ZONE MELTING OF ORGANIC COMPOUNDS

WILLIAM R. WILCOX[1]

Aerospace Corporation, El Segundo, California

ROBERT FRIEDENBERG, AND NATHAN BACK

School of Pharmacy, State University of New York at Buffalo, Buffalo, New York

Received January 16, 1964

CONTENTS

I. INTRODUCTION

The purpose of this paper is to review critically the considerable quantity of experimental and theoretical work related to the zone melting of organic compounds. Because zone melting has been used to purify organic compounds for only a few years, the entire period will be covered. During this short period, zone melting has served to open broad vistas of experimentation and theory. However, the full impact of the zone melting method upon advances in the field of organic chemistry will probably not be fully realized for some time. The rapid growth of literature in this area indicates increasing interest and application for this new method. It will be shown in this review that the utilization of zone melting for organic materials has already influenced the thinking of those working with the properties of organic substances. For example, zone melting has focused attention on several theoretical problems concerned with the physical properties of organic compounds as well as on new uses for ultrapure materials.

Zone melting and related techniques are fundamentally a family of fractionation processes. Although purification has been its principal concern, numerous other areas of study have also evolved. Fundamental differences between the behavior of typical metallic and organic systems have been discovered by theoretical investigation. These discoveries are only now being exploited in practical experimentation. Yet application of the zone melting results obtained on metals has already brought forth experimental success in ultrapurification of pharmaceuticals, primary standards, organic semiconductors, and materials for single crystal growth. In a broader sense, these fractionation techniques are capable of concentrating microquantities of impurities for identification, isolating individual isomers, resolving polymeric materials into fractions by molecular weight, and separating and purifying enzymes and other heat-labile biological substances. A section of this paper is specifically devoted to surveying the need for ultrapure organic materials in order to spur further efforts to obtain them.

Although a separate section on ultrapurification is included and is the principal concern of the zone refining approach today, the potential of this method lies in its broad applications as a fractionation process. The advantages and unique properties of this family of techniques is clearly emphasized in the applications section.

As in many scientific endeavors, experimentation has preceded theory in the zone melting of organics. But it is of interest to note that in zone melting, theoretical developments have now surpassed empirical work in some areas and so suggest new areas of experimentation. It is to these areas that this review is particularly directed. For example, it is shown that new apparatus should be developed in order to obtain "ideal thermodynamic equilibrium conditions." In addition, experimental confirmation of newly developed zone melting equations is needed.

Conversely, many of the new techniques related to zone melting need to be theoretically analyzed. Their relation to the parent method must not conceal the fact that they involve new parameters scarcely studied. Zone precipitation holds particular promise for ultrapurifying and separating heat-labile organic compounds. The theoretical aspects of such allied methods are yet to be born.

A survey of the advantages of the zone melting method as compared with other ultrapurification techniques has been described in the literature. The characteristics described are those of (a) generality, (b) sensitivity, (c) contamination, (d) efficiency, and (e) theoretical basis. The outstanding advantage of the zone melting procedure is that there is no contact between the compound being purified and any other solvent or chemical. Zone melting and related techniques may be considered to be the most generally applicable and efficient way of producing ultrapure organic substances.

It is emphasized that zone melting and related techniques have potential applications of much broader scope than only purification. Zone melting, in principle, is a general separation technique comparable to distillation. For example, it may be used for separation of multicomponent mixtures, although this has not yet been widely done. Potential uses include separation of azeotropic mixtures, separation of mixtures too heat-sensitive to be distilled, and growth of pure single crystals. A host of industrial-scale processes and equipment related to zone melting have been developed recently.

II. THEORY

A. DEFINITIONS

The redistribution of components in a mixture during

(1) The work contributed by this author was supported by the U. S. Air Force under Contract No. AFO4(695)-169.

a phase change is common knowledge to chemists. A classic example is a solution of water and salt contained in a beaker placed in a Dry Ice bath. As the outer portions of the solution approach the freezing temperature, pure ice crystals form on the inner circumference of the beaker growing slowly toward the center, while the salt is concentrated in the remaining water. The movement of the dissolved salt and the freezing out of pure ice are used to illustrate the phenomena of "segregation" common to a host of related purification processes. In this instance, the process is known as "directional freezing" or "progressive freezing" (see Fig. 1). Thus "segregation" may be defined as the redistribution of a component or components of a mixture at an interface during a phase change. Whereas "directional freezing" makes use of the slow freezing of an entire solution, "zone freezing" utilizes a relatively narrow zone of solution in a frozen charge slowly moving through its entire length (see Fig. 2).

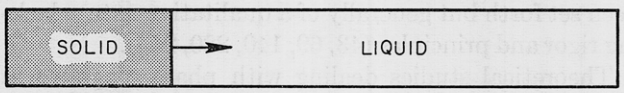

Fig. 1.—Directional or progressive freezing.

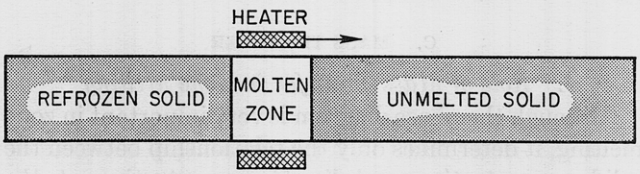

Fig. 2.—Zone melting (zone freezing for liquids).

The redistribution of impurities occurs at the freezing interface, while the melting interface continually adds liquid to the zone. If at room temperature the charge is solid and a heating unit is used to create the liquid or melt zone, the process is known as "zone melting" (see Fig. 2). Zone melting is also often used as a generic name designating zone freezing, and other closely related processes. In solids, the counterpart of "directional freezing" is "directional solidification."

Pfann's (171) initial development of zone melting for purposes of ultrapurifying germanium and other semiconductor materials has equated the term *components* with *impurities*. Thus historically the terminology of this process has evolved from solution chemistry with emphasis on impurities as the components or solutes. The segregation phenomenon at the freezing interface is therefore usually described as a solubility difference of impurities (solutes) in the liquid and solid phases. If part of the impurity remains with the solid phase as the interface moves into the liquid melt, a "segregation coefficient" or "distribution coefficient" arises (see Fig. 3a). This coefficient relates the concentration of solute in the solid to that of the liquid at the interface.

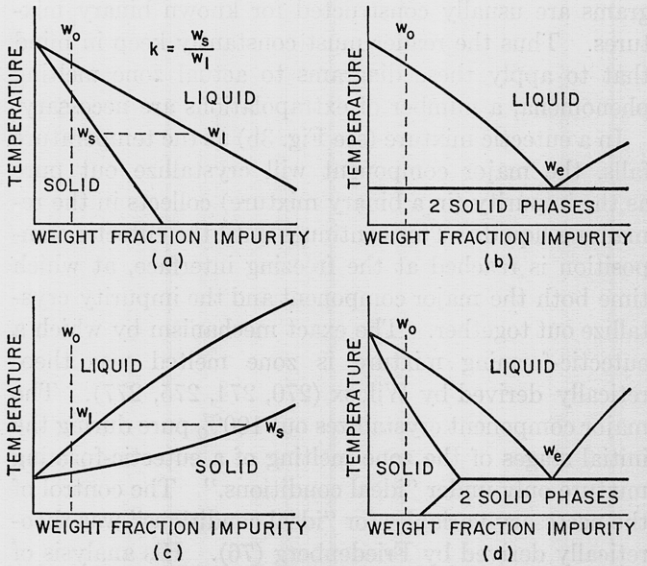

Fig. 3.—Typical binary solid–liquid equilibrium phase behavior: (a) solid solution with constant distribution coefficient k; (b) simple eutectic system; (c) solid solution with variable distribution coefficient; (d) partial solid solution with eutectic point.

The concept of "solid solution" developed by Bruni in 1901 (35) has been logically considered the basis for such definitions.

Although this terminology has been widely accepted, and in many instances found to be useful (81), dangers attending indiscriminant use of the term "solid solution" will become more apparent as various attempts at exploring segregation phenomena are described. The alternative use of the term "components" for "solutes" and adherence to a distribution process rather than a solubility process may ultimately yield a clearer explanation of how impurities segregate at the freezing interface of organic compounds. For an understanding of segregation phenomena in zone melting, it is essential to consider first the behavior of the major component and its impurities as described by their phase diagrams; and second, the conditions under which zone melting is carried out.

B. PHASE DIAGRAMS

The theoretical principles of phase diagrams have changed little from White's classic investigation in 1920 (269). Well summarized by Findlay (69), there are two basic types of phase diagrams: those describing eutectic mixtures (see Fig. 3b) and those related to solid solutions (see Fig. 3a,c). Nearly all of the binary organic systems appear to be of the simple eutectic type. All other phase diagrams may be constructed as modifications or combinations of these two (69) as illustrated by Fig. 3d. Most theoretical treatments of zone melting start with an analysis of these diagrams (163). Although in actual practice impurities are usually multiple in number and unknown in identity, phase dia-

grams are usually constructed for known binary mixtures. Thus the reader must constantly keep in mind that to apply these diagrams to actual zone melting phenomena, a number of extrapolations are necessary.

In a eutectic mixture (see Fig. 3b) as the temperature falls, the major component will crystallize out pure as the impurity (in a binary mixture) collects in the remaining liquid. This continues until the eutectic composition is reached at the freezing interface, at which time both the major component and the impurity crystallize out together. The exact mechanism by which a eutectic-forming mixture is zone melted was theoretically derived by Wilcox (270, 274, 275, 277). The major component crystallizes out 100% pure during the initial stages of the zone melting of a eutectic-forming mixture only under "ideal conditions." The control of the necessary variables for "ideal conditions" was theoretically derived by Friedenberg (76). His analysis of "ideal conditions" related thermodynamic equilibrium at the freezing interface to segregation phenomena. It was concluded that "ideal conditions" require a temperature gradient of 0.100 to 0.010°/mm. with a zone travel rate on the order of 5×10^{-1} to 1×10^{-3} cm./hr. With the boundary temperature sharp and the growth rate slow (due to the similarly slow movement of the zone), the impurities have sufficient time to be transported into the bulk of the molten zone without occlusion. With mechanical stirring of the zone this mass transfer of impurity is facilitated. Experimental studies by Higuchi and Simonelli (224, 225) with methyl stearate and other organic compounds tend to confirm this point of view. Their investigations were primarily concerned with volume effects in dilatometry in the growth of interfaces under thermodynamic equilibrium conditions. Although the nomenclature of dilatometry is quite different from zone melting, their point of view is consistent.

In practice, although instrumentation for such control is available, the complete segregation of impurity at the freezing interface in zone melting has not been accomplished. It is also to be noted that with this type of phase diagram, the impurity lowers the melting point in all cases (69).

In solid solutions, the circumstances of segregation of the second component or impurity are very different. The impurity may either raise or lower the melting point, and a few such isolated organic systems have been studied. Further, segregation coefficients are necessary to describe the impurity distribution at the freezing interface. If the phase diagram is known, the distribution coefficient can be obtained directly from the slopes of the liquidus and solidus curves. However, caution must be used in applying such information directly to zone melting practice. As described more fully later in this section, the conditions during zone melting may alter the constancy of the segregation coefficient considerably. Theoretically, only by extrapolating to "ideal conditions" can one obtain the results expressed by the solid solution phase diagram. Only the extreme ends of the phase diagram are considered if ultrapurity is the objective (100). It should also be noted that for concentrated mixtures the equilibrium segregation coefficient is a function of concentration.

The thermodynamic aspects of these two types of phase diagrams have been sparsely studied. In treating ideal substances under equilibrium conditions, no thermodynamic explanation can be given for the difference in formation of a eutectic mixture or solid solution. Some explanations at the molecular level have been set forth but generally of a qualitative nature lacking rigor and principles (43, 69, 140, 220, 253).

Theoretical studies dealing with phase diagrams in zone melting rarely discuss the conditions and methods used to determine these diagrams (100, 163, 171). With the advent of more refined instrumentation for thermal analysis measurements (76, 224, 225), it may be possible to show that many hitherto considered solid solutions behave as eutectics under more rigorously controlled conditions. The application of zone melting to determine the phase diagram (the converse of the subject discussed here) is treated in section IV.

C. MASS TRANSFER

1. *Role of Mass Transfer in Zone Melting*

Although the phase diagram is very important in zone melting, it determines only the relationship between the solid concentration and liquid concentration at the freezing interface. The degree of separation attained in zone melting is determined, however, by the relationship between the solid concentration and the concentration of the bulk zone. Hence the success of a zone melting operation depends strongly on the effectiveness of mass transfer between liquid at the freezing interface and in the bulk zone, as well as on the phase diagram of the mixture. This mass transfer is aided by mixing in the zone and hindered by the net flow of material towards the freezing interface. The flow of material through the zone leads to a dependence of the separation on the zone travel rate.

2. *Solute Segregation Problems*

The ultimate goal of zone melting theory is the ability to predict from basic principles or empirical correlations the concentration profile which would result from any number of zone passes of any mixture. The degree to which this has been attained is shown in Table I. All mathematical solutions obtained thus far have been for binary mixtures.

The first step to obtain such concentration profiles is to calculate the profile resulting from a single zone pass of an infinitely long charge. Related to this is the

TABLE I

SOLUTIONS TO SOLUTE REDISTRIBUTION PROBLEMS IN ZONE MELTING

	Phase diagram[a]											
	Constant distribution coefficient (Fig. 3a)			Simple eutectic-forming system (Fig. 3b)			Variable distribution coefficient (Fig. 3c)			Limited solid solubility (Fig. 3d)		
	Liquid mixing			Liquid mixing			Liquid mixing			Liquid mixing		
	Complete	Incomplete	None	Complete	Incomplete	None	Complete	Incomplete	None	Complete	Incomplete	None
Single pass, semi-infinite rod	102, 166, (171), (251), 270	44, (171), (251), 270	270, 274	275	275	270, 274, 277	102, 114, (251), 275	275		102, 275	275	
Semi-infinite zone (progressive freezing, infinite charge)	(171)	[b]	22, 109, 133, 146, 232, 248	275	275	276	275	275		275	275	
End condition (progressive freezing, finite charge)	102, (171), 251	[b]	232	275	275		102, 275	275		102, 275	275	
Multipass, semi-infinite rod	40, 102, 119, 131, 149, (171), 187	[b]										
Multipass, finite rod	28, 42, (171)	[b]										
Ultimate distribution, finite rod	34, 41, 42, 58, 102, 119, 171			102			102					102

[a] Numbers refer to references where solutions are derived. Numbers in parentheses refer to references in which solutions are merely given. [b] The solutions for incomplete mixing are found by substituting the effective distribution coefficient for the distribution coefficient appearing in the results for complete mixing.

problem of infinite progressive freezing, which corresponds to an infinite zone size. Next it is necessary to correct for the end conditions in zone melting of a finite rod. It is actually simpler to obtain the ultimate distribution than the one resulting from any number of zone passes. The ultimate distribution is defined as that which does not change by passage of another zone. The available theoretical solutions to these problems for various conditions of liquid mixing and for various phase diagrams are discussed in the following sections. In general the reader is referred to the references listed in Table I for detailed derivations and equations.

3. *Assumptions*

In order to solve the above problems the following assumptions have been made:

a. Constant zone size
b. Constant zone travel rate
c. Constant and equal cross-sectional area in solid and zone
d. Constant density in solid and in liquid (some derivations have assumed equal solid and liquid densities and some have not)
e. Uniform initial concentration
f. Equilibrium (according to phase diagram) at freezing interface
g. Planar freezing interface
h. Constant diffusion coefficient in melt
i. No diffusion in solid

No doubt in the future the effect of removing some of these conditions will be investigated. Pfann, for example, has recently discussed situations in which zone and solid have different cross-sectional areas (175).

4. *Classes of Liquid Mixing*

The degree of mixing in the molten zone greatly affects mass transfer rates and thereby the separation attained by zone melting. For convenience, liquid mixing has been divided into three classes. First is complete mixing—the concentration in the zone is completely uniform. This occurs either with very slow zone travel rates or with large amounts of forced convection. Theoretical solutions to segregation problems are much simpler for complete mixing, and represent the optimum separation that can be attained under any given condition. No dependence on zone travel rate is predicted.

Second, at the other end of the spectrum is the case of no mixing in the zone—mass transfer is by diffusion alone. This would be expected to occur only in very small capillaries—microzone refining. When no mixing occurs, the separation is the least that can be expected under the assumptions outlined above. The separation is predicted to depend on zone travel rate.

The third class falls in between the above two extremes and corresponds to the usual experimental conditions in zone melting of organics. When the zone is insufficiently mixed, the concentration in the molten zone is not uniform and the separation is dependent on the zone travel rate. For convenience this is called incomplete liquid mixing. In order to treat this case theoretically, a boundary-layer approach was suggested by Burton, Prim, and Slichter (44). It is assumed that the bulk of the zone is well mixed and uniform. Near the freezing interface a stagnant boundary layer resides in which no mixing occurs. The thickness of this boundary layer then becomes a basic parameter in the theoretical treatments. Techniques for estimating the boundary-layer thickness were developed by Wilcox for free-convection mixing conditions (270, 273).

An objection to the boundary-layer approach is that the boundary-layer thickness probably varies slightly with the zone travel rate. The difficulty is that there is

a uniform flux of fluid through the boundary layer in zone melting. The quantitative effect of this flux on the boundary-layer thickness cannot presently be predicted, either theoretically or empirically. The great strength of the boundary-layer treatment is that it has successfully explained many zone melting experimental results.

5. *Complete Solid Solutions*

As seen in Table I, the majority of theoretical treatments have been made assuming a constant distribution coefficient. This is partly because such solutions are easier to find and partly for historical reasons. Early zone refining work was done on high-purity semiconductors and metals, for which the distribution coefficient is usually constant.

For the more complex case of variable distribution coefficient, comparatively little has been done.

6. *Simple Eutectic-Forming Systems*

For complete mixing the solute redistribution, resulting from zone melting a eutectic-forming mixture, may be arrived at easily. According to the phase diagram, Fig. 3b, material will come out completely pure while the zone concentration builds up to the eutectic composition. When the eutectic point is reached, the original composition then solidifies out to give a step-function concentration profile. The length L_p of purified material is easily found by a material balance between it and the zone to be

$$L_p = L_z\left[\frac{w_e}{w_0} - 1\right]\left(\frac{\rho_l}{\rho_s}\right) \qquad \text{(Eq. 1)}$$

where L is the length of the zone, w_e is the eutectic composition in weight fraction,[2] w_0 is the original composition in weight fraction, and ρ_l, ρ_s are liquid and solid densities, respectively. For multiple passes of a long rod, it is clear that each pass will leave behind an additional length L_p of purified material. For a finite rod, the ultimate concentration profile would be a region at the head end of pure material and a region at the tail end of material of eutectic composition. A plot of the concentration profiles from repeated zone passes of a hypothetical material is given in Fig. 4. The relative sizes of the two regions would be given by the elementary material balance requirement that the solute removed from the head end must be found in the tail end. The most interesting thing about this result is that the ultimate distribution shows no dependence on zone size, contrary to the results for materials with a constant distribution coefficient in which smaller zones give higher separations. Only the rate of approach to the ultimate distribution is influenced by zone size—the rate being larger for larger zones. In fact, progressive freezing should give the ultimate distribution in one step, if the assumptions outlined earlier are all valid.

(2) Although weight fractions seem to be the preferred units for zone melting theory, other units may be used with suitable precautions (175).

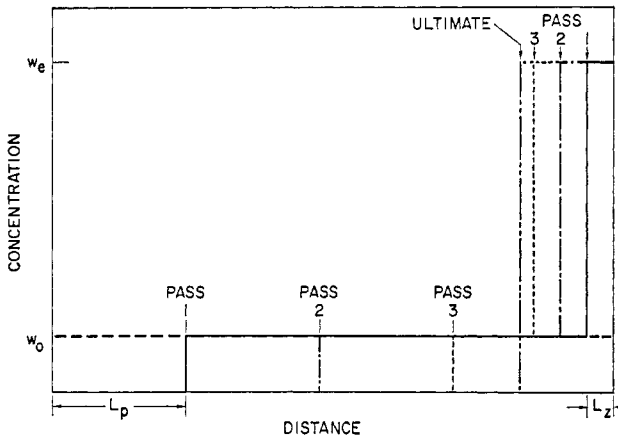

Fig. 4.—Calculated concentrated profiles for repeated zone melting of a concentrated eutectic-forming mixture, assuming thermodynamic equilibrium (complete mixing) between freezing interface and bulk zone with $w_e = 5w_0$.

Calculation of the solute redistribution resulting from zone melting with no mixing in the melt is considerably more complex than with complete mixing. Even specification of the boundary condition at the freezing interface is uncertain. This is because a solid consisting of two insoluble phases consists of intermixed but discrete microcrystals of the two phases. The exact effect of this secondary diffusion on the primary diffusion from freezing interface to bulk zone cannot readily be calculated. Therefore, in order to calculate the mass transfer in the zone, the secondary diffusion is neglected.

As a consequence of nonmixing of the melt, the transition from pure product to initial composition is not a step function as it is for perfect mixing. Instead, it is an approximately exponential increase to the initial composition. This fact is illustrated in Fig. 5 where the concentration profile is compared with the prediction for complete mixing. The parameters are assumed to be $w_0 = 0.1$, $w_e = 0.4$, $L = 1$ cm., $D = 0.1$ cm.^{2}/hr., $V = 1$ cm./hr., $\rho_s = \rho_l$.

After a zone has moved far down a long charge, the concentration profile in the zone itself is given by (270, 274)

$$w = w_0\left[1 + \left(\frac{w_e}{w_0} - 1\right)\exp\left(-z\frac{V\rho_s}{D\rho_l}\right)\right] \qquad \text{(Eq. 2)}$$

where w is the weight fraction at z, the distance from the freezing interface.

Integrating Eq. 2 over the zone gives an average zone concentration w_1 of

$$w_1 = \frac{\int_0^L w\,dz}{L} = w_0\left\{1 + \frac{D\rho_l}{LV\rho_s}\left(\frac{w_e}{w_0} - 1\right)\left[1 - \exp\left(-\frac{LV\rho_s}{D\rho_l}\right)\right]\right\} \qquad \text{(Eq. 3)}$$

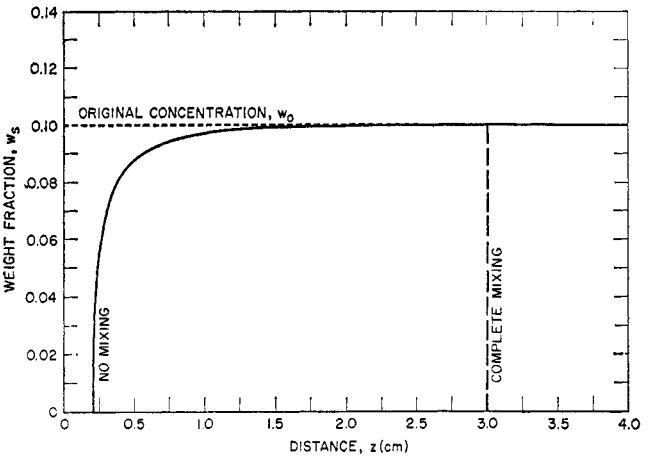

Fig. 5.—Calculated concentrated profiles resulting from a single zone pass of a mixture with $w_0 = 0.1$, $w_e = 0.4$, and $L = 1$ cm. The profile for complete mixing of the molten zone is compared with that for no mixing with $D = 0.1$ cm.²/hr. and $V = 1$ cm./hr.

This means that each zone moving along a semi-infinite charge will carry along with it

$$Q \cong L\rho_1(w_1 - w_0) = \frac{D}{V\rho_s}(w_1 - w_0)\left[1 - \exp\left(-\frac{LV\rho_s}{D\rho_1}\right)\right] \quad \text{(Eq. 4)}$$

quantity of impurity for each zone pass per unit cross-sectional area. This is very similar to that found for complete mixing, except that the quantity moved is less. Although the ultimate concentration profile in a finite rod has not been calculated for no mixing in the zone, it may be approximated as follows: the same procedure as for complete liquid mixing is used, except that w_1 as given by Eq. 3 is employed for the tail concentration instead of w_e. The transition from pure material to w_1 will of course be smeared out somewhat instead of sharp as with complete mixing. The relative sharpness should be greater as the parameter LV/D decreases, approaching complete mixing for $LV/D < 0.1$.

A similar treatment has been made using the boundary-layer approach. The results are, as might be expected, intermediate between the above two cases. The average zone concentration after moving through a long charge is (270, 277)

$$w_1 = w_0\left\{1 + \left(\frac{w_e}{w_s} - 1\right)\exp\left(-\frac{\delta V\rho_s}{D\rho_1}\right)\right\} \quad \text{(Eq. 5)}$$

where δ is the boundary-layer thickness. Consequently, the impurity per unit cross-sectional area moved with the zone is

$$Q = L\rho_1(w_e - w_0)\exp\left(-\frac{\delta V\rho_s}{D\rho_1}\right) \quad \text{(Eq. 6)}$$

Estimation of the ultimate distribution is identical with that for no liquid mixing, only w_e is given by Eq. 5.

An interesting sidelight at this point is the structure of a solid frozen under the above conditions. Considerable experimental data have recently been obtained on the structures of metal mixtures solidified from melts of eutectic composition (46–49, 54, 110, 122–125, 158, 239, 283, 292, 294). The structures often consisted either of filaments of one compound in a matrix of the other, or alternate planar layers, called "lamellar," of the two components. No comparable work has been done on structures resulting from solidifying organic eutectic mixtures. Tiller has developed a theory predicting the interlamellar spacing to be proportional to the inverse square root of the solidification rate (246). This has been generally borne out by the experiments. No theoretical work has been done on solidification of mixtures which are not at the eutectic concentration, such as are found in zone melting.

7. *Constitutional Subcooling*

Of the assumptions made in obtaining the foregoing solutions to solute redistribution problems, the assumption of a planar freezing interface is the most troublesome. In actual fact the interface is quite often not planar, but rough or even composed of multiple dendrites or needles. The rough interface formed during rapid solidification of organics is shown vividly in a motion picture by Thomas and Westwater (241, 242, 268). The cause of a rough freezing interface has been shown to be a phenomenon known as constitutional subcooling (106, 154, 176, 194, 241–245, 247, 262, 268, 284). The source of this phenomenon is an interaction between solute segregation and the temperature gradient at the freezing interface. Near the freezing interface the temperature falls nearly linearly with distance. The concentration of the component rejected at the freezing interface falls approximately exponentially with distance. Because of this, the melting point of the material increases with distance as shown in Fig. 6. Under certain conditions the imposed temperature will actually fall below the melting point in a region near the freezing interface, as shown in Fig. 6. The melt in this region is said to be constitutionally subcooled. It is unstable with respect to perturbations of the shape of the solid–liquid interface. This phenomenon has been analyzed theoretically for mixtures with a constant distribution coefficient (27, 111, 244). The theoretical predictions have been strikingly confirmed by experimental work on inorganic systems (16, 17, 59, 106, 120, 154, 176, 194, 245, 262, 284). Although comparable work has not yet been done on eutectic-forming systems or on organic compounds, the following qualitative results for constant distribution coefficient should carry over. For low subcoolings a cellular interface is formed. At higher subcoolings the interface progressively breaks down until it consists of dendrites or needles. The rougher the interface, of course, the more that mass transfer is hindered and so the more impurity solidifies out. Portions of the melt are even occluded when the

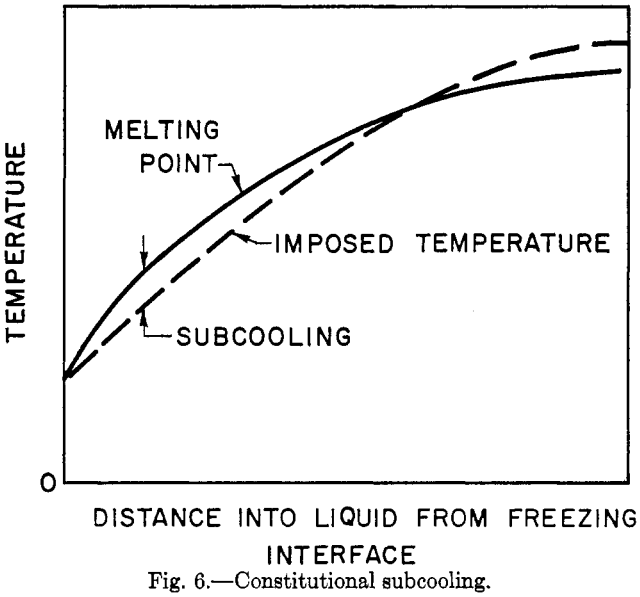

Fig. 6.—Constitutional subcooling.

interface is dendritic. Constitutional subcooling increases as (1) the zone travel rate increases; (2) the imposed temperature gradient decreases; (3) the general impurity level rises; (4) the degree of segregation, according to the phase diagram, decreases; (5) the dependence of melting point on composition increases.

Unfortunately, the quantitative effect of constitutional subcooling on mass transfer in the zone cannot yet be predicted—not even for mixtures with a constant distribution coefficient. A start in that direction has been made, however, by Tiller (249) and by Kramer (126).

Constitutional subcooling has also been thought to give rise to a periodic freezing phenomenon at the freezing interface (228, 255, 270). As segregation proceeds in a zone refining operation, the constitutional subcooling gradually increases. It is imagined that the subcooled layer finally reaches the point where nucleation occurs in it. When this happens, the whole layer rapidly freezes out, trapping considerable quantities of the rejected component in the process. This periodic freezing would lead to a periodic banding, or "striations," in the resulting solid. Although such "striations" are a common occurrence in solidification and indeed in single crystals grown by several techniques, they may often be attributed to causes other than constitutional subcooling. Indeed it has not yet been proven that a periodic process as described above ever occurs.

8. *Coring*

Zone melting techniques are sometimes used either to grow or to purify single crystals. In the growth of single crystals from a melt, a phenomenon called "coring" sometimes occurs. This happens when the freezing interface is concave into the solid because of heat transfer effects. If heat transfer alone were operating, this interface would be smooth. Because a single crystal is involved, however, the interface sometimes develops facets. On the edges the facets grow in the direction of zone travel. In the center, however, the growth is primarily one of growth of facets from the outside inward—perpendicular to the zone travel direction. From purely geometric considerations, it is seen that the rate of movement of the facets is actually much faster in the center than on the edge of the crystal. Because impurities are trapped more readily with higher growth rates, the impurity content is much higher in the center of the crystal than on the edges—a "core" of high impurity content is found. This phenomenon has been observed so far only with inorganic crystals (5, 15, 62, 157). It would, however, also be expected in the growth of organic crystals. A theoretical treatment of this effect for mixtures with a constant distribution coefficient has been made by Trainor (252). Similar, but less regular and predictable phenomena would be expected for polycrystalline materials, particularly with high purity materials, for which the size of the crystallites tends to become quite large.

9. *Surface Adsorption*

Hall and others have proposed a surface adsorption mechanism to explain anisotropic segregation in the growth of single crystals (15, 92). In this mechanism, impurity is assumed to be adsorbed in relatively large amounts on the freezing interface. It is then covered up by new layers of solid before it has a chance to diffuse away and reach its bulk equilibrium value (according to the phase diagram). Such a mechanism leads to a dependence of purification on zone travel rate. The degree of adsorption would depend, unfortunately, on the nature of the impurity and the crystal and so is not predictable at present. Intuitively, it would seem to be a relatively larger effect at very low impurity concentrations such as occurs in ultrapurification.

It should be noted that anisotropic segregation could alternatively be explained by the coring effect described in the previous section. Conversely, the coring results could probably be explained by anisotropic impurity adsorption.

10. *Experimental Segregation Data for Organic Compounds*

Few measurements of concentration profiles of zone melted organic materials have been made (12, 113, 144, 193, 236, 270, 273). The few results (113, 144, 236, 270, 273) on binary eutectic-forming organic systems may be summarized as follows. Although the over-all separation can be correlated on the basis of the boundary-layer treatment, the concentration profiles are vastly

different from any of those expected for a eutectic-forming mixture. The break from pure material occurs much sooner and is much more gradual than predicted. Constitutional subcooling is believed responsible.

Because many passes are necessary to prepare highly pure organic compounds, instead of the ideal single pass predicted for simple eutectic-forming systems, use of an effective distribution coefficient has sometimes been proposed (102, 118, 208). The justification for this is that the amount of impurity trapping is expected to increase with the impurity content of the melt. If the increase is assumed proportional, then the proportionality constant would be an effective distribution coefficient. Two flaws in this approach are readily apparent. First, the experimental concentration profiles generally do not correspond to a constant effective distribution coefficient. Second, the effective distribution coefficient is not predictable and should be a function of all the things that constitutional subcooling depends on and perhaps more. Dependence on the over-all impurity level would make any prediction of an ultimate distribution impossible.

It is clear from the foregoing that much experimental and theoretical work remains before solute segregation in zone melting of eutectic-forming organic mixtures is fully understood and capable of confident prediction.

III. ULTRAPURITY AND ULTRAPURIFICATION

A. DEFINITIONS AND NEED

Definitions of purity have been considered from three points of view in the literature: (a) idealized concepts of purity expressed in physical chemical terms, (b) analytical aspects used to determine purity, (c) the purification process itself. To illustrate, one may define an idealized pure substance (a) in terms of the phase rule by the singleness of an "entity" or "chemical species," (b) by some "absolute" measure of the physical properties of a pure substance as determined by one of several analytical methods (thermal analysis, gas–liquid chromatography, phase solubility method, etc.), and (c) by the repeated purification process itself until further purification yields fractions whose properties signal no detectable change. A number of excellent reviews may be consulted for more detailed descriptions of these concepts (67, 68, 134, 266).

Ultrapurity, as distinguished from purity, may be considered as an extension of any one or combination of these points of view into the microregion of impurities.

The application of these points of view to zone melted organic materials has been limited. There are three factors which have deterred the progress of such studies: (a) the inherent difficulties involved in the conversion of the results of one analytical technique to the units used in another, (b) the advent of new instrumental methods capable of analyzing impurities in the parts per million region only in the past decade (discussed in part B), (c) a lack of collated data on the effects of trace quantities of impurities in organic substances.

The use of several systems of units to measure impurities in the microregion has made it difficult to assess the validity of such ultrapurity studies. For example, thermal analysis and other cryoscopic methods yield quantities in terms of mole per cent of total impurities. If the identify of impurities is unknown and the mole fraction depends upon the molecular weights of the impurities and the major component, the conversion to weight per cent or parts per million of impurities is not possible. Thus it can be readily shown that if impurities have proportionately large molecular weights, small mole per cents may represent large weight per cents of impurities. Since the National Bureau of Standards and other laboratories have adopted mole per cent as the standard measure for impurities, one may well question if other methods are not more desirable.

The question of what constitutes the limits of ultrapurity has only been sparsely studied. Herington points out that samples of organic compounds purer than 99.99 mole % are uncommon. For convenience a special nomenclature has been developed dealing with such quantities, illustrated as follows. For example, "three-nine purity" indicates not less than 99.9% pure while 4N indicates 99.99%.

Definitions of ultrapurity based on intended use may well serve in the limiting process. For example, the requirements of chemical standards, of organic electronic materials, or of pharmaceutical and biological compounds, may serve as guideposts to the necessary lower limits of impurities.

It follows that ultrapurity may be distinguished from purity by orders of magnitude greater than that commonly called "purification." The need for organic materials whose contaminants have orders of magnitude in the parts per million range (p.p.m.) (500 p.p.m. as the arbitrary upper limit of ultrapurity) is described in the following subsections.

1. The Need for Ultrapure Physical–Chemical Organic Standards

A number of investigations have recently appeared in the literature which make use of zone melted organic materials to study the physical and chemical properties of highly purified substances. Unfortunately, these studies rarely give purity assays but assume contaminants in the parts per million region when the organic has been zone refined. Sulfones (135) and sulfoxides (136) have been zone refined for thermochemical studies. The solidification kinetics of zone refined benzene has been studied (108). Ball, Ferrin, and Helm used zone melting to provide pure spectroscopic reference

compounds (12–14). Zone melting has also provided many pure compounds for increasingly accurate melting point data.

2. *The Need for Ultrapure Electronic Materials*

Many electronic properties of organic materials are extremely sensitive to trace contaminants. Because of this, anthracene (128), naphthalene (219), and sexiphenyl (159), to be used in scintillation counters, have been zone refined. Anthracene has been purified for studies of photocarrier generation (105). Organic compounds have also been ultrapurified by zone melting for semiconductor research (22–24, 161). Zone refined dimethyl terephthalate has also been used in attempts to fabricate organic lasers (160). Biphenyl and deuterated naphthalene have been zone refined for use in resonance studies (energy transfer involving triplet states) (278).

3. *Use of Ultrapure Compounds for Single Crystal Growth*

Single crystals of appreciable size can easily be grown only by solidification of high purity materials. Consequently, anthracene (105, 223) and biphenyl (278) have been zone refined prior to the growth of single crystals.

4. *The Need for Ultrapure Pharmaceuticals and Biological Preparations*

Prior to distribution of a new drug for clinical testing in man, present Food and Drug Administration regulations require the identification of the methods, facilities, and controls used for manufacturing, processing, and packaging the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity (148). No definition is provided for the term purity. However, pharmaceutical preparations and chemicals used in their preparation invariably contain impurities originating from the starting material, be it natural or synthetic, or from *in vitro* degradation processes.

The need for ultrapurification of pharmaceutical preparations depends, in great measure, both on the agent and its intended use, *i.e.*, use as a therapeutic agent or as a reference standard. These two uses will be discussed separately as their requirements differ considerably.

a. Ultrapurification of Therapeutic Agents

The near complete removal of impurities as would be achieved by ultrapurification techniques is not always required for a large number of pharmaceutical agents. Extensive clinical use of many agents containing trace amounts of impurities has demonstrated that the presence of the impurity may affect neither the pharmacologic nor toxicologic action of the active agent. However, the "United States Pharmacopeia" (U.S.P.), the official book that provides standards of purity and potency for established drugs, describes the limits of contaminants for official medicinal agents.

For many agents, minimum degrees of purity are established in terms of ash content, heavy metals, arsenic, sulfate, chloride, as well as iron, lead, and copper, specifically. These impurities are limited in concentrations of parts per million (p.p.m.), the range in which ultrapurification techniques are uniquely applicable. The list of impurities recorded in the U.S.P. generally is compiled from knowledge of the raw materials used, the method of manufacture, and the product stability (21). Thus, chemicals known to contain lead or iron would be expected to contain traces of these contaminants. Reagents, solvents, and reaction vessels used during the manufacturing process are certain to add traces of such impurities as calcium, iron, magnesium, lead, sodium, and chloride. Such light-sensitive agents as (a) diethyl ether may give rise to peroxides and irritating aldehydes; (b) chloroform yields the highly toxic lung irritant phosgene which is capable of causing death from pulmonary edema in concentrations as low as 100 p.p.m.; (c) the basal anesthetic tribromethanol oxidizes to an irritant hydrobromic acid and dibromacetaldehyde; (d) the hypnotic paraldehyde decomposes to acetaldehyde and acetic acid (4).

Naturally occurring medicinals may be contaminated with substances so structurally similar as to make purification quite difficult. Thus, the amine alkaloid ergonovine, useful as a highly effective oxytocic agent in obstetrics, may contain amino acid alkaloids ergotoxine or ergotamine which have strong adrenergic blocking activity (261). Similarly, codeine (methylmorphine) may be contaminated with traces of morphine, and the cardioactive glycoside ouabain (*g*-strophanthin) may have *k*-strophanthin. Although it is probable that the contaminants that may form in the anesthetics mentioned may alter their toxicity, it is unlikely that the pharmacologic activity of codeine or ouabain is influenced by trace amounts of those contaminants listed. In fact, it has been stated that purified cardioactive glycosides offer no advantages over digitalis itself other than uniform potency from lot to lot (82). However, the same source stresses the need for purified preparation when intravenous therapy is indicated, and emphasizes the value and importance of purified cardiac glycosides.

Table II lists some representative medicinals described in U.S.P. XVI (257) and some limits of purity. It can be seen that limits for impurities for some agents are peculiar to those agents, as with amylene hydrate.

Synthetic substances also may be contaminated with traces of contaminants arising from intermediate products during the synthetic process. Examples of some of these intermediates are seen in Table III. The

TABLE II

IMPURITIES IN PHARMACEUTICALS LISTED IN U.S.P. XVI[a]

Pharmaceutical	Impurity				
	Cl^-	SO_4^{-2}	Heavy metals	As	Others
Acetazolamide	140	400	20		
Acetic acid, U.S.P.			10		
Acetylsalicylic acid	140	400	10		
Aluminum monostearate			50	5	
Aminosalicylic acid	420		30		*m*-Aminophenol <0.2%
Ammonium carbonate	35	50	10		
Amobarbital sodium			30		
Amylene hydrate			5		Nonvolatile residue <3%
Antimony potassium tartrate				200	5 (Pb^{+2})
Ascorbic acid			20		
Bacitracin			30		
Benzoic acid			20		
Benzoin					Acid-insol. ash <0.5%
Betazole hydrochloride	37.8–37.9%				
Bethanechol chloride	17.7–18.3%				Nitrogen 14.0–14.6%
Bismuth sodium tryglycollamate	360	480		10	
Bismuth subcarbonate	700			10	Nitrate 0.75%, alkalies 0.5%
Bismuth subsalicylate				10	Alkalies 0.5%, free salicylic acid 0.5%
Boric acid			20	10	
Caffeine			20		
Caffeine and sodium benzoate			20		
Calamine				10	Acid insol. 2%
Calcium carbonate (pptd.)			30		Mg and alkali salts 1.0%, acid insol. 0.2%
Calcium cyclomate			20		Nitrogen 6.3–6.6%
Calcium gluconate	700	500	20	8	
Calcium leucovorin				50	
Calcium pentothenate			20		Nitrogen 5.7%, calcium 8.2–8.6%
Camphor					Halogens 350
Carbon dioxide					Carbon monoxide 10
Cherry juice				0.4	
Chloroamphenical palmitate					Free acid 1%
Chlorobutanol	700				
Chlorophenothane	140				Chloral hydrate 0.025%, organic combined Cl 48–51%
Chlorothiazide	<0.2%		10		
Citric acid			10		
Cyclopropane					CO_2 300
Dextrose	180	250	5	1.3	
Dibucaine hydrochloride	9.0–9.5%				
Diethylcarbamazine citrate			20		
Digitalis					Foreign org. matter, <2.0%, acid insol. <5.0%
Diiodohydroxyquin					Free I and I^- 500
Diphenylhydantoin sodium			20		
Edrophonium chloride			20		
Emetine hydrochloride					Cephaeline <2.0%
Ephedrine sulfate	0.15%				
Epinephrine					Arterenol 4.0%
Ether					Normal residue 30, aldehyde and peroxide (test for)
Eucatropine hydrochloride					Atropine, scopolamine hyoscyamine
Eugenol					Phenol, hydrocarbons
Evans blue			70		
Ferrous glyconate	700	0.1%			Oxalic acid, ferric ion <2.0%, reducing sugars
Fluorescein sodium					zinc acriflavine
Gelatin			50	1	Sulfur dioxide 40, bacterial content
Liquid glucose			10	1.3	Sulfate, residue on ignition <0.5%
Glycerin	10	20	5	2	Residue on ignition 0.01%, chlorinated compd. 30

TABLE II (*Continued*)

Pharmaceutical	Impurity				
	Cl^-	SO_4^{-1}	Heavy metals	As	Others
Glycobiarsol					14.0–16.0%, free aosanilic acid 0.5%, bismuth 36–42%
Glycyorhiza					Acid-insol. ash 2.5%
Heparin sodium					Nitrogen <3.0%, barium
Hexachlorophene					Residue on ignition <0.1%
Hexachlorophene liquid soap					Free alkali OHS <0.05%, alkali carbonates <0.35%, alcohol-insol. subst. <3.0%
Hexylresorcinol					Residue on ignition <0.1%, resorcinol and phenols
Homatropine hydrobromide					Residue on ignition negligible, atropine and other alkaloids
Homatropine methyl bromide					Residue on ignition negligible, atropine and other alkaloids
Hydrocortisone					Loss on drying <1.0%
Hydrocortisonal sodium succinate					Sodium content 4.60–4.89%
H_2O_2 solution			5	2	Preservative 500
Hydroxy amphetamine HB					Bromide 33.6–35.2%
Hydroxystilbamidine isethionate			10		
Insulin injection					Nitrogen <0.70 mg./100 U.S.P. units, zinc 0.1–0.4 mg./1000 U.S.P. units
Globin zinc insulin injection					Nitrogen <1.50 mg./100 U.S.P. units, zinc 0.25–0.35 mg./100 U.S.P. units
Isophane insulin suspension					Nitrogen <0.85 mg./100 U.S.P. units, zinc 0.25 mg./100 U.S.P. units
Protamine zinc insulin suspension					Nitrogen <1.25 mg./100 U.S.P. units, zinc 0.20–0.25 mg./100 U.S.P. units
Insulin zinc suspension					Nitrogen <0.70 mg./100 U.S.P., zinc (p. 353 U.S.P.)
Iodochlorhydroxyquin					Residue on ignition <0.5%
Iopanoic acid			20		Residue on ignition <0.1%, test for free I (p. 360 U.S.P.)
Iophandylate injection					Residue on ignition <0.1%, free acids, 0.5%, free iodine 7.5
Iophenoxic acid			10		Residue on ignition <0.3%, free I
Ipecac					Overground items 5%, foreign organic matter 2%
Isoniazid			20		Residue on ignition 0.2%
Isoproterenol hydrochloride	14.0–14.7%	0.2%			Isoproterenone (p. 371 U.S.P.)
Lactic acid			10		Tests for citric, oxalic, phosphoric, or tartaric acids
Lactose			5		Residue on ignition 0.1%, other sugars 2.4
Lidocaine	Tests for (p. 382 U.S.P.)				
Magnesium sterate				2	Lead 10
Mecamylamine hydrochloride	18.0–19.3%				
Mechlorethamine hydrochloride	18.0–19.3%				
Meperidine hydrochloride	12.2–12.7%				
Meralluride					Hg ion 75
Mercaptopurine					Phosphorus 100
Methanamine mandelate	100	15			
Methoxamine hydrochloride	14.1–14.5%				
Methyl salicylate					
Methylene blue					Cu or Zn 0.2%, Cu
Methylglucamine diatrizoate injection			20		
Methylglucamine iodipamide injection			20		
Methyl paraben	350				
Methylrosaniline chloride				10	Lead, 30
Methylthiouracil			20		Sulfur 22.2–22.8%
Nicotinamide			30		

TABLE II (*Continued*)

Pharmaceutical	Impurity				
	Cl^-	SO_4^{-2}	Heavy metals	As	Others
Nicotinic Acid	200	200	20		
Paraldehyde					Nonvolatile residue 600, acetyldehyde 0.4%
Pentobarbital sodium			30		
Phenobarbital sodium			30		
Phenolsulfonphthalein				10	
Phentolamine methanesulfonate		0.2%			
Phenylephrine hydrochloride	17.0–17.7%	0.2%			
Phthalylsulfathiazole	150	400	20		
Pipenocaine hydrochloride	11.6–12.1%				
Lactated potassic saline injection			0.3		
Probenecid			20		
Procainamide hydrochloride			20		
Propantheline bromide					Bromide 17.3–18.0%
Propylene glycol	70		5		
Propyliodine			20		
Propylparaben	350				
Propylthiouracil			20		
Pyridoxine hydrochloride	16.9–17.6%		30		
Quinidine sulfate					Chloroform-insol. subst. 0.1%
Raspberry juice				0.4	
Ringer's injection			0.3	0.1	
Stronger rose water			2		
Saccharin			20		
Saccharin calcium			20		
Salicylic acid	140	200	20		
Secobarbital sodium		30			
Sodium acetrizoate injection			70		
Sodium benzoate			20		
Sodium citrate			10		
Anticoagulant acid citrate dextrose solution	35				
Sodium diprothizoate injection			20		
Sodium diprothizoate	35		10		
Sodium gluco-sulfone injection					Iron 20, sulfate 3.0–3.5%
Sodium levothyroxine	0.71%				
Sodium liothyronine	1.2%				Na 4.0%, inorganic I 0.08%
Sodium salicylate			20		
Sorbital solution	50	100	10	1.3	
Stearic acid			20		
Stibophen	70				
Succinylcholine chloride	19.3–19.6%				
Sucrose		60	5		Invert sugar 0.3%
Sulfacetamide sodium			20		
Sulfadiozine			20 (ref. 5)		
Sulfadiozine sodium			20 (ref. 50)		
Sulfamerizine			20 (10)		
Sulfamethiozine			20 (10)		
Sulfa-bromophthalein sodium					Calcium 0.05%
Suramin sodium	1.2%		20		
Thiamine mononitrate	600				
Thiamylal sodium for injection			30		
Thiopental sodium			20		
Tolbutamide			20		
Trichloracetic acid	350	800			
Triethylenemelamine			50		
Trihexyphidyl hydrochloride	10.7%				
Tubocurarine chloride	10.3%				
Urethan	140		10		
Warfarin sodium			10		
Water					Total solids 0.1%
Wool fat	350				
Zinc stearate				2	Lead 1.0%, 10

[a] Parts per million, unless otherwise noted.

TABLE III
CONTAMINANTS ARISING FROM INTERMEDIATE PRODUCTS DURING THEIR SYNTHESIS

Active agent	Intermediate contaminant
Acetylsalicylic acid	Salicylic acid
Benzocaine	Free acid
Bradykinin	Dipeptides
Methoin	5-Ethyl, 5-phenyl hydantoin
Methyl thiouracil	Thiourea
Plenacetin	*p*-Phenetidin
Riboflavine	Lumiflavine
Suramin	Free amine
Theophylline	Caffeine, theobromine
Trypersamide	Asanilic acid
Urethan	Urea

presence of some of these trace contaminants could influence the toxicologic or pharmacologic activities of the active agent, and their removal would be desirable.

The methods presently used for purification such as chromatography crystallization from solvents, distillation, electrolysis, and extraction are sometimes able to satisfy the purity demands of the U.S.P. However, unique situations arise which suggest the need for ultrapure therapeutic agents, justifying initiation of ultrapurification techniques. Antiparasitic agents as antimony potassium tartrate and methylrosanaline chloride have limits for lead in parts per million (257). Antimony potassium tartrate (tartar emetic) is administered intravenously for the treatment of schistosomiasis, a trematodal disease afflicting more than 200 million people in the Far East and Southwest Pacific Islands (39). Tartar emetic is used extensively and is considered one of the most effective agents against schistosomiasis. Although only a small percentage of lead taken orally is absorbed, that which is absorbed accumulates in the liver and kidney depositing finally in the bones (45). Lead poisoning is nearly always chronic. Accidental chronic lead poisoning has been reported resulting from the daily drinking of water from a lead pump and in infants breast fed by mothers using lead nipple shields (182). Incipient intoxication causes jaundice, constipation, insomnia leading to confusion, tremors, and paralysis. Sufficient is known about the toxicology and insidious cumulative nature of lead to warrant complete removal, if possible, from medicinals taken chronically.

Most recently, hepatic necrosis has been reported following the use of the volatile anesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) (38). Gas chromatographic analysis of freshly opened bottles of halothane revealed the presence of the responsible agent, 2,3-dichloro-1,1,1,4,4,5-hexafluorobutene-2, in concentrations of 1 p.p.m. (57). The pharmacologic properties of the butene contaminant has been studied only partially but its convulsant and lethal nature in rats has been revealed (123). Severe degenerative changes in the liver and kidneys of rats following exposure to 0.01% halothane for 4 hr. have been reported (57). Quality control specifications for halothane require that no other ingredients may be present in quantities greater than 5 p.p.m. (221). The importance of removal of even such minute levels of trace contaminants is exemplified by this specific agent.

Zone melting and allied techniques would appear to find application in the purification of such classes of therapeutic agents as steroids, intravenous contrast media, hormones, blood coagulation proteins, and proteolytic, fibrinolytic, and other enzymes. Impurities in trace amounts of foreign steroids in a steroidal preparation have altered significantly the pharmacologic activity (116). Trace amounts of an impurity in a contrast medium intended for angiography could alter the toxicity of the medium considerably since such large quantities of medium are required for the procedure (11). Pure preparations of such hormones as growth hormone, parathyroid hormone, and gonadotrophins are unavailable. All these hormones may contain biologically active contaminants not detectable by presently employed chemical or physicochemical methods (65). Similarly, all the blood coagulation proteins as fibrinogen, prothrombin, thrombin, factor V, factor VII, and antihemophilic globulin are contaminated with trace amounts of other plasma proteins (65). Antihemophilic globulin, U.S.P., is not completely free of other globulin and thus is standardized on its ability to shorten the clotting time of hemophilic blood (257). Commercial preparations of streptokinase are only partially pure, and only recently has a more pure streptokinase preparation become available in connection with fibrinolytic therapy (6). The increased use of plasmin, a fibrinolytic enzyme obtained from human plasma, in thromboembolic disorders (6) has pointed to the necessity of purer preparations. Those available are contaminated with other plasma proteins difficult to remove by available procedures. The therapeutic application of enzymes for debridement of wounds, lysis of clots, anti-inflammatory effect, and pulmonary disease has been advanced greatly by the availability of purified enzyme preparations (56).

b. Ultrapurification of Agents as Reference Standards

Ultrapurification methods should find specialized use in the preparation of highly pure agents for use as reference standards and for the study of the pharmacology of pure agents. U.S.P. reference standards are prepared by whatever purification or treatment appears necessary (258). Purity is established by studying the physical characteristics of the drug. Physical and chemical tests are inapplicable with such agents as digitalis. Ultrapurification methods should be applied to present U.S.P. reference standards to determine how ultrapurity influences the pharmacologic activity. Pos-

sibly the removal of certain ions from a preparation may decrease its activity. On the other hand, enhancement of activity might be achieved. Studies in this area are indicated strongly.

Some of the confusion as to the action of certain agents, as epinephrine or insulin, might have been avoided had ultrapurification techniques been available. Epinephrine, the first neurohumoral factor to be isolated, was crystallized in 1905. Not until 1944 was it discovered that the epinephrine isolated from the adrenal glands contained levarteranol (norepinephrine) also. In man, responses to these two closely related agents are remarkably different (261). Epinephrine increases heart rate, systolic pressure, and cardiac output. Epinephrine has a vasodilating action while levarteranol is more strongly vasoconstrictor in action. Synthetic epinephrine is available, but difficulties in the resolution of the racemic mixture to the active levorotatory form makes the natural epinephrine the most generally used preparation. U.S.P. XVI sets the limit of 4% for levarterenol in epinephrine solutions. The presence of this contaminant, it must be pointed out, does not influence the therapeutic properties of the epinephrine. Thus, ultrapurification would be selectively useful to prepare a pure drug as a reference standard from natural sources or in use in the pharmacologic study of that agent.

Insulin also has a similar history in that initial preparations of insulin from hog pancreas were contaminated with a hyperglycemic–glycogenolytic factor termed glucagon (147). Early insulin studies in animals showed that insulin caused an initial rise in blood sugar followed by the characteristic decrease. This hyperglycemic effect was thought to be due to the action of insulin, but newer methods of crystallization of insulin revealed the presence of the glycagon contaminant.

These are but two of many possible examples of agents whose pharmacologic action might have been clarified more readily had techniques been available for their preparation in highly pure form. Purification of hormones mentioned above and other agents obtained from natural sources would allow their unqualified use as reference standards.

B. GENERAL APPROACHES

1. *Initial Purity of Sample*

In ultrapurification, it has been standard procedure to bring the substance from the crude impure state to one of relative purity before applying the final ultrarefining process (25). The most important reason for this approach is that various types of impurities are simple to remove *in toto* early in the purifying process rather than applying ultrapurification techniques directly to the crude product. A number of exceptions to this approach have recently appeared in the literature. Of interest is the work of Hines, *et al.* (104), who ultrapurified sea water by zone freezing and claimed 100% purity with one zone pass, starting with naturally occurring sea water. Although not of organic materials, sea water forms eutectic mixtures with its salts and is thus relevant. Wilcox (270) and Friedenberg (76) have zone refined naphthalene from initially impure commercial samples and show analytical data to support ultrapurity. Beynon and Saunders (23) in a full investigation demonstrated that it is possible to ultrapurify directly crude samples of naphthalene by the zone melting technique. In addition they identified an extensive list of impurities by mass spectrometry from these raw materials.

Other investigators (25, 29, 157, 199) in like manner have indicated ultrapurity by zone refining techniques from several crude materials. Herington (102) has pointed out that the two critical factors that must be considered in zone refining *any* substance are (a) the amount and (b) the nature of impurities present. Sufficient data are not yet available at the present time to generalize which substances that form eutectic mixtures with their impurities may be ultrapurified directly from raw materials by zone melting.

2. *Methods of Zone Melting Eutectic Mixtures*

The theoretical aspects of these methods have been treated in a previous section. Here it is desirable to establish the practical point of view of how to ultrapurify organic materials assuming they form eutectic mixtures with their impurities. The reasonableness of this assumption will be discussed at a later point.

If one chooses to zone melt a crude material, there is always the danger that the eutectic composition will be reached in the fractionation process. In this instance, difficulties in ultrapurification are manifold (277). However, if one assumes the classical approach, and an *initially* pure substance is zone refined, it has been shown theoretically that under *ideal conditions*, only one zone pass is necessary to obtain an ultrapure fraction. The theoretical analysis of *ideal conditions* has been given by Friedenberg (76). The realization of these conditions in zone melting experiments has not been utilized to date although they are thought to be within the scope of known experimental techniques. Savings in time and ultrapurity might be achieved by this procedure.

If nonideal conditions are imposed, a distribution coefficient is relevant but arises as a function of the conditions and is not due to the nature of the material or its phase diagram. Here multiple zone passes are necessary to ensure an ultrapure fraction.

It is important to distinguish between multiple zone passes (referring to a single zone passing repeatedly through the charge) and multiple zones in the charge which may also be passed repeatedly through the sample. In the latter case, with the use of multiple

zones (instrumentation is available for such techniques), a much higher efficiency is reported in ultrapurification than with a single zone or with progressive freezing techniques. Thus multiple zones with multiple passes offer, based on what is known at the present time, the most efficient method of ultrapurification.

It is to be noted that with a eutectic mixture the ultrapure fraction is to be found always at the beginning of the charge. Since this fact is well known, it is assumed throughout the discussions in this review.

3. *Zone Melting Solid Solutions*

If it is established that solid solutions are formed with impurities, a distribution coefficient arises as a function of the nature of the substances. In this case, multiple zone passes are necessary to ensure an ultrapure fraction, and the methods of zone melting inorganic materials are applicable. Since impurities that form solid solutions may either raise or lower the melting point (69), the ultrapure fraction may be found towards either end of the charge. It has been shown that the safest procedure in all cases (if analytical methods are not available) is to choose the middle fraction as the ultrapure material. Such methods in fractionation processes are common (165).

4. *Evidence of Lower Limits of Impurities*

In the parts per million range, the problem arises as to what extent impurities and a major organic component will form eutectic mixtures or solid solutions. Evidence gathered fall into two classes: (a) data obtained prior to compilations of the "International Critical Tables," and (b) more recent experimental evidence from thermal analysis measurements. A recent discussion of this evidence (76) indicates that there is sufficient grounds for believing that most organic materials do form eutectics at both high and low concentrations with their impurities. Isolated calorimetric studies supporting the formation of solid solutions at low concentrations have dealt with the few known impurities that form solid solutions with their major component at high concentrations (141, 231, 254).

5. *Thermal Stability Requirements*

The thermal requirements of an organic substance for zone melting take first priority in considering an ultrapurification experiment. Thus a substance that decomposes at or below its melting point is unfit for the standard zone melting ultrapurification procedure. However, a number of allied techniques have been developed (presented in the applications section) which are able to refine heat-labile and noncrystalline materials which have no sharp definitive melting points. Thus the first step for ultrapurification is to determine the substance's thermal stability and then proceed with the appropriate technique.

C. SPECIFIC ANALYTICAL METHODS

The classification of analytical methods to determine purity are usually grouped into physical and chemical procedures. A more recent classification is based on the definitions of "absolute and relative methods" (76). A "relative analytical method" depends on the comparison of data to that of a known primary standard. Since the ultrapurity of the primary standard itself is unknown such methods are of questionable usefulness in the microregion. An "absolute analytical method" is based upon an "internal" standard of the physical property being measured. The only limitations of these methods is the refinement of procedure in the determination of some chosen physical property. Spectrophotometric methods, scintillation analysis, fluorimetry, and specific chemical methods are examples of relative methods, while thermal analysis, gas chromatography, phase solubility methods, mass spectrographic methods, radioactive tracers, and electrical conductivity are examples of absolute methods.

It is clear that a substance is only as pure as the sentivity of the method used to detect its absolute, total impurities. Numerous references (13, 55, 93, 98, 135, 204, 236, 286, 288) are available in the literature to ultrapurity of substances when in reality their purity have not at all been established by "absolute" methods. A typical analysis of such data is given by Friedenberg (76).

For ultrapure materials, melting points do not constitute proof of purity (226, 260). In the same light, elemental analysis may be completely deceiving since isomers and closely related substances may yield similar values.

For rigorous results, thermal analysis and differential thermal analysis methods have yielded the most reliable data (80, 99, 217, 230). The inherent difficulties in dealing with mole per cent as a measure of impurities has already been described. Gas–liquid chromatography yields only total *organic* impurities, although radioactive sensing devices are available for detecting trace quantities of inorganic impurities as well. The limitations and ramifications of this method have scarcely been investigated (61). Phase solubility methods applied to the microregion (137) have only recently been applied to zone refined materials (76). The use of radioactive tracers suffers from the disadvantage that for rigorous results the major component must be labeled. If a labeled impurity is added to the system, one must establish the relationship between the added impurities and the unknown impurities present. Thus zone melting a material free of one labeled impurity in no way establishes the absolute proof of removal of other impurities from the system (74, 113, 144, 159, 198, 237).

Electrical conductivity measurements have been used to determine trace quantities of known metal impurities. This method has also been used to study organic semiconductors (1–3).

Mass spectrometry under favorable conditions may yield total impurity concentrations and has the additional advantage of identifying individual impurities (23).

In summary, one may discount numerous "relative" methods including the addition of dyes and impurities before zone melting and analyzing for these substances at a later point in the refining process. Such methods do not establish *total, absolute* impurities. Those analytical techniques that do yield absolute values must be used with the realization of their limitations.

IV. Additional Applications and Related Techniques

A. ZONE MELTING APPLICATIONS

1. *Concentration of Impurities*

Often in the purification of organic substances, good reasons can be established for identifying the impurities. In order to do this, emphasis is placed in concentrating the contaminants for further identification by means of the zone melting procedure. If the identity of such impurities is completely unknown, both types of phase diagrams (see theory section) may be assumed and the normal zone melting procedure followed. Thus under nonideal conditions with multiple zone passes, impurities may collect at either end of the charge. It must be remembered that with solid solutions, the impurities usually move much slower than those that form eutectics. Therefore, the assessment of solid solution impurities is usually more difficult and time consuming. On the other hand, isomers of a major component which may be of great interest are the particular substances most likely to form solid solutions.

Investigations involving the concentration of impurities by zone melting have been few. A classic work by Beynon and Saunders (23) concentrated a large number of components present in samples of crude naphthalene and identified them by mass spectrometry. A similar work by Briggs (29) was also directed at the impurities in naphthalene, and extensive analytical studies were successfully performed by gas–liquid chromatography. No other studies focusing on concentrating impurities for identification purposes have been reported in the literature. With the advent of instrumentation capable of detecting and identifying impurities in the microregion, investigations on this aspect of ultrapurity are long overdue.

2. *Zone Leveling*

The purpose of zone leveling is to obtain a uniform distribution of impurity throughout a sample. This method is commonly employed with inorganic semiconductor materials after zone refining to redistribute the remaining impurities evenly throughout the charge. Although, to date, there are no published examples of the use of this technique with organic materials, the application of this method to ensure *uniformity* of purity is readily apparent. As a practical technique, the impurities are first removed from the ends of the charge after a zone melting process. The zone velocity is then increased and moved in the reverse direction to that used in the zone refining process. One point of view is that one pass with a high zone velocity in the opposite direction will evenly redistribute the remaining impurities (102). Thus the equations involving a distribution coefficient of solid solutions are applicable and several "back and forth" treatments have been suggested.

Other investigations indicate the following procedure for zone leveling organic compounds: several zone passes in both directions, at least equal to the number of zone lengths in the charge. One technique with promise suggests a ring charge with the zone moving continuously in a circle. This technique appears to be independent of zone velocity. However, zone travel rate and size must be constant.

3. *Study of Phase Diagrams*

Zone melting experiments have been related to phase diagram studies in two ways: (a) data obtained independently from thermal analysis have been used in zone melting experiments; (b) zone melting data have been utilized directly in constructing phase diagrams.

The first of these methods involves the use of time–temperature curves at specific concentrations (thermal analysis) to construct the phase diagram. From the phase diagram, if its form fits one of the classic graphs, its segregation properties may be calculated directly (122). The two most significant graphs involve the solidus and liquidus curves of a solid solution and the eutectic mixture as described in an earlier section. Thermal analysis techniques have been described elsewhere in great detail (230) and no attempt will be made to review them here; however, it may be noted that no standard or consistent procedure has been established for regulating conditions during thermal analysis. Thus, temperature changes may occur at 5°/min. or 1.0°/hr. or anywhere in between. Studies involving the second derivative of temperature as a function of concentration are not available. Since it is well known that the conditions alter the distribution of a second component at the freezing interface, it is likely that variation in the temperature change with respect to time will alter the shape of the time–temperature curve. Thus modifications of phase diagrams that have been established may well represent the influence of the in-

consistent conditions used to obtain them. Theoretically, these conditions should be maintained at thermodynamic equilibrium to allow a true representation of the nature of the substances. Although two workers (76, 224, 225) have attempted to approach thermodynamic equilibrium conditions with a rate of temperature change of 0.001°/hr., this data was not used for purposes of constructing phase diagrams. This does indicate, however, that such instrumental techniques are available and that standard conditions for thermal analysis could be established. For critical investigations of this nature, other factors, as well should be considered, *e.g.*, the effect of stirring.

In general, phase diagram data are desired either for small or for large concentrations of the second component. With dilute mixtures most authors (69, 81, 102, 163, 269, 277) assume a 100% segregation of impurities with eutectics. Since thermal analysis is rarely conducted under thermodynamic equilibrium conditions, the region of ultrapurity is unknown. Therefore, the resulting phase diagrams actually yield no information for the lower ranges of impurity concentration. It is just this region that is of interest in many zone melting applications.

With solid solutions it is a well-known fact (254) that the equilibrium distribution coefficient is never known since the distribution coefficient obtained is a function of the thermal analysis conditions, which have never been at true thermodynamic equilibrium. Since investigators use different freezing rates, variation in distribution coefficients are the rule, and variations in the shape and form of phase diagrams for the same substance, completed by different workers, are common.

The second method above involves the use of single or multiple zone passes to redistribute the components and so provide information about the phase diagram (102, 171, 172). This technique has been used successfully on metallic systems to determine eutectic compositions (291, 293) and maximum solid solubilities (290, 293). Only two organic phase diagrams have been studied by zone melting (74, 113, 236). These studies both gave relatively complex phase diagrams. In particular, Bailey obtained a peritectic for the anthracene–phenanthrene system, whereas other investigators had not reported this (113, 144). It is suggested that the complexity of these phase diagrams may actually have been caused by use of nonequilibrium zone refining conditions. Similar difficulties have been encountered in work on semiconductors (18). Herington has devised calculation techniques for determining the correct phase diagram under nonequilibrium conditions (102). These techniques are, however, difficult to work with and of uncertain validity. Interpretation of experimental results would be much more straightforward and of unquestionable validity if thermodynamic equilibrium conditions were employed.

B. RELATED SEPARATION TECHNIQUES

1. Zone Freezing and Directional Freezing

A number of organic liquids and solids have been ultrapurified by zone freezing and directional freezing (53, 61, 63, 104, 189, 218, 237). Zone freezing as a technique used for organic liquids is comparable to zone melting for solids. The theoretical aspects are completely analogous, although equipment needs are different. In contrast, directional freezing is often compared with fractional crystallization. Herington (102) has made a theoretical study of the distribution curves of fractional crystallization and zone melting, comparing average compositions of the charge and concentrations at a point. However, his equations for zone melting are not rigorous (as given in the theory section of this review), and there is considerable controversy on the use of fractional crystallization equations for directional freezing. Thus, his conclusions are suspect on theoretical grounds. A number of investigators have found experimentally and theoretically that directional freezing is a more efficient purification process than zone melting for a single pass. As given in sections IIC and VA5, directional freezing appears to be very useful as the initial step of a multistep zone refining process. The specific disadvantages of directional freezing may be summarized as follows: (1) Automation is difficult since portions of the charge must be removed periodically for a multiple-step process. (2) Contamination is a problem in removing unfrozen sections. (3) In directional freezing, the sample is liquid for a greater time than in zone melting; thus the risk of thermal decomposition is greater with directional freezing. (4) A recent comparison of multiple-pass zone melting with cropping and multiple-directional freezing indicates that the yield of purified material is less than that possible with zone refining (278).

The classic studies of Schwab and Wichers at the National Bureau of Standards (218) have established the instrumentation and specifications of fractional crystallization from melts and directional freezing procedures. Other investigators (61, 63) more recently have refined equipment and operating procedure such that stirring, temperature control, rate of movement of the freezing interface, and the mechanics of operation have in some respects advanced directional freezing beyond zone melting. Benzoic acid has been considered the classic material of an ultrapure gravimetric standard by the National Bureau of Standards through the application of directional freezing techniques. Other organic compounds so refined include benzene, *p*-bromotoluene, nitromethane, and pyridine.

2. Zone Precipitation and Related Techniques

The most important disadvantage of the zone melting technique is that heat-labile organics that decompose at

or near their melting points cannot be purified by this method. To overcome this problem, Eldib (66), in attempting to zone refine microcrystalline petroleum waxes, devised a method of adding a solvent to the charge and separating his material through differences in solubility while passing a molten zone through the gel-like mixture. Eldib named this technique of adding a solvent to the charge "zone precipitation." It has been given other names elsewhere (*e.g.*, "freezing out" (222)) and a number of investigators (78, 164, 177, 180, 193, 199, 201, 237, 256) have used this idea in different ways to zone refine heat sensitive materials. The chief advantage of this technique is that it makes all organic materials eligible for zone refinement. Its disadvantage lies in the fact that contamination by the solvent is a major hazard.

The specific method that Eldib developed requires a nonaqueous solvent to be used in small whole ratios to the major component. Thus a typical example would be a *sec*-butyl acetate:wax ratio of 3:1. This mixture forms a solid gel at room temperature. The highly volatile solvent is removed after purification by gentle heating. The technique is suggested for use on polymers, proteins, dyes, rubber, animal fats, gums, asphaltines, vitamins, glass, and plastics.

Schildknecht has modified this procedure by using dilute aqueous solutions of various organic compounds (0.1% hydroquinone, resorcinol, and pyrogallol) (201). By a directional freezing procedure he was successful in concentrating individually pure portions. Other solutions included aldehydes, quinones, and ascorbic acid. In a further modification of this, a centrifugation step was used in conjunction with directional freezing of aqueous solutions (76). Thus, density stratifications were established during the freezing process. A similar adaptation by Shapiro (222) involved a mechanical shaker and use of a freezing chamber. Recovery of 99% of the solute has been reported as a means of concentrating a heat-labile substance in ultrapure form. Single directional freezing experiments have been reported with such heat sensitive materials as skim milk.

Some rather unique solvents have been used to aid in the fractionation process. Naphthalene has been utilized in zone melting polystyrene (164). At the end of the procedure the naphthalene was removed by sublimation. Turbidimetric studies (145) indicated that the polymer had been fractionated into a series of pure components. The successful use of benzene to fractionate polystyrene has also been described (130) by unidirectional freezing methods. The relation between molecular weight and freezing rate has been analyzed in detail.

In summary, the investigations of Schildknecht, *et al.* (199, 201), are the most definitive in the zone melting and directional freezing of aqueous solutions of heat-labile organic substances. The extension of this technique, as well as that of Eldib's, as a general zone refining method is experimentally more advanced than its theory. The development of the mathematical principles underlying these methods may well bring into being the separation and ultrapurification of heat-labile closely related organic isomers (64).

3. Vapor-Zone Refining

A second disadvantage of zone melting organic compounds is that many such materials have high vapor pressures at their melting points. Such volatile substances produce rapid loss of material from the melt zone. Weisberg and Rosi (265) developed a technique where temperature control along the heated zone allows the compound to sublime across a gap where it is collected on previously sublimed material. The movement of the charge by Teflon plugs allows for successive sublimations with a minimum of contamination. The difference in sublimation rates of impurities and major component allows for a separation at both ends of the charge. Sloan has refined tetracene by this technique (229). Although vapor zone refining equipment is therefore now available, the theoretical aspects of this method have not been clarified.

4. Fractional Melting

Fractional melting has been largely supplanted by zone refining methods (102). Its principal use has been on solids with high impurity contents. A fractional melt is produced with solid and liquid hopefully in equilibrium. This method is considered to be useful only with eutectic forming mixtures, and as a batch process its efficiency is low. The low efficiency is attributed to low solid-state diffusion rates. The method is outdated and the reader is referred to references for further information (10, 79, 140).

5. Single Crystal Growth

A large number of experimental methods are available for growing single crystals (88, 215, 279). Many of these methods are applications of the directional freezing technique previously described, *e.g.*, the Bridgman technique. Although there are some references in the literature (79, 129, 155, 188, 213, 224, 286) to formation of single crystals in the last step of zone refining process, the applications of zone refining appears more pertinent in the preparation of the ultrapure material for crystal growth procedures.

A new and powerful related crystal growth technique is called "temperature gradient zone melting" (169, 171, 250) or alternatively the "traveling solvent method" (87, 152). It consists of placing a very thin zone of a suitable solvent between a seed and a rod-shaped charge. A high temperature gradient is placed across the solvent zone, causing the material to dissolve on the hot side and crystallize on the cooler side. The

TABLE IV

DATA ON ZONE REFINING CONDITIONS FOR ORGANIC COMPOUNDS

Compound	M.p.,[a] °C.	V,[b] mm./hr.	Number of passes	Zone length, mm.	Rod diam., mm.	Rod length, cm.	Impurity	Measure of purity[c]	Purity: Before refining	Purity: After refining	References
Ethanol	−115		4				Water	?	4×10^{-2}	10^{-2}	112
Methyl methacrylate	−50	300	10	8–9		80		?	8×10^{-3}	5×10^{-4}	7–9
3-Methylpyridine	−18	106 dn	8		25	127		x	1.5×10^{-2}	$<10^{-3}$	12, 14
Piperidine	−9	35					Pyridine	?	10^{-1}	$<10^{-2}$	208
4-Methylpyridine	3.8	52 dn	44		51 (steel)	127		x	5×10^{-3}	10^{-3}	14
Benzene	5.5	3 hr	15				Thiophene	?	10^{-3}	$\leq 10^{-4}$	237, 238
Benzene	5.5	3 hr	10				Acetic acid	?	2×10^{-2}	$\leq 10^{-3}$	237, 238
Benzene	5.5	50	5					x	6.3×10^{-3}	$<8 \times 10^{-5}$	189
p-Xylene	13.2		6				*o*-Xylene	?	10^{-1}	5×10^{-3}	237, 238
Vinylene carbonate	22	25 dn	3			38	Chlorine	?	5×10^{-2}	5×10^{-3}	296
p-Bromotoluene	28		9				*o*-Bromotoluene	?	2×10^{-2}	2×10^{-4}	237, 238
2-Methylnaphthalene	35	52	108	20	20	4.5		?	$>3 \times 10^{-2}$	5×10^{-4}	138
Phenol	41	21 dn	12	25	12	50	*p*-Nitrophenol	?	2.5×10^{-2}	2.5×10^{-6}	236
Phenol	41	25–50			6	30	Methyl red	Color	Pink	Colorless	60
4-Chloro-*o*-cresol	49	20 dn	68	25	12	60		m.p.	40.9	48.7	236
Benzophenone	51	2–3	90	10				x	4×10^{-2}	$<2 \times 10^{-4}$	209
Pentamethylpyridine hemihydrate	52	30 dn		25	4	20					30, 36
Indole	53	25 dn	20		51 (steel)	127		x	5×10^{-3}	10^{-3}	12
Stearyl alcohol	59	1	7	5		11	Cetyl alcohol	w	1.2×10^{-1}	$<5 \times 10^{-3}$	103, 198, 207
Octadecanol-1	60	25 dn	10		22.5	85		m.p.	58.5	60.1	289
3,4-Dimethylphenol	65	2	17	20–30	20	43		m.p.	62.3	62.6	204
Azobenzene	68	3	127	9				m.p.	66–68		209
								x		$<10^{-4}$	
Stearic acid	69	95 up	45				Oleic acid, etc.	w	1.5×10^{-1}	$>10^{-2}$	288, 289
Biphenyl	71	8 dn	1	28	18	35		Odor		Removed	278
Naphthalene	80	38 dn	7	51–127	38	127	Anthracene	w	2×10^{-3}	$<2 \times 10^{-7}$	98
Naphthalene	80	32 dn	5		2	15	2,4-dinitrophenylhydrazine	w	10^{-3}	$<10^{-4}$	190
Naphthalene	80	3.7 up	30	38	10	30		x	2.7×10^{-2}	9.5×10^{-6}	76
Naphthalene	80	20 up	18		8	7	Methyl violet, 1%	Color	Pink	Clear	263
Naphthalene	80	1.5 up	1	30	8	30	Benzoic acid	w	10^{-1}	$<10^{-3}$	270
Naphthalene	80	25 dn	18	14	5	15	Methyl violet	w	10^{-3}	2×10^{-7}	113, 144
Naphthalene	80	3	31	20				m.p.	94–96	3×10^{-4}	209
								x			
Naphthalene	80	10		20		18	Anthracene		10^{-3}	$<10^{-6}$	287
Naphthalene	80	30 dn		25	4	20					30, 36
9-Methylcarbazole	89	25 dn	60		38	127		x	3×10^{-3}	5×10^{-5}	14
Benzil	95	2–3	45	15				x		2×10^{-4}	209
Acetamide	114	15 dn	10		22.5	85		m.p.		114.8	288, 289
Benzoic acid	122	25 dn	7	38	38			?	7×10^{-3}	3×10^{-4}	24, 196
Benzoic acid	122	25 dn	1	14	5	15	Naphthalene	w	5×10^{-5}	3×10^{-7}	113, 144
Benzoic acid	122	25 dn		3–5	2.5–6.4	10–15		m.p.	119.5–121.5	121–121.5	94
Benzoic acid	122	~10 dn	274				Benzoic acid-*d*	x	2.4×10^{-3}	1.7×10^{-3}	229

β-Naphthol	122	1.5 up	1	30	18	30		Color	Tan	Colorless	270
β-Sitosterol	129	6.2 up	21		8	4		m.p.	124.5–129.5	127.5–129	263
Progesterone	130	6.2 up	21		8	4		m.p.	128–129	130–132	263
Cholestanol	142	6.2 up	20		8	6	Cholesteryl stearate	w	10^{-3}	$\sim 10^{-3}$	263
								m.p.	138–139.5	139.7–140.5	
Cholesteryl benzoate	150	20 up	21		8	7	Methyl violet, 1%	Color	Pink	Clear	263
Cholesteryl benzoate	150	6.2 up	17		8	6	Benzoic acid	w	10^{-3}	$\sim 10^{-3}$	263
								m.p.	143–146	145.5–147	
Cholesterol	151	9 dn	10		22.5	85		m.p.		151–151.2	289
Pyrene	152	25 dn		3–5	2.5–6.4	10–15		m.p.	150–152	152	94
Testosterone	153	6.2 up	21		8	3.5		m.p.	152.5–154	152.7–154.2	263
Stigmasterol	164	6.2 up	21		8	3.5		m.p.	161–164	159–163	263
Diethylstilbesterol	177	6.2 up	34		8	6		m.p.	175–177	175–177.7	263
Hexestrol	187	6.2 up	18		8	6	Diethyl stilbesterol	m.p.	181–182.5	185.5–187	263
								x	5×10^{-3}	$<10^{-3}$	
2-Phenylindole	189		8		13	127		m.p.	188	189.1	14
Anthracene	220	25 dn	18	38	38	122	Methyl anthracene	?	1.9×10^{-3}	5×10^{-3}	24, 196
Anthracene	220	25 dn	10	3–5	2.5–6.4	10–15		m.p.	217.5–221	219.5–220	223
Anthracene	220	25 dn		25	10	70					127
Chrysene	251	25 dn		3–5	2.5–6.4	10–15		m.p.	248–249.5	250–250.5	94

[a] M.p. is the approximate melting point of the compound; compounds ordered by m.p. [b] V is the zone velocity; dn indicates that the zone was moved down; up, that it was moved up; and hr, horizontally. [c] x is mole fraction of impurity, w is weight fraction of impurity, m.p. is melting point, ? may be either mole or weight fraction of impurity.

zone moves thereby and in the process produces a single crystal. The process has been analyzed theoretically by Pfann (167, 171) and by Tiller (250). So far the technique has been applied only to semiconductors (87, 152). Because of the usual absence of solid solubility of solvents in organic systems, however, the technique shows great promise for growth of single crystals of organic compounds.

6. *Separation of Isotopes*

A number of experiments with heavy water have indicated that separation of isotopes by zone freezing is too slow for practical use (87, 237). Sloan has affected some separation of benzoic acid-*d* from benzoic acid, however, by 274 zone melting passes.

7. *Separations Involving Colloids, Enzymes, Bacteria, and Plankton*

A few applications of the zone melting technique have been described (199, 237) which show a fractionation of highly complex, organized organic matter. These studies at first sight seem incongruous to the principles of crystallinity which pervades all zone refining methods. Yet as a fractionation procedure, the procedures are apparently equally applicable.

The requirements for the zone freezing of colloids are that they are not degraded nor coagulated by freezing (237). Enzymes in aqueous solution have been zone melted and active fractions have been concentrated (199). Suspensions of bacteria and phage have in a similar manner yielded concentrated separations. In contrast, studies with plankton were unsuccessful in that repeated freezing destroyed the cells.

The ultimate use of the principles of zone melting as a general fractionation process on highly organized organic matter has been barely touched.

V. METHODS AND EQUIPMENT

A. LABORATORY PURIFICATION

Up to the present time the greatest use of zone melting of organic compounds has been in small-scale laboratory purifications, primarily for research purposes. Consequently, considerable space will be devoted to the operating conditions necessary to obtain optimum purifications on a laboratory scale.

1. *Parameters of Importance*

Optimum operating conditions in zone melting are those which give the greatest purification possible in a given length of time. The parameters of greatest importance to the purification are the following:

a. zone travel rate
b. direction of zone movement
c. zone size
d. container diameter and length
e. temperature gradients and control thereof

In addition to these there are several other factors which serve to affect the ease of operation, such as container material and automation. Although it is not possible to specify the exact optimum operating conditions, certain broad guidelines can be given. These are discussed in some detail in the following paragraphs.

Values for certain of the operating parameters reportedly used in zone refining various organics are shown in Table IV. Unfortunately the data are often not complete. Initial and final purities were frequently not given, so it is difficult to judge the degree of success obtained by most investigators.

2. *Mixing of the Zone*

For laboratory purifications of organics, it is usually not convenient to mechanically stir the zone, although it is possible and serves to increase the rate of purification. Ultrasonic mixing has proved helpful in organic reactions and in growth of crystals from solution (115). Its employment in zone refining of organics should be investigated.

Forced convection has rarely been used in zone melting of organics. Stirring is accomplished, however, by free convection in the zone, if the tube size is not of capillary dimensions. Wilcox has made a theoretical and experimental study of free-convection conditions on the boundary-layer thickness in zone melting of organics (270–273). We may summarize the results in a qualitative fashion as follows.

Free convection is fluid motion caused by density variations resulting from temperature and/or concentration variations within the fluid. In zone melting we have nonhomogeneity of both temperature and concentration in the melt. The concentration variation results from segregation at the freezing interface. The temperature variation results from heat transfer to and from the melt and to the freezing and melting solid.

In the usual experimental arrangement, the zone is heated primarily by conduction from a resistance heater. In such an arrangement, bulk mixing of the zone results primarily from the free-convection currents generated at the tube walls by transfer of heat from the heater, through the tube walls, to the zone. Under these conditions the bulk of the zone is actually well stirred. Near the solid–liquid interfaces, however, these free-convection currents die out, leaving a boundary layer of nearly stagnant fluid adjacent to the interfaces. As shown in section IIC, the purification in zone melting is strongly dependent on the boundary-layer thickness at the freezing interface. This boundary-layer thickness, in turn, depends primarily on the free convection generated at the freezing interface itself by the density difference between fluid at the freezing interface and in the bulk zone. The larger the density difference, the smaller the boundary-layer thickness, and the greater the purification attained. This means that with high purity materials a higher temperature gradient will normally give a larger density difference and hence a larger purification.

Stirring is also much greater when the fluid of higher density (between the bulk zone and the freezing interface) is on the top rather than on the bottom. For a vertical tube with high purity materials, this normally means that the freezing interface should be on top; *i.e.*, the zone is moving down. For material with large impurity contents a complication is introduced. Because of segregation a new density effect appears—that caused by the difference in concentration between freezing interface and bulk zone. This density effect may either work with or against the temperature-induced density effect, depending on the concentration–density relationship. As a result more efficient stirring may result if the freezing interface is on the bottom. If the two density effects are opposite and the concentration-induced density effect is greater, then increasing the temperature gradient will reduce the resultant density difference and reduce the separation.

A simple way of increasing the free convection at the freezing interface is to introduce a thin axial rod of high thermal conductivity (*i.e.*, a metal) into the center of the charge (271). The boundary-layer thickness has been reduced by a factor of two to three in experiments on naphthalene using this technique (270, 273).

High speed rotation of the zone melting tube has also been suggested as a method of increasing free-convection stirring, but has not yet been attempted (270).

3. *Gas Liberation*

In general, gases are more soluble in liquids than in solids. Because of this, gases are trapped among the solid crystallites formed during the normal filling operation, in which the molten organic material is placed in the zone melting tube and then rapidly frozen. Unless special precautions are taken, therefore, gas will be dissolved at the melting interface and liberated at the freezing interface in zone melting. In some cases in which a horizontal tube is used, this gives rise to a channel along the top of the material. In a vertical tube, if the zone is moved down, the bubble collects at the freezing interface. In large tubes this causes no trouble and may even be beneficial. It normally forms a gas tube inside the frozen solid, which alleviates somewhat breakage in multiple passes (as discussed later). In small tubes, however, it can block the tube entirely and almost completely stop the purification. If the zone is moved up instead, the bubbles collect at the melting interface in large tubes and so are swept out. In small tubes blockage again occurs. The bubbles can, however, often be encouraged to move up by periodically tapping on the tube or vibrating it (278).

4. *Zone Travel Rate and Direction*

The purification per zone pass increases as the zone travel rate decreases. Unfortunately, the time required to complete a pass increases simultaneously. The optimum travel rate has not been established. The rates shown in Table IV (summarized in Fig. 7) represent in most cases an empirical compromise, although almost no systematic work has been done on this problem. Most instances of failure of zone melting can be attributed to zone travel rates being too high for the experimental conditions.

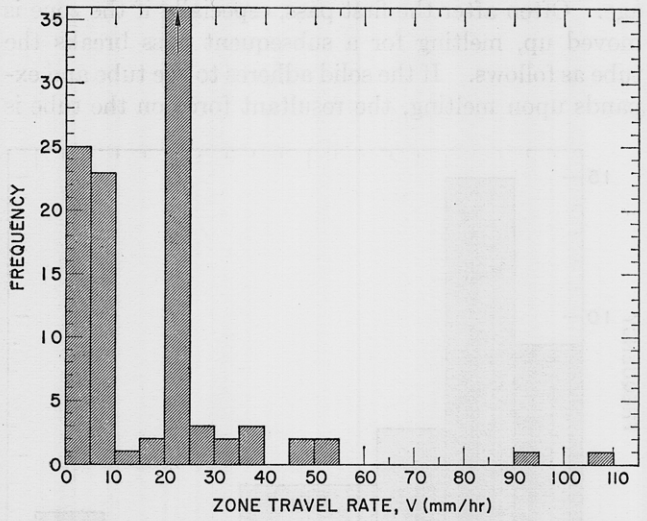

Fig. 7.—Frequency histogram of published data on zone travel rates producing appreciable separations in zone melting—each different travel rate for each compound counted.

Zone travel rates slow enough to give equilibrium between the freezing solid and bulk zone have never been experimentally tested on organic compounds. To achieve this would take smooth zone travel rates below about 0.1 mm./hr. The difficulty is that the motion must be completely smooth and uniform. Although mechanisms thus far devised to provide zone motion and temperature control may be adequate to accomplish this, no attempt to do so is known. Fluctuations of the freezing interface would, however, nullify any macroscopically slow movement. Use of motion-picture microphotography should be employed to verify the successful operation of any such apparatus.

In the theoretical section, it was shown that constitutional subcooling, which lowers the separation, increases as impurity content increases. Because of this, it is often advantageous to have a lower zone travel rate at the beginning of a zone purification than in later passes, where the purity is higher. (Note, however, that the ultimate separation increases as the zone travel rate decreases.) Presence of constitutional subcooling may be detected by examining the freezing interface with a magnifying glass for surface irregularities.

As discussed previously, the direction of zone travel is significant to the degree of separation attained. Generally, horizontal zone melting of organic compounds has proved to be less efficient than vertical zone melting, so this is eliminated from further consideration here. Applications may, however, be found for horizontal zone melting of organic compounds. From a free-convection standpoint, the direction of zone movement is usually best determined empirically. Because some organic reagents contain small amounts of insoluble matter, it is often convenient to include a downward zone pass somewhere in the processing schedule of a charge. If it is desired to remove gases from the product, an upward zone pass should also be included, probably initially.

5. *Zone Size*

There is some confusion in the literature about the desirability of small zones *vs.* large zones. This confusion arises as follows. It may be intuitively seen that the capacity of a zone to carry impurities increases with its size. This fact has also been shown in this paper in the section on theory. On the other hand, a large zone gives more intermixing with the impure tail end of a charge, thus reducing the ultimate purification attainable.

Therefore, the optimum operation of a zone refining process, in which a single zone is passed repeatedly through the charge, would be as follows. The first pass would actually be directional freezing—the whole charge would be melted and slowly frozen from one end. Zone passes would then be made with the zones initially about one-third of the total charge length and then decreasing to as small values as possible. As a rough rule of thumb the smallest zone length possible equals the diameter of the container used, as shown in Fig. 8.

For zone refining processes in which many zones are passed simultaneously through the charge, the analysis is not so simple as the foregoing. To a first approxima-

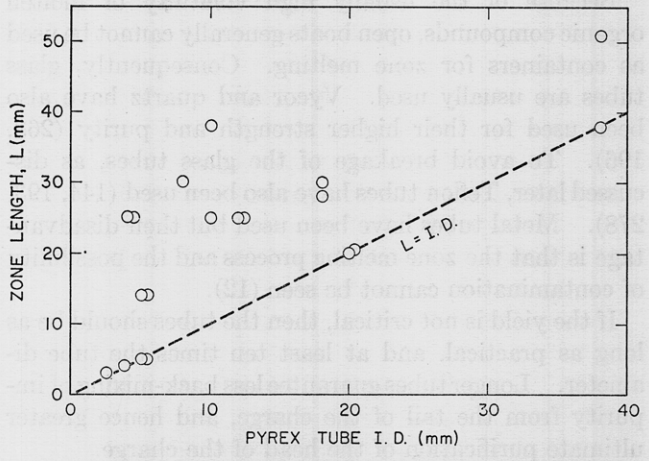

Fig. 8.—Plot of literature data on zone length and container diameter used in zone melting experiments. This demonstrates the empirical rule that minumum zone length equals tube diameter.

tion, the rate of purification at the beginning of a zone refining operation is proportional to the number of freezing interfaces present and to the total volume of melt in the charge. Hence, the product of the number of zones and the total melt volume should be made as large as possible in order to maximize the purification rate. Since the total volume of melt is proportional to the product of the number of zones and the zone length, the purification rate increases with the square of the number of zones times the zone length. Therefore, the maximum purification rate is obtained when the zones are spaced as close together as possible—which usually entails a small zone size.

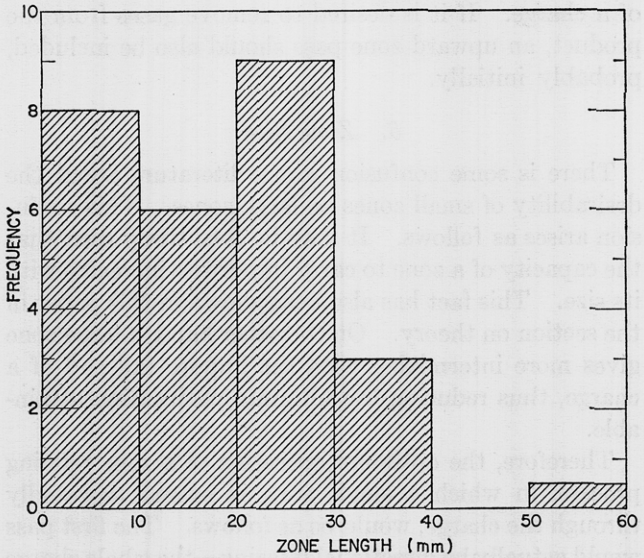

Fig. 9.—Frequency histogram of published data on zone lengths used in zone melting experiments.

Experimental zone sizes are shown in Table II and summarized in Fig. 9.

6. *Container*

Because of the usually high volatility of molten organic compounds, open boats generally cannot be used as containers for zone melting. Consequently, glass tubes are usually used. Vycor and quartz have also been used for their higher strength and purity (263, 196). To avoid breakage of the glass tubes, as discussed later, Teflon tubes have also been used (144, 193, 278). Metal tubes have been used but their disadvantage is that the zone melting process and the possibility of contamination cannot be seen (12).

If the yield is not critical, then the tubes should be as long as practical, and at least ten times the tube diameter. Longer tubes guarantee less back-mixing of impurity from the tail of the charge, and hence greater ultimate purification of the head of the charge.

Under free-convection conditions, larger diameter tubes give greater stirring and greater separation. The maximum size of the tube is limited by control of the zone sizes and shapes of the solid–liquid interfaces, which become increasingly curved as tube diameter increases. In laboratory operations a 40-mm. i.d. tube is probably the maximum that can be used, as shown in Fig. 10. Tubes 10 to 20 mm. i.d. probably lie in the most convenient operating range.

A serious problem in use of glass tubes is their breakage. Often after the first pass, especially if the zone is moved up, melting for a subsequent pass breaks the tube as follows. If the solid adheres to the tube and expands upon melting, the resultant force on the tube is sufficient to fracture it. The problem is more severe with larger tubes, and apparently with high purity materials which seem to adhere better to the glass (102). Numerous methods have been devised to avoid this problem. Walter suggested the use of a close-fitting glass plug with a rubber policeman at the end of the tube, permitting expansion upon melting (263). Ferrin and Helm coated the tubes with "Dri-Film SC-87" (General Electric Co., Silicon Products Division, Waterford, N. Y.) to prevent adhesion of the organic material (14). For horizontal zone refining, O'Neal devised a hot finger to keep a space open above the charge (161, 162). Lacey and Lyons provided a heater at the top of a vertical tube of anthracene to prevent sublimation from plugging the top (127).

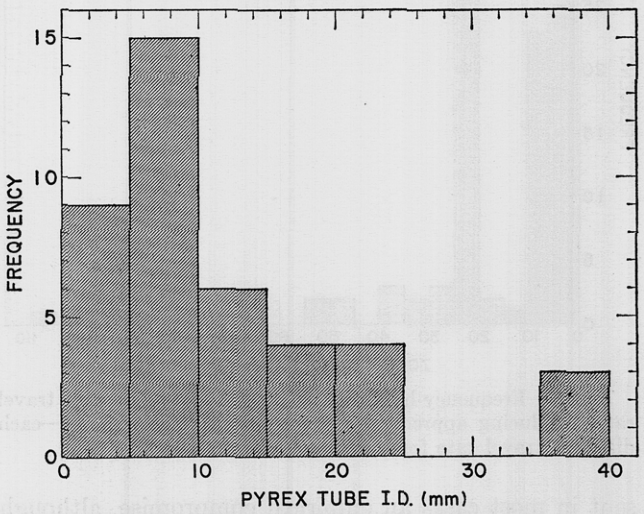

Fig. 10.—Frequency histogram of published data on Pyrex tube diameters used in zone melting experiments.

7. *Temperatures*

The temperatures and temperature gradients in the zone melting system can greatly affect the success of the operation. (Normally the temperature gradients are far below the level required for appreciable thermal diffusion. Consequently thermal diffusion effects will not be considered.) As seen in the discussion on free convection, a high temperature gradient at the freezing interface usually gives better mixing in the zone. Physically this means a large temperature difference

between the heater and the ambient or cooling chamber. It also means a close fitting heater the same size as the zone, such that the line of demarcation between heated and cooled material is sharp.

As shown in section IIC7, a high temperature gradient also helps to reduce constitutional subcooling, which can act to drastically reduce the separation.

A high temperature gradient is disadvantageous, however, if the zone motion is not entirely smooth. A high temperature gradient enforces any jerks in zone motion, while a low gradient (because of latent heat effects) tends to smooth them out.

Above all, the thermal stability requirements of the organic material must be considered. The zone cannot be heated so hot that the compound thermally decomposes. As shown in section IV, related techniques using solvents at lower temperatures may often be used on such compounds.

Generally, a more critical consideration than the temperature level of heaters and coolers is the temperature control. Fluctuations in temperature lead to fluctuations in the rate of movement of the freezing interface and can greatly reduce the separation. The temperature of the heater can be controlled by any of the usual techniques. Elaborate systems for sensing the specimen temperature, and thereby controlling the heater, have also been devised. The simplest technique is to keep a constant voltage input to a resistance heater. A relatively cheap constant voltage transformer is usually adequate. Control of the temperature of the coolers, or room temperature in most cases, is almost as important as the heater control. Long term fluctuations (hours) should ideally be kept below about 0.2° and short term fluctuations (minutes) below about 0.01°. The sample should also be kept shielded from drafts or similar uncontrolled factors which would affect the heat transfer to or from it in any way.

The melting point and the heat-transfer characteristics of a zone refined sample normally vary with position. Because of this the zone size also varies with position. This does not greatly affect the separation, although it influences the concentration profile obtained. Some effort has been expended toward correcting for these effects and maintaining a constant zone size (184–186).

8. *Equipment*

Generally each experimenter has constructed his own apparatus. These are summarized in Table V. The basic design is quite simple. The heater is nearly always an electrical resistance heater and is concentric to the tube containing the material to be refined. For most materials special coolers are not provided, the ambient temperature being low enough. To provide zone motion, either the heater or the tube may be moved, the results being identical. Motion is usually provided either by a rotating threaded shaft or by winding cord on a rotating spool and hanging the tube by the cord. The apparatus becomes more complex when provision for automatic switching and recycle is made.

TABLE V

SPECIAL FEATURES IN LABORATORY ZONE REFINERS

Feature	References
Heater design	25, 55, 60, 81, 94, 95, 97, 98, 188, 195, 211
Temperature control	184–186
Zone travel mechanism	25, 97, 190, 281, 295
Automatic multipass	97, 98, 188, 190, 227
Devices to avoid tube breakage	14, 144, 161, 162, 195, 263
Complete apparatus	12, 14, 25, 33, 60, 97, 98, 151, 188, 211
Simple demonstration apparatus	101
Small-scale apparatus	25, 94, 190, 202, 205, 207, 281
Low temperature apparatus	12, 14, 60, 199, 238, 281, 296
Variations	179, 200, 238

A commercial apparatus coming into usage recently is sold by the Fisher Scientific Company (97). It has been modified in several ways by different experimenters. Wilcox has installed a lower speed drive motor to change the minimum zone travel rate from 6.4 to about 0.8 mm./hr. (278). A Sola constant voltage transformer was also provided for the power input. Walter installed a bridge-type rheostat in series with the original one on the heater to give more sensitive control of the heat input (263). He also modified the air-cooling ring manifold to give a more constant zone size. Changes to permit processing three tubes simultaneously were made. Brown added a third zone together with individual controls and ammeters for each zone and a cycle counting device (33). Gumprecht provided for counting the number of cycles by installing a thermocouple near the end of the tube and wiring it to a recorder (90, 91).

Other commercial zone refiners suitable for organic compounds are sold by J. Herrmann-Horitz (40, rue Pascal, Paris XIIIe, France) and by Baird and Tatlock (Freshwater Road, Chadwell Heath, Essex, England) (77).

B. COMMERCIAL PURIFICATION AND ECONOMICS

Small lots (2–0.5 g.) of a few zone refined organic chemicals are commercially available at prices at about $1.40 per gram (72). Zone refined naphthalene in 50-g. lots sells for $0.80 per gram (219). These materials were prepared by the usual laboratory zone refining techniques. It is clear that such a process is relatively expensive.

In the drive to reduce the cost of refining organic compounds by fractional solidification, zone refining has been greatly modified, and related processes have been invented (171). Some of these are summarized in

Table VI. In 1958, a review of industrial equipment was made by Findlay and Weedman (70). Schoen, *et al.*, make a yearly review of crystallization, including zone melting and related industrial processes (89, 214–216).

TABLE VI
COMMERCIAL FRACTIONAL SOLIDIFICATION EQUIPMENT DESIGNS

Feature	References
Batch zone refiners	204
Continuous zone refiners	37, 117, 150, 168, 171, 173, 174, 267
Column crystallization	205, 206, 208, 210
Rotary drum	19, 50, 171, 270
Fractional freeze-melt	73, 77, 153, 181, 234, 235
Miscellaneous	20, 70, 71, 73, 75, 77, 84–86, 96, 121, 142, 143, 153, 156, 181, 183, 233–235, 240, 243, 259, 264, 280, 295

One of the processes closest to simple zone refining is the multistaged semicontinuous zone-void refiner (167, 170, 171, 270). A cost of about $2.50 per pound of product was estimated for the separation of 500,000 lb. per year of 1% (by weight) β-naphthol in naphthalene into 0.1% (by weight) β-naphthol and 30% (by weight) β-naphthol (270). It should be noted, however, the β-naphthol is isomorphous with naphthalene, and the distribution coefficient k is an unfavorable 1.85 in the above concentration range. For an equivalent eutectic-forming system, the cost should be approximately an order of magnitude below this.

A continuous vertical tube zone freezing unit has also been used for purification of saline water (150). A cost of about $4.21 per 1000 gal. of product was estimated for a plant producing 10^7 gal./day of water containing 500 p.p.m. of dissolved solids from sea water.

Quantum, Inc. has developed a horizontal continuous zone freezing unit for purifying liquids (63, 179). It was estimated that a unit to produce 10 lb. per hour would cost about $10,000. Further cost estimates are not available.

A promising development has been a rotary drum crystallizer (18, 50, 180, 270). In principle, this apparatus is the same although different enough in appearance so that it is no longer called a zone refiner. A cost of $0.038/lb. has been estimated to produce 5.7×10^6 lb./year of 99.5% pure naphthalene from 95% naphthalene–5% benzoic acid (50).

Other fractional solidification processes further removed from zone melting have been developed for industrial separations. Some of these are already in use. One is the Proabd Refiner, offered by Chemical Engineering Wiltons, Ltd. (77, 153, 234, 235). It consists simply in slowly freezing the organic material, and then slowly melting and drawing off the impure melt first. Units are already in use industrially. Although no cost figures have been published, purification of naphthalene and benzene is claimed to be economical.

Schildknecht has devised a continuous process called "column crystallization," which is apparently quite successful (205, 206, 208, 210). No cost data are available, however.

Judging from the devices which have already come forth, there is almost no limit to the varieties of equipment for fractional solidification that ingenious workers may devise. Zone melting and related fractional solidification techniques are clearly of lasting interest for industrial separations as well as for laboratory purification.

VI. SUMMARY

In this paper many important aspects of zone melting and related techniques have been critically reviewed. It was shown that these techniques have in common a partial or complete separation (segregation) of the components of a mixture at a solid–liquid interface during crystallization. Together they form a general and powerful group of fractionation processes, comparable to distillation.

The root of the segregation phenomenon was shown to be the mixture's phase diagram. Because most organic compounds have eutectic-type phase diagrams, their zone melting behavior was predicted to be quite different from that of metallic or semiconductor mixtures, which generally exhibit considerable solid solubility.

It was explained that the degree of separation attained in zone melting depends not only on the phase diagram but also on the mass transfer conditions in the zone. Consequently, the theoretically predicted effect of different mass transfer conditions on the separation was reviewed in some detail. The scant experimental data available did not confirm these predictions for eutectic-forming systems. This lack of agreement was attributed to a phenomenon known as "constitutional subcooling." It was concluded that new theoretical developments are needed to account quantitatively for the effect of this phenomenon on the separation. An attempt to achieve ideal thermodynamic equilibrium between freezing, solid, and bulk zone was also suggested to be very worthwhile, particularly in order to obtain ultrapure organics.

The various requirements for ultrapure organics were reviewed. A particularly extensive coverage of the need for ultrapure pharmaceuticals was included. In the same section various methods of defining and measuring ultrapurity of organic compounds were discussed.

Zone melting was shown to have several applications other than ultrapurification. No doubt many other applications await discovery. Several variations of the basic zone melting technique were also described. With these related methods virtually all organic compounds can be refined.

A detailed and critical survey of the practical problems involved in zone melting of organic compounds was given. A summary was made of operating data reported to give successful purification of organic compounds. Finally recommendations were made for optimum operating conditions.

Commercial equipment related to zone melting was reviewed briefly. The small amount of cost data available was given. From this it was concluded that some of the industrial processes inspired by zone melting are definitely economical. In fact, at least one is already in use.

In the appendixes a list of organic compounds successfully zone refined and a list of zone melting failures are given.

VII. GLOSSARY OF TERMS

Boundary layer.—A stagnant layer in the liquid or molten zone at the freezing interface. This layer is always present despite mixing in the zone, although it decreases in size as the amount of mixing increases.

Bulk zone.—The molten or liquid zone, excluding the boundary layer at the freezing interface.

Charge.—The original sample or material that undergoes the zone refining process.

Concentration profile.—The concentration of impurities *vs.* distance along the charge.

Coring.—A process in which the freezing interface is concave into the solid because of heat transfer effects. In single crystal growth this leads to great differences in segregation between center and outer portions of crystal.

Constitutional subcooling.—A phenomenon in which the imposed temperature falls below the melting point in a region near the freezing interface. This is caused by an interaction between segregation and heat transfer.

Directional freezing.—In a liquid, the slow freezing of the solution starting from one end.

Directional solidification.—The liquefaction of a solid and its progressive freezing from one end.

Distribution coefficient.—The ratio of impurity concentration in the freezing solid to that in the bulk liquid phase.

Freezing interface.—The solid–liquid interface at which freezing occurs.

Ideal conditions.—Conditions necessary to guarantee thermodynamic equilibrium (according to phase diagram) between bulk zone and freezing solid.

Mass transfer.—The movement of impurities from the freezing interface, through the boundary layer, into the bulk zone.

Progressive freezing.—In a liquid, the slow freezing of the solution starting from one end.

Progressive solidification.—The liquefaction of a solid and its progressive freezing from one end.

Segregation.—Freezing of a solid of composition differing from the liquid from which it solidifies.

Segregation coefficient.—The ratio of impurity concentration in the freezing solid to that in the bulk liquid phase.

Thermal analysis.—A method used to determine phase diagrams by plotting temperature against time at different concentrations; also a highly developed technique for determining purity.

Ultrapurity.—Materials whose contaminants have orders of magnitude in or less than the p.p.m. range (500 p.p.m. arbitrarily chosen as the upper limit of ultrapurity).

Vapor zone refining.—A zone fractionation process for volatile organic compounds where the heated zone causes sublimation across a gap where it is collected: a vapor zone instead of a liquid zone.

Weight fraction.—Weight of component A/weight of total components.

Zone freezing.—A liquid zone is passed through a frozen charge of a solution melting below room temperature.

Zone leveling.—A method used to obtain uniformity of distribution of remaining impurities throughout the charge (usually used after zone melting).

Zone melting.—A general method where a heated zone is passed slowly through a solid charge, such that segregation of impurities occurs at the freezing interface (usually understood to include zone freezing).

Zone pass.—Passage of a single zone entirely through the charge.

Zone refining.—Zone melting (or freezing) used for purification.

Zone precipitation.—The use of a volatile solvent added to a charge such that a lower temperature is needed to pass the heated zone through the sample; applicable to noncrystalline and heat-labile organic compounds.

VIII. APPENDIX A. ORGANIC COMPOUNDS ZONE REFINED

Organic compounds which are reported to have been successfully zone refined are listed in Table VII by their approximate melting points. Figure 11 shows the frequency distribution of the compounds by their melting points. It is seen the melting point range most frequently used was 50 to 75°. The reasons for this are probably: (a) Use of coolant for zone refining compounds melting below room temperature is less convenient than operating without coolant for higher melting compounds. The difficulty increases as the melting point decreases. (b) High melting organic compounds are both less common and tend to be less thermally stable at their melting points than those melting closer to room temperature.

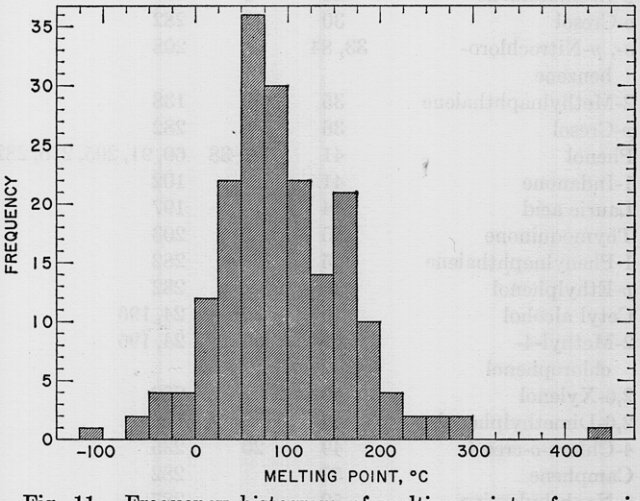

Fig. 11.—Frequency histogram of melting points of organic compounds reported to have been purified successfully by zone melting.

TABLE VII

ORGANIC COMPOUNDS ZONE REFINED

Compound	M.p., °C.	V, mm./hr.	References
Ethanol	−115		112
m-Xylene	−54		102
Methyl methacrylate	−50	300	7–9
Styrene	−31		8
1-Methylnaphthalene	−30	0.83	102, 287
n-Decane	−30		287
o-Xylene	−29		102
3-Methylpyridine	−18	106	12, 14
Neopentane	−17		102
Piperidine	−9		208
Aniline	−6	25	24, 196
4-Methylpyridine	3.8	52	14
Benzene	5.5	3–50	7, 189, 209, 237, 238, 282, 297
Nitrobenzene	5.7		26
Cyclohexane	6.5		287
Formic acid	8.4		203
Acrylic acid	12		282, 297
Dioxane	12		51, 52
m-Cresol	12		102
p-Xylene	13	3	237, 238
Acetic acid	17		202
Vinylene carbonate	22	25	296
Isoquinoline	23		282
2,4-Xylenol	26		282
Diphenylmethane	27		297
p-Bromotoluene	28	3	237
o-Cresol	30	48	282
o-, *p*-Nitrochlorobenzene	33, 84		208
2-Methylnaphthalene	35	52	138
p-Cresol	36		282
Phenol	41	21–38	60, 91, 205, 236, 282
1-Indanone	41		102
Lauric acid	44		197
Thymoquinone	45		203
1-Phenylnaphthalene	45		282
p-Ethylphenol	46		282
Cetyl alcohol	49	25	24, 196
2-Methyl-4-chlorophenol	49	25	24, 196
2,6-Xylenol	49		282
2,6-Dimethylphenol	49		102
4-Chloro-*o*-cresol	49	20	235
Camphene	50		282
1-Naphthylamine	50		287
Benzenesulfonic acid	50	38	91
Benzophenone	51	3	202, 209
4-Indanol	51		282
3-Ethyl-5-methylphenol	52		102
Pentamethylpyridine hemihydrate	52	30	30, 36
4-Chloro-1,3-dinitrobenzene	52		202
p-Dichlorobenzene	53	25	55
Indole	53	25	12
Dibenzyl	53	25	2, 29, 196
5-Indanol	55		282
o-Phenylphenol	56	38	91, 282
Myristic acid	58		197, 282
p-Anisidine	59	25	2, 29, 196
Stearyl alcohol	59	1	207

TABLE VII (*Continued*)

Compound	M.p. ,°C.	V, mm./hr.	References
Octadecanol-1	60	25	289
Maleic anhydride	60	25	24, 196
2-(α-Methylcyclohexyl)-4-methylphenol	60	25	24, 196
Tolane	62		202
Tiglic acid	64		203, 208
Palmitic acid	64		197
3,4-Xylenol	65		282
3,4-Dimethylphenol	65	2	204, 208
3-Methylphenanthrene	65		282
Azobenzene	69	3–25	24, 196, 203, 205, 209
3,5-Xylenol	68		282
3,5-Dimethylphenol	68		102, 202, 205
Stearic acid	70	95	197, 287–289
$C_{20}H_{41}OH$	70	10	207
$C_{21}H_{43}OH$	70	10	207
Caprolactam	70		203
Diphenyl sulfoxide	70		136
2,4-Dinitrotoluene	71		202
Diphenyl	71	2.1–8	278, 282, 287
$C_{22}H_{45}OH$	74	2	207
$C_{23}H_{47}OH$	74	2	207
2,5-Xylenol	75		282
2,3-Xylenol	75		282
2,5-Dimethylphenol	75	25	24, 196
$C_{24}H_{49}OH$	77	2	207
$C_{25}H_{51}OH$	78	2	207
Naphthalene	80	1–38	24, 30, 36, 55, 72, 76, 77, 113, 144, 155, 164, 190, 196, 203, 209, 263, 270, 282, 285–288
Durene	80		282, 287
Hexacosanol	80		202
Acetamide	81	25	24, 196, 205
$C_{26}H_{53}OH$	81	2	207
$C_{27}H_{55}OH$	82	3	207
Vanillin	82	25	72, 238
$C_{28}H_{57}OH$	84	2	207
Fluorenone	84	25	24, 196
p-Tolylmethyl sulfone	84		135
Hexacosyl hexacosanate (wax of insect *Eriopeltis festucae*)	84		202, 212
$C_{29}H_{59}OH$	85	2	207
N,N-Dimethyl-*p*-nitrosoaniline	85	25	24, 196
$C_{30}H_{61}OH$	87	1	207
m-Terphenyl	87		282
3,5-Dimethylphenol	88		205
9-Methylcarbazole	89	25	12, 14
Imidazole	90		2, 32
Skatole	95	25	24, 196
Acenaphthene	95		282
Benzil	95	2	209, 282
2,3,5-Trimethylphenol	96		282
Flavone	97		203
Azulene	99		203, 287
p-(*t*-butyl)phenol	99	25	24, 196
Phenoxyacetic acid	99	25	24, 196

TABLE VII (*Continued*)

Compound	M.p., °C.	*V*, mm./hr.	References
1-Hydroxanthraquinone	100	25	24, 196
Phenanthrene	100	25	24, 196, 203, 282
Aldrin	101	25	24, 196
o-Diaminobenzene	102		203
2-Phenylnaphthalene	103		282
Acridine	108		162
2,3-Dimethylindole	108	25	24, 196
Resorcinol	110	25	24, 196
Naphthylamine	110		287
Fluoanthene	110		282
Lindane	113		102
Antipyrine	114	25	24, 196
Acetamide	114	15	203, 288, 289
Acetanilide	114		72
2-Nitro-4-methylaniline	114	25	24, 196
Cholesteryl acetate	114		205
4-Chloro-2-nitroaniline	115	25	24, 196
p-Benzoquinone	116		205
Fluorene	116		282
Dichloromaleic anhydride	119	25	24, 196
Benzoic acid	122	6–25	24, 72, 94, 113, 144, 196, 229, 232, 288, 289
β-Naphthol	122	1.5	102, 270
Stilbene	124	3	128, 204, 205, 209, 238
Diphenyl sulfone	125		135
Extract of water beetle	128		208
β-Sitosterol	129	6.2	263
Benzamide	130	25	24, 196
Progesterone	130	6.2	263
Urea	133	25	24, 196
Cinnamic acid	133		202
Sitostearic acetate	137		205
Dimethyl terephthalate	140	25	24, 160, 196
1-(*p*-Tolyl)-3-methyl-5-pyrazolone	140	25	24, 196
Methylaniline	141	25	24, 196
Cholestanol	142	6.2	263
Anthranilic acid	145	25	24, 196
p-Nitroaniline	148	25	24, 196
Diphenylacetic acid	148	25	24, 196
Cholesterol	151	9	203, 204
Pyrene	152	25	24, 94, 196, 287
2-Methyl-4-nitroaniline	152	25	24, 196
Testosterone	153	6.2	263
4-Aminoquinoline	154		287
Di-*p*-tolyl sulfone	158		135
Salicylic acid	159	6	72, 288, 289
1,1′-Binaphthyl	160		282
1:2-Benzanthracene	162	25	24, 196
o-Iodobenzoic acid	162		72
Stigmasterol	164	6.2	263
Pyrazolone	165	25	24, 196
Sulfanilamide	165	6	55, 72, 288
1-Chloro-2-methylanthraquinone	165	25	24, 196
Hexamethylbenzene	166		287
p-Bromoacetanilide	168	6	55, 72, 288
1-Methylaminoanthraquinone	170	25	24, 196

TABLE VII (*Continued*)

Compound	M.p., °C.	*V*, mm./hr.	References
Benzanthrone	170	25	24, 196
Hydroquinone	171		203
Acetamide	171	25	24, 196, 202
Phenazine	171		1, 199
Diethylstilbesterol	177	6.2	263
Camphor	177		72
p-Chloroacetanilide	179	6	55, 72, 288
Phenothiozine	180		31
Succinic acid	185	25	24, 72, 196
p-Fluorobenzoic acid	186	6	55, 72, 288
Hexestrol	187	6.2	263
2,2′-Binaphthyl	188		282
2-Phenylindole	189		14
Triphenylene	199		282
1-Amino-2-methylanthraquinone	202	25	24, 196
1,8-Dihydroxyanthraquinone	210	25	24, 196
o-Terphenyl	213		128, 138
Anthracene	220	6–25	24, 72, 94, 105, 128, 161, 199, 223, 282, 287, 288, 289
1-Amino-2-cyanoanthraquinone	236	25	24, 196
Carbazole	246		282
Chrysene	253	25	94, 287
1,4,5-Trichloroanthraquinone	260	25	24, 196
p-Iodobenzoic acid	271	6	288, 289
1,5-Dihydroxyanthraquinone	280	25	24, 196
Anthraquinone	286	6–25	24, 55, 72, 196, 288
Sexiphenyl (coronene)	440	30	159
6-(*t*-Butyl)-5-indanol	*a*		282
cis-, *trans*-β-Chlorocrotonic acid	*a*		208
δ-Cyanovaleramide	*a*	25	24, 196
9-Ethyl-10-methylphenanthrene	*a*		282
3-Methoxybenzanthrone	*a*	25	24, 196
2-Methyl-4-chlorophenoxyacetic acid	*a*		282
2-Methyl-4-chlorophenoxypropionic acid	*a*		282
3-Methyl-5-ethylphenol	*a*		282
1,2,3,5,7-Pentamethylindole	*a*	25	24, 196
1,3,5,7-Tetramethylindole	*a*	25	24, 196

[a] Melting points unknown, listed in alphabetical order.

IX. APPENDIX B. FAILURES OF ZONE MELTING

Zone melting is not a completely general purification technique. As shown in Table VIII numerous instances of the failure of zone melting to affect appreciable purification have been reported. No doubt many other instances of failure have not been reported. Nevertheless, most of these failures need not have occurred, as presently explained.

TABLE VIII

ORGANIC COMPOUNDS AND MIXTURES NOT APPRECIABLY REFINED BY ZONE MELTING

Compound	V, mm./hr.	Reason for failure[a]	References
Aminopyrine	20	tf	263
Antipyrine	20	tf	263
Aromatic with Br or OH (frequently)	30	tf or d	36
Benzocaine	20	tf	263
Betazol hydrochloride	6.2	d	83
Chlorpheniramine maleate	6.2	d	83
Chlorpromazine hydrochloride	6.2	d	83
Cholestonol	20	tf	263
Cholesteryl benzoate with 2% cholestanol	6.2	tf	263
Cholesteryl benzoate with 10% cholestanol	3.9	tf or p	263
Cholesteryl benzoate	6.2	tf	263
Cholesteryl stearate	20	tf	263
Cyclizine hydrochloride	6.2	d	83
Desoxycorticosterone	6.2	d	83
Dibycaine hydrochloride	6.2	d	83
Doxylafine succinate	6.2	d	83
Ethinyl estradiol	6.2	d	83
Hexestrol	2.0	tf	263
Hexylresorcinol	6.2	tf	263
Hippuric acid		d	107
Isoproterenol hydrochloride	6.2	d	83
Levallorphan tartrate	6.2	d	83
Levaterenol bitartrate	6.2	d	83
Medizine hydrochloride	6.2	d	83
6-Mercaptopurine	6.2	d	83
α-Naphthyl benzoate	6.2	d	83
Orcinol (some)	30	tf or d	36
Phentolamine methanesulfonate	6.2	d	83
Prochlorperazine maleate		d	83
Promethazine hydrochloride	6.2	d	83
Pyrimethamine	6.2	d	83
Sterol mixtures		tf	191
Testosterone enanthate	6.2	d	83
Tetrocaine hydrochloride	6.2	d	83
Tolazoline hydrochloride	6.2	d	83
Trihexylphenidyl hydrochloride	6.2	d	83
Tripelennamine	6.2	d	83
Tripelennamine citrate	6.2	d	83
Vioform	6.2	d	83
Warfarin sodium	6.2	d	83

[a] Most probable reason for failure as given either by quoted author or by present authors: d means the compound was thermally unstable, tf means the zone travel rate was too high, p means the composition was probably near the eutectic composition.

There are only two basic reasons for the failure of zone melting to purify a crystalline compound: (a) The compound is unstable at or slightly above its melting point. (b) The starting composition is near that where solid and liquid in equilibrium have the same composition (*e.g.*, the eutectic composition). Both of these limitations can often be overcome by use of a solvent in the related technique "zone precipitation," as described in section IVB.

Conditions which may make the separation difficult are: (a) unfavorable phase diagram, *i.e.*, a solid solution is formed with a distribution coefficient near unity; (b) very low diffusion coefficients for the impurities in the melt. This can be expected for compounds with a high molecular weight and/or a high melt viscosity. These conditions do not, however, mean that purification is impossible. They merely necessitate a low zone travel rate and possibly a high number of zone passes with a long charge. It should never be concluded that zone melting is inapplicable for a particular purification until zone travel rates below 1 mm./hr., with at least ten zone passes, are employed.

X. REFERENCES

(1) Aftergut, S., and Brown, G. P., *Nature*, **189**, 827 (1961).
(2) Aftergut, S., and Brown, G. P., *Nature*, **191**, 379 (1961).
(3) Aftergut, S., and Brown, G. P., *Nature*, **193**, 361 (1962).
(4) Agranet, A. L., and Trubshaw, W. H., *S. African Med. J.*, **29**, 1021 (1955).
(5) Allred, W. P., and Bate, R. T., *J. Electrochem. Soc.*, **108**, 258 (1961).
(6) Ambrus, J. L., Ambrus, C. M., Sokal, J. E., Back, N., and Metzgar, R. S., in "Proceedings of the Canadian Conference on Blood Coagulation and Fibrinolysis," Lea and Febiger, Philadelphia, Pa., 1961, p. 473.
(7) Anikin, A. G., Dugacheva, G. M., Presnyakova, U. M., and Bykova, S. P., *Russ. J. Phys. Chem.*, **36**, 1115 (1962).
(8) Anikin, A. G., Gerasimov, Ya. I., Dugacheva, G. M., and Presnyakova, V. M., *Plasticheskie Massy*, No. 12, 13 (1962).
(9) Anikin, A. G., and Ormanetz, H. V., *Dokl. Akad. Nauk SSSR*, **142**, 817 (1962).
(10) Aston, J. G., and Mastrangelo, S. V. R., *Anal. Chem.*, **22**, 636 (1950).
(11) Baeder, D. H., private communication, St. Louis, Mo., 1963.
(12) Ball, J. S., Helm, R. V., and Ferrin, C. R., *Refining Eng.*, **30**, No. 13, C36 (1958).
(13) Ball, J. S., Helm, K. V., and Ferrin, C. R., *Chem. Eng.*, **66**, 80 (1959).
(14) Ball, J. S., Ferrin, C. R., and Helm, R. V., "Zone Refining for Purification of Spectroscopic Reference Compounds," Preprint from Division of Petroleum Chemistry, American Chemical Society, Washington, D. C., 1961, Vol. 6, No. 2, A125.
(15) Banus, M. D., and Gatos, H. C., *J. Electrochem. Soc.*, **109**, 829 (1962).
(16) Bardsley, W., Callan, J. M., Chedzey, H. A., and Hurle, D. T. J., *Solid-State Electron.*, **3**, 142 (1961).
(17) Bardsley, W., Boulton, J. S., and Hurle, D. T. J., *Solid-State Electron.*, **5**, 395 (1962).
(18) Bardsley, W., Hurle, D. T. J., and Mullin, J. B., *J. Electrochem. Soc.*, **109**, 64 (1962).
(19) Baron, T., B. S. Thesis, University of Illinois, Urbana, Ill., 1943.
(20) Beattie, I. R., and Gold, V., British Patent 900,108 (1962).
(21) Beckett, A. H., and Stenlake, J. B., "Practical Pharmaceutical Chemistry," The Athlone Press, University of London, London, 1962.
(22) Belozoruv, D. P., Kulok, I. O., and Zil'berman, G. E., *Kristallografiya*, **6**, 279 (1961); *Chem. Abstr.*, **57**, 11929*i* (1962).
(23) Beynon, J. H., "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Press, Amsterdam, Holland, 1960.

(24) Beynon, J. H., and Saunders, R. A., *J. Appl. Phys.*, **11**, 128 (1960).
(25) Beynon, J. H., and Saunders, R. A., *Chem. Ind.* (London), 128 (1960).
(26) Biermann, M., German Patent 1,070,606 (1959).
(27) Bolling, G. F., and Tiller, W. A., *J. Appl. Phys.*, **31**, 2040 (1960).
(28) Braun, J., and Marshall, S., *Brit. J. Appl. Phys.*, **8**, 157 (1957).
(29) Briggs, D. K. H., Report No. 0221, The Coal Tar Research Association, Gomersal, Leeds, England, 1958.
(30) Brown, A. L., and Buck, K. R., *Chem. Ind.* (London), 1347 (1961).
(31) Brown, G. P., and Aftergut, S., *Nature*, **193**, 361 (1962).
(32) Brown, G. P., and Aftergut, S., *J. Chem. Phys.*, **38**, 1356 (1963).
(33) Brown, G. P., private communication, General Electric Advanced Technology Lab., Schenectady, N. Y., 1963.
(34) Brown, I., *Brit. J. Appl. Phys.*, **8**, 457 (1957).
(35) Bruni, G., and Meneghini, *Atti accad. nazl. Lincei*, **11**, 5, 565 (1902).
(36) Buck, K. R., private communication, Heriot-Watt College, Edinburgh, Scotland, 1963.
(37) Buford, J. T., and Starks, R. J., in "Ultrapurification of Semiconductor Materials," The Macmillan Co., New York, N. Y., 1962, p. 25.
(38) Bunker, J. P., and Blumenfeld, C. M. Y., *New Engl. J. Med.*, **268**, 531 (1963).
(39) Burger, A., "Medicinal Chemistry," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1960.
(40) Burman, J. L., *J. Appl. Phys.*, **26**, 1195 (1955).
(41) Burris, J., Stockman, C. H., and Dillon, I. G., *Trans. AIME*, **203**, 1017 (1955).
(42) Burris, L., Jr., Stockman, C. H., and Dillon, I. D., "Contribution to the Mathematics of Zone Melting," ANL-5294, Argonne National Laboratory, Lemont, Ill., 1962.
(43) Burton, J. A., *J. Chem. Phys.*, **21**, 1991 (1953).
(44) Burton, J. A., Prim, R. C., and Slichter, W. P., *J. Chem. Phys.*, **21**, 1987 (1963).
(45) Cantarow, A., and Trumper, M., "Lead Poisoning," Williams and Wilkins Co., Baltimore, Md., 1944.
(46) Chadwick, G. A., *J. Inst. Metals*, **91**, 169 (1962).
(47) Chadwick, G. A., *J. Inst. Metals*, **91**, 299 (1962).
(48) Chadwick, G. A., *J. Inst. Metals*, **92**, 18 (1963).
(49) Chalmers, B., "Physical Metallurgy," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 265.
(50) Chaty, J., "An Engineering Study of a Rotary Drum Crystallizer," Ph.D. Thesis, University of Virginia, Charlottesville, Va., 1961.
(51) *Chem. Eng.*, **66**, 74 (1959).
(52) *Chem. Eng.*, **66**, 80 (1959).
(53) *Chem. Eng.*, **68**, 118 (1961).
(54) Chilton, J. P. and Winegard, W. C., *J. Inst. Metals*, **89**, 162 (1961).
(55) Christian, J. D., *J. Chem. Educ.*, **33**, 32 (1956).
(56) Cliffton, E. E., "Enzymes in Health and Disease," C. C. Thomas Co., Springfield, Ill., 1960.
(57) Cohen, E. N., Bellville, J. W., Budzikiewicz, H., and Williams, D. H., *Science*, **141**, 899 (1963).
(58) Davies, L. W., *Phil. Mag.*, **3**, 159 (1958).
(59) Dean, F. V., Kerr, J. R., and Hellawell, A., *J. Inst. Metals*, **90**, 234 (1962).
(60) Deluzarche, A., Maillard, A., Maire, J., and Moritz, J., *Bull. soc. chim. France*, 89 (1963).
(61) Dickinson, J. D., and Eaborn, C., *Chem. Ind.* (London), **29**, 959 (1956).
(62) Dikhoff, J. A. M., *Solid-State Electron.*, **1**, 202 (1960).
(63) Doede, C. M., *Ind. Chemist*, **38**, 462 (1962).
(64) Dorn, V. R., and Kirschner, S., *Chem. Eng. News*, **39**, 38 (1961).
(65) Drill, V. A., "Pharmacology in Medicine," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1958.
(66) Eldib, I. A., *Ind. Eng. Chem., Process Design Develop.*, **1**, 2 (1962).
(67) Eyring, H., Johnson, F. H., and Gensler, R. L., *J. Phys. Chem.*, **50**, 453 (1946).
(68) Eyring, H., *Anal. Chem.*, **20**, 98 (1948).
(69) Findlay, A., "Phase Rule," 9th Ed., Dover Publishing Co., New York, N. Y., 1951.
(70) Findlay, R. A., and Weedman, J. A., in "Advances in Petroleum Chemistry and Refining," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1958, Chapter 4.
(71) Findlay, R. A. and McKay, D. L., *Chem. Eng. Prog. Symp. Series*, **55**, 163 (1959).
(72) Fisher Scientific Co., "Chemical Index 62-C," Fairlawn, N. J., 1962, p. V.
(73) Forsyth, J. S., and Wood, J. T., *Trans. Inst. Chem. Engrs.* (London), **33**, 122 (1955).
(74) Fort, T., Ph.D. Thesis, University of Tennessee, Memphis, Tenn., 1957.
(75) Frevel, L. K. and Kressley, L. J., U. S. Patent 2,659,761 (1953).
(76) Friedenberg, R. M., "Ultrapurity and Ultrapurification of Pharmaceuticals by Zone Melting," Ph.D. Thesis, University of Connecticut, Storrs, Conn., 1963.
(77) Fryer, F. A., *Mfg. Chemists*, **33**, 100 (1962).
(78) Gibor, A., *Science*, **133**, 193 (1961).
(79) Glasgow, A. R., Ross, G. S., Horton, A. T., Enagonio, D., Dixon, H. D., Saylor, C. P., Furukawa, G. T., Reilly, M. L., and Henning, J. M., *Anal. Chim. Acta*, **17**, 54 (1957).
(80) Glasgow, A. R., and Ross, G. S., *J. Res. Natl. Bur. Std.*, **57**, 137 (1956).
(81) Goodman, G. H. L., *Research*, **7**, 168, 465 (1954).
(82) Goodman, L. S., and Gilman, A., "The Pharmacological Basis of Therapeutics," 2nd Ed., The Macmillan Co., New York, N. Y., 1958.
(83) Goyan, J. E., private communication, University of California, San Francisco Medical Center, San Francisco, Calif., 1963.
(84) Green, R. M. and Clark, J. W., U. S. Patent 2,833,835 (1958).
(85) Green, R. M., U. S. Patent 2,848,516 (1958).
(86) Griffiths, K. F., U. S. Patent 3,005,691 (1961).
(87) Griffiths, L. B., Wright, M. A., and Mlavsky, A. I., "The Travelling Solvent Method of Crystal Growth," Tyco Laboratories, Inc., Waltham, Mass., 1962, ASTIA AD-295,726.
(88) Grove, C. S., Jr., and Schoen, H. M., *Chim. Ing.* (Rome), **4**, 2 (1957); *Chem. Abstr.*, **52**, 15176 (1958).
(89) Grove, C. S., Jr., and Schoen, H. M., *Ind. Eng. Chem.*, **51**, 347 (1959).
(90) Gumprecht, D. L., *Chem. Eng.*, **69**, 140 (1962).
(91) Gumprecht, D. L., private communication, Reichhold Chemicals, Inc., White Plains, N. J., 1963.
(92) Hall, R. N., *J. Phys. Chem.*, **57**, 836 (1953).
(93) Handley, R., *Ind. Chemist*, **31**, 535 (1955).
(94) Handley, R., and Herington, E. F. G., *Chem. Ind.* (London), 304 (1956).
(95) Handley, R., and Herington, E. F. G., *Chem. Ind.* (London), 1184 (1957).
(96) Harper, J. I., U. S. Patent 2,846,292 (1958).
(97) Heneage, P., and Taylor, B. W., U. S. Patent 2,990,257 (1961).

(98) Herington, E. F. G., Handley, R., and Cook, A. J., *Chem. Ind.* (London), 292 (1956).
(99) Herington, E. F. G., *Anal. Chim. Acta*, **17**, 15 (1957).
(100) Herington, E. F. G., *Analyst*, **84**, 680 (1959).
(101) Herington, E. F. G., *School Sci. Rev.*, **149**, 35 (1961).
(102) Herington, E. F. G., "Zone Melting of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963.
(103) Hesse, G., and Schildknecht, H., *Angew. Chem.*, **68**, 641 (1956).
(104) Hines, R. C., Miller, S. E., and Goering, H. L., *Ind. Eng. Chem.*, **51**, 1345 (1959).
(105) Hoesterey, D. C., *J. Chem. Phys.*, **36**, 557 (1962).
(106) Holmes, E. L., Rutter, J. W., and Winegard, W. C., *Can. J. Phys.*, **35**, 1223 (1957).
(107) Hubbard, W. N., Frow, F. R., and Waddington, G., *J. Phys. Chem.*, **65**, 1326 (1961).
(108) Hudson, J. B., Hillig, W. B., and Strong, R. M., *J. Phys. Chem.*, **63**, 1012 (1959).
(109) Hulme, K. F., *Proc. Phys. Soc.* (London), **B68**, 393 (1955).
(110) Hunt, J. D., and Chilton, J. P., *J. Inst. Metals*, **92**, 21 (1963).
(111) Hurle, D. T. J., *Solid-State Electron.*, **3**, 37 (1961).
(112) Izergin, A. P., *Izv. Vysshikh Uchebn. Zavedenii*, 115 (1958).
(113) Joncich, M. J., and Bailey, D. R., *Anal. Chem.*, **32**, 1578 (1960).
(114) Johnston, W. C., and Tiller, W. A., *Trans. AIME*, **224**, 214 (1962).
(115) Kapustin, A. P., "The Effects of Ultrasound on the Kinetics of Crystallization," Consultants Bureau Inc., New York, N. Y., 1963.
(116) Katz, M., private communication, Morris Plains, N. J., 1963.
(117) Kennedy, J. K., *Rev. Sci. Instr.*, **33**, 387 (1962).
(118) Kirgintsev, A. N., and Auvakumov, E. G., *Soviet Phys.-Solid State*, **4**, 2509 (1963).
(119) Kirgintsev, A. N., Kudrin, V. D., and Kudrina, K. W., *Fiz. Tverd. Tela*, **5**, 928 (1963).
(120) Kodera, H., *Japan J. Appl. Phys.*, **2**, 527 (1963).
(121) Kolner, S. J., U. S. Patent 2,835,598 (1958).
(122) Kraft, R. W., and Albright, D. L., *Trans. AIME*, **221**, 95 (1961).
(123) Kraft, R. W., *Trans. AIME*, **221**, 704 (1961).
(124) Kraft, R. W., *Trans. AIME*, **224**, 65 (1962).
(125) Kraft, R. W., Lamkey, F. D., and George, F. D., *Trans. AIME*, **224**, 1037 (1962).
(126) Kramer, J. J., Bolling, G. F., and Tiller, W. A., *Trans. AIME*, **227**, 374 (1963).
(127) Lacey, A. R., and Lyons, L. E., *Rev. Sci. Instr.*, **34**, 309 (1963).
(128) Light and Co., England, *Chem. Eng.*, **66**, 74 (1959); **66**, 80 (1959).
(129) Lipsett, F. R., *Can. J. Res.*, **35**, 284 (1957).
(130) Loconti, J. D., and Cahill, J. W., *J. Polymer Sci.*, **1**, 3163 (1963).
(131) Lord, N. W., *Trans. AIME*, **197**, 1531 (1953).
(132) Lu, G., Johnson, S. L., Ling, M. S., and Grantz, J., *Anesthesiology*, **14**, 466 (1953).
(133) Lyubov, B. Ya., and Temkin, D. E., in "Growth of Crystals," Vol. 3, Consultants Bureau, Inc., New York, N. Y., 1962, p. 40.
(134) MacDougall, D. P., *Phys. Rev.*, **38**, 2296 (1931).
(135) Mackle, H., and O'Hare, P. A. G., *Trans. Faraday Soc.*, **57**, 1521 (1961).
(136) Mackle, H., and O'Hare, P. A. G., *Trans. Faraday Soc.*, **57**, 2119 (1961).
(137) Mader, W. J., in "Organic Analysis II," Interscience Publishers, New York, N. Y., 1954, p. 253.
(138) Maire, J., and Moritz, J., *Bull. soc. chim. France*, 210 (1963).
(139) Mastrangelo, S. V. R., and Aston, J. G., *Anal. Chem.*, **26**, 764 (1954).
(140) Mastrangelo, S. V. R., and Dornte, R. W., *J. Am. Chem. Soc.*, **77**, 6200 (1955).
(141) McCullough, J. P., and Waddington, G., *Anal. Chim. Acta*, **17**, 80 (1957).
(142) McKay, D. L., U. S. Patent 2,823,242 (1958).
(143) McKay, D. L., Dale, G. H., and Weedman, J. A., *Ind. Eng. Chem.*, **52**, 197 (1960).
(144) McKenzie, D. R., "Zone Melting and Phase Studies of Some Organic Compounds," M.S. Thesis, University of Tennessee, Knoxville, Tenn., 1958.
(145) Melville, H. W., and Stead, B. D., *J. Polymer Sci.*, **16**, 505 (1955).
(146) Memlink, D. W., *Philips Res. Rept.*, **11**, 183 (1956).
(147) Metz, R., and Best, C. H., *Practitioner*, **185**, 593 (1960).
(148) Meyers, E. L., *J. New Drugs*, **3**, 115 (1963).
(149) Milliken, K. S., *J. Metals*, **7**, 838 (1955).
(150) Mink, W. H., Sachsel, G. F., and Filbert, R. B., Jr., in "Symposium on Saline Water Conversion," No. 27 in Advances in Chemistry Series, American Chemical Society, Washington, D. C., 1960, p. 75.
(151) Minnesota Mining and Manufacturing Co., British Patent 890,668 (1962).
(152) Mlavsky, A. I., and Weinstein, M., *J. Appl. Phys.*, **34**, 2885 (1963).
(153) Molinari, J. G. D., *Ind. Chem.* (London), 1 (1961).
(154) Morris, W., Tiller, W. A., Rutter, J. W., and Winegard, W. C., *Trans. Am. Soc. Metals.*, **47**, 463 (1955).
(155) Motrorcic, G., *Bull. Sci. Conseil Acad. RPF Yougoslavie*, **1**, 43 (1953).
(156) Movchan, A. T., and Kirilenko, G. V., U.S.S.R. Patent 148,015 (1962).
(157) Mullin, J. B., and Hulme, K. R., *J. Phys. Chem. Solids*, **17**, 1 (1960).
(158) Munson, D. and Hellawell, A., *J. Inst. Metals*, **92**, 27 (1963).
(159) Nozaki, T., Tamura, M., Harada, Y., and Saito, K., *Bull. Chem. Soc. Japan*, **33**, 1329 (1960).
(160) Nugent, L. J., Lee, S. M., Burns, J., and Stevens, R., "Research on Organic Coherent Electromagnetic Radiation Materials," Electro-Optical Systems, Pasadena, Calif., 1963, ASD-TDR-63685.
(161) Oneal, G., Jr., *Rev. Sci. Instr.*, **33**, 490 (1962).
(162) Oneal, G., Jr., *Rev. Sci. Instr.*, **34**, 1150 (1963).
(163) Parr, N., "Zone Refining and Allied Techniques," George Newnes, Ltd., London, 1960.
(164) Peaker, F. W., and Robb, J. C., *Nature*, **182**, 1591 (1958).
(165) Pecsok, R. L., Ed., "Principles and Practice of Chromatography," John Wiley and Sons, Inc., New York, N. Y., 1959.
(166) Pfann, W. G., *Trans. AIME*, **194**, 747 (1952).
(167) Pfann, W. G., *Trans. AIME*, **203**, 297 (1955).
(168) Pfann, W. G., *J. Metals*, **7**, 297 (1955).
(169) Pfann, W. G., *J. Metals*, **7**, 961 (1955).
(170) Pfann, W. G., U. S. Patent 2,739,045 (1956).
(171) Pfann, W. G., "Zone Melting," John Wiley and Sons, Inc., New York, N. Y., 1958.
(172) Pfann, W. G., and Theuerer, H. C., *Anal. Chem.*, **32**, 1574 (1960).
(173) Pfann, W. G., U. S. Patent 2,926,075 (1960).
(174) Pfann, W. G., U. S. Patent 2,949,348 (1960).
(175) Pfann, W. G., *J. Appl. Phys.*, **35**, 258 (1964).

(176) Plaskett, T. S., and Winegard, W. C., *Can. J. Phys.*, **37**, 1555 (1959).
(177) Porath, J., *Nature*, **196**, 47 (1962).
(178) Posey, J. C., and Smith, H. A., *J. Am. Chem. Soc.*, **79**, 555 (1957).
(179) Quantum, Inc., *Chem. Eng.*, **68**, 118 (1961).
(180) Rangappa, K. S., *Nature*, **191**, 1087 (1961).
(181) Rangappa, K. S., and Sood, R. N., *J. Irrigation Power*, **19**, 1013 (1962).
(182) Rappaport, M., and Kenney, A. S., *J. Am. Med. Assoc.*, 2040 (1939).
(183) Ratje, J. D., U. S. Patent 2,809,884 (1957).
(184) Reich, R., Montariol, F., *Mesures Controle Ind.*, **294**, 1343 (1961).
(185) Reich, R., Montariol, F., *Mesures Controle Ind.*, **295**, 1455 (1961).
(186) Reich, R., Montariol, F., *Mesures Controle Ind.*, **296**, 71 (1962).
(187) Reiss, H., *Trans. AIME*, **200**, 1053 (1954).
(188) Riano, E., and Portales, J. L. A., *Rev. Cienc. Apl.* (Madrid), **15**, 489 (1961); *Chem. Abstr.*, **57**, 5378*h* (1962).
(189) Rock, H., *Naturwissenschaften*, **43**, 81 (1956).
(190) Ronald, A. P., *Anal. Chem.*, **31**, 964 (1959).
(191) Ronald, A. P., private communication, Technological Research Lab., Fisheries Research Board of Canada, Vancouver, British Columbia, Canada, 1963.
(192) Rothlin, E., *Bull. acad. suisse sci. med.*, **2**, 1 (1946).
(193) Ruskin, A. M., "Zone Melting of Cyclohexane-Rich Polystyrene–Cyclohexane Solid-Solutions," Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1961.
(194) Rutter, J. W., and Chalmers, B., *Can. J. Phys.*, **31**, 15 (1953).
(195) Sanders, R. A., *Chem. Ind.* (London), 1218 (1961).
(196) Saunders, R. A., private communication, Imperial Chemical Industries, Ltd., P.O. Box 42, Hexagon House, Bladkley, Manchester 9, England, 1963.
(197) Schaeppi, W. H., *Chimia* (Aarau), 16, 291 (1962); *Chem. Abstr.*, **58**, 7051*g* (1963).
(198) Schildknecht, H., *Z. Naturforsch.*, **126**, 23 (1957).
(199) Schildknecht, H., and Mannl, A., *Angew. Chem.*, **69**, 634 (1957).
(200) Schildknecht, H., German Patent 1,044,770 (1958).
(201) Schildknecht, H., Rauch, G., and Schlegelmilch, F., *Chemiker-Ztg.*, **83**, 549 (1959).
(202) Schildknecht, H., *Z. Anal. Chem.*, **181**, 254 (1961).
(203) Schildknecht, H., "Journal de Internationale d'Etude des Methodes de Separation Immediate et de Chromatographie," G.A.M.S., Paris, 1961.
(204) Schildknecht, H., and Hopf, U., *Chem. Ingr.-Tech.*, **33**, 352 (1961).
(205) Schildknecht, H., and Vetter, H., *Angew. Chem.*, **73**, 240 (1961).
(206) Schildknecht, H., Mass, K., and Kraus, W., *Chem. Ingr.-Tech.*, **34**, 697 (1962).
(207) Schildknecht, H., Renner, G., and Kaess, W., *Fette, Seifen, Anstrichmittel*, **64**, 493 (1962).
(208) Schildknecht, H., *Chimia* (Aarau), **17**, 145 (1963).
(209) Schildknecht, H., and Hopf, U., *Z. Anal. Chem.*, **193**, 401 (1963).
(210) Schildknecht, H., Rossler, H., and Mass, K., *Fachzeitschrift Lab.*, **7**, 281 (1963).
(211) Schildknecht, H., and Schnell, J., "Uber den Bau eines Zonenschmelzapparates mit Peltierelementen," from Symposium für Zonenschmelzen und Kolonnenkristallisieren, Kernforschungezentrum Karlsruhe, Aachen, Germany, 1963.
(212) Schildknecht, H., and Vetter, H., *Fette, Seifen, Anstrichmittel*, **65**, 551 (1963).
(213) Schlichta, P. J., *J. Sci. Instr.*, **39**, 392 (1962).
(214) Schoen, H. M., *Ind. Eng. Chem.*, **52**, 173 (1960).
(215) Schoen, H. M., and Van den Bogaerde, J., *Ind. Eng. Chem.*, **53**, 155 (1961).
(216) Schoen, H. M., and Van den Bogaerde, J., *Ind. Eng. Chem.*, **54**, 57 (1962).
(217) Schwab, F. W., and Wichers, E., in "Temperature—Its Measurement and Control in Science and Industry," Reinhold Publishing Co., New York, N. Y., 1941.
(218) Schwab, F. W., and Wichers, E., *J. Res. Natl. Bur. Std.*, **32**, 253 (1944).
(219) Scintillation Products (Rahn Corp.), private communication, Boston, Mass., 1963.
(220) Seltz, H., *J. Am. Chem. Soc.*, **57**, 391 (1935).
(221) Sexton, W. A., and Hendrickson, W. G., *Science*, **142**, 621 (1963).
(222) Shapiro, J., *Science*, **133**, 2063 (1961).
(223) Sherwood, J. N., and Thomson, S. J., *J. Sci. Instr.*, **37**, 242 (1960).
(224) Simonelli, A. P., and Higuchi, T., *J. Pharm. Sci.*, **50**, 861 (1961).
(225) Simonelli, A. P., and Higuchi, T., *J. Pharm. Sci.*, **51**, 584 (1962).
(226) Skau, E. L., Arthur, J. C., and Wakeham, H., in "Techniques of Organic Chemistry," 2nd Ed., Vol. I, Interscience Publishers, Inc., New York, N. Y., 1949, Part 1, Chapter 7.
(227) Sloan, G. J., and McGowan, N. H., *Rev. Sci. Instr.*, **34**, 60 (1963).
(228) Sloan, G. J., in "Physics and Chemistry of the Organic Solid State," Interscience Publishers, New York, N. Y., 1963, p. 179.
(229) Sloan, G. J., private communication, E. I. du Pont de Nemours and Co., Wilmington, Del., 1963.
(230) Smit, W. M., "Purity Control by Thermal Analysis," Elsevier Press, Amsterdam, Holland, 1957.
(231) Smit, W. M., *Anal. Chim. Acta*, **17**, 22 (1957).
(232) Smith, V. G., Tiller, W. A., and Rutter, J. W., *Can. J. Phys.*, **33**, 723 (1955).
(233) Snyder, A. E., *Sci. Am.*, **207**, 41 (1962).
(234) Societe pour l'Exploitation des Procedes ab-der Halden, British Patent 837,295 (1960).
(235) Societe pour l'Exploitation des Procedes ab-der Halden, British Patent 899,799 (1962).
(236) Sorensen, P., *Chem. Ind.* (London), 1593 (1959).
(237) Sue, P., Pauly, J., and Nouaille, A., *Bull. soc. chim. France*, 593 (1958).
(238) Sue, P., Pauly, J., and Nouaille, A., German Patent 1,085,498 (1960).
(239) Sundquist, B. E., Bruscato, R., and Mondolfo, L. F., *J. Inst. Metals*, **91**, 204 (1963).
(240) Tarr, T. A., U. S. Patent 2,874,199 (1959).
(241) Thomas, L. J., "Microscopic Study of Solid–Liquid Interfaces During Melting and Freezing," Ph.D. Thesis, University of Illinois, Urbana, Ill., 1962.
(242) Thomas, L. J., and Westwater, J. W., *Chem. Eng. Progr., Symp. Series*, **59**, 155 (1963).
(243) Thomas, R. W., U. S. Patent 2,854,494 (1958).
(244) Tiller, W. A., Jackson, K. A., Rutter, J. W., and Chalmers, B., *Acta Met.*, **1**, 428 (1953).
(245) Tiller, W. A., and Rutter, J. W., *Can. J. Phys.*, **34**, 96 (1956).
(246) Tiller, W. A., in "Liquid Metals and Solidification," American Society for Metals, Cleveland