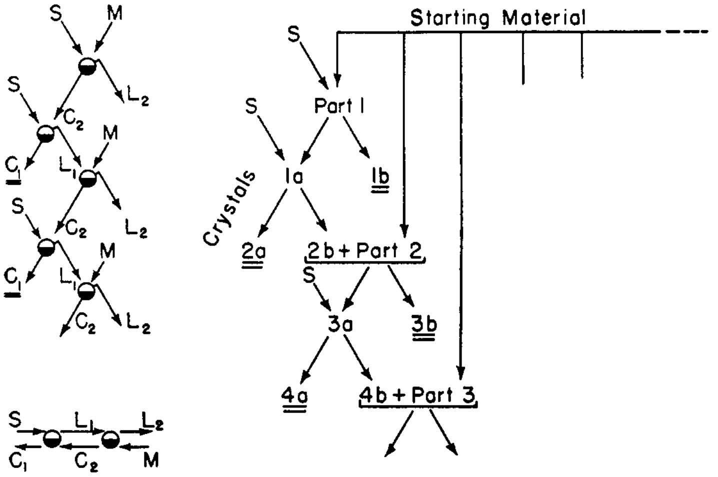

Figure 19. Two-Stage Batch Countercurrent Recrystallization

The same system is used in liquid-liquid extraction. Hunter and Nash (*12*) call it "pseudo-countercurrent extraction." Where the ratio between the distribution constants is very large, and extreme purity is not desired, the procedure may be shortened by using a two-stage or three-stage scheme, similar to those used in liquid-liquid extraction (*22*), as shown in Figures 19 and 20. If both A and B are desired, the system of crystallizing must be complete—that is, each fraction in a "positive" direction must conform with a fraction in the "negative" direction—but this does not mean that the crystals from each recrystallization must necessarily be transferred to the next dish positively, or that the mother liquor from every recrystallization must go into the next dish negatively. The crystals may be transferred to the second, third, or fourth dish positively, and the mother liquor may go into the second, third, or fourth dish negatively, depending upon the value of the enrichment factor (*24*). Of course, if only one component is desired, the foregoing schemes can often be greatly simplified by discarding highly impure fractions (*1*).

Continuous Recrystallization. Continuous recrystallization is a differential countercurrent method which consists in treatment in a vertical column or horizontal trough so arranged that the crystals continuously move in one direction and the liquid in the opposite direction. The crystals are brought in contact with mother liquor from a previous stage, and the crystals leaving the crystallizer meet fresh solvent. The applicability of the process is governed by the conditions previously outlined for systems which do or do not form solid solutions. If set up in a vertical tower, the crystals fall and the solvent rises, so that the phases flow continuously and countercurrently. In one form, crude material is introduced near the middle, purified crystals leave at the bottom where fresh solvent enters, and mother liquor leaves at the top. The column, in which equilibrium is not established at any point, may be visualized as a number of layers, each of which is equivalent to a plate. The efficiency can be increased by returning redissolved purified material to the apparatus, and the effect thus obtained is comparable theoretically to that of reflux in distillation. A similar principle is employed in countercurrent extraction with "extract reflux." The process is used industrially but has apparently not been employed extensively in the laboratory.

In a device patented (*3*) in 1947, a vertical column packed with a filter bed—e.g., of sand—is employed to give a system greatly resembling a chromatogram. The column is initially jacketed with a coolant. The material to be fractionated is placed at the top of the column and solvent is added there. The coolant is then very slowly drained away, the top of the column is warmed, and a temperature-gradient is established. Material dissolves at the top and then crystallizes out again lower down the column. As solvent moves downward, these crystals redissolve and again crystallize out lower down, so that there is multiple redissolution and recrystallization. Although solvent, solution, and crystals move in the same direction, the effect is countercurrent if the rates of movement are different. The apparatus may be used for recrystallization of quantities of 1 kg. or more, and for recrystallization from a melt, without added solvent.

SOME ADVANTAGES AND DISADVANTAGES OF RECRYSTALLIZATION

The advantages of recrystallization as a method for separation and purification are as follows. It yields the material in a form susceptible to special tests characteristic of the crystalline state. Oftentimes it may be accomplished without elaborate apparatus. It may readily be carried out on a macro or semimicro scale, but special apparatus and techniques are necessary for microrecrystallization. It may often be applied to materials not readily separated by other means—e.g., an azeotropic mixture. It may be applied to materials which decompose on attempted distillation. Recrystallization from a solvent is particularly indicated for substances sensitive to heat—e.g., those which decompose at their melting points—for it can often be accomplished either without heating at all, or by heating of very short duration. It is also applied to substances whose supercooled melts are very viscous. Recrystallization is superior to Craig's countercurrent extraction method (*8*) in its present state of development, when applied to separations on a large scale, but as a microtechnique for estimation of purity, it is probably not so useful as the latter. However, a pure substance or a constant-composition mixture will, under equilibrium conditions, give a symmetrical distribution curve at the rows of a systematic triangular recrystallization, and this might be employed as a form of solubility analysis.

On the other hand, mixtures inseparable by recrystallization may often be separated by other methods. Furthermore, recrystallization procedures cannot be applied until crystal nuclei have been obtained, and this may require long waiting. Batchwise, countercurrent recrystallization may be slow and tedious. Only a few stages are possible without great expenditure of labor, whereas liquid-liquid distribution lends itself admirably to mechanical

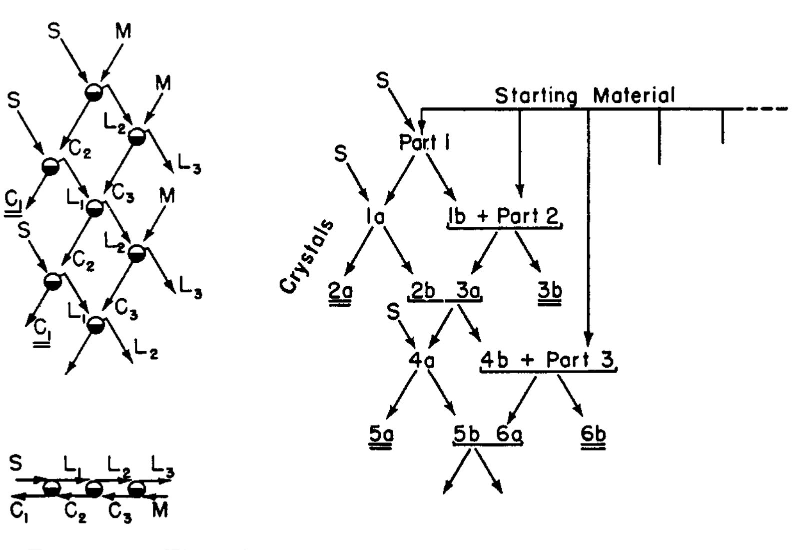

Figure 20. Three-Stage Batch Countercurrent Recrystallization

transfers and a large number of stages are readily achieved. Thus, with Craig's present apparatus, 3000 to 4000 quantitative extractions per hour can be performed.

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Purification by Fractional Melting

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The use of the solid-liquid equilibrium for purification by the method of fractional melting is shown to be highly efficient. This method makes it possible to observe the progress of purification inasmuch as the liquid fraction is always separated from the solid fraction under equilibrium conditions. Examples of the progress of purification of several materials are given.

ALTHOUGH crystallization from a solvent is, of course, one of the oldest and most widely used methods of separation, the possibility of using solid-liquid equilibria in a manner analogous to vapor-liquid equilibria for efficient separation has not been widely recognized. The separation of a single pure solid from a liquid of two components is similar to the removal of the vapor of a pure substance from a liquid mixture with a nonvolatile substance.

Whenever the solid-liquid equilibrium has been used for separations similar to those that are possible in the various types of liquid-vapor equilibria, the process used has been essentially crystallization (*3*). Such separations can be carried out by fractional melting with much greater convenience and ease of control. The present paper describes the work on the single-step separation of a purer substance as a solid from a liquid mixture in equilibrium with it, usually where no solid solution occurred, by fractional melting, and points out its advantages over fractional crystallization.

In theory, the substance may be obtained 100% pure and the maximum possible yield of pure substance by such a process is easily calculated by a material balance from the initial composition, if the eutectic diagram is known or can be computed using Raoult's law. In practice, if this process is carried out by cooling and removing the crystals which separate until the eutectic is reached, such yields of pure material are frequently not obtained.

The reason for this is illustrated best by an attempt to free *cis*-2-butene from the accompanying *trans*-2-butene by freezing. Starting with a sample of *cis*-2-butene with 3.1 mole % impurity, of which 2.9 mole % was the trans variety, about 10% of the liquid was frozen with vigorous stirring, using a bath no colder than necessary to get a convenient rate of cooling. In spite of the fact that the impurities (including the *trans*-2-butene) were both shown not to form solid solutions with the *cis*-2-butene, the solid that separated contained 3.4 mole % impurity. This was shown to be due to the fact that the eutectic mixture separated at the walls and while the liquid was poured off some crystals of the pure *cis*-2-butene melted by conduction down the stirring mechanism and were poured off as liquid, and the impurity remained behind as eutectic on the supercooled walls. Efforts to eliminate the temperature gradients responsible, by customary methods, such as an imposition of an air bath between the sample tube and refrigerant, produced little improvement.

The role of the solvent in fractional crystallization is to make it easier to get equilibrium by stirring, and this offsets the disadvantage of introducing a third component. The present paper shows how these difficulties can be removed by fractional melting of the solidified sample, under equilibrium conditions throughout.

APPARATUS

Four batch-type purifiers have been built and used at one time or another. All consist of a vessel with a large conducting surface inside to produce thermal equilibrium, and a heater. In this vessel the system is first entirely frozen and then fractionally melted. A predetermined amount of heat can be added electrically to this vessel; adiabatic conditions are maintained by an electrically heated shield which surrounds it to eliminate radiation and conduction. The radiation shield is surrounded by a copper sheath to equalize temperature and the whole is immersed in a refrigeration bath. Adiabatic conditions are maintained by keeping the shield at the same temperature as the melting vessel with the aid of copper-constantan difference thermocouples.

Apparatus 1. This has a capacity of 100 ml. and has conduction vanes in the form of a spiral stirrer similar to that used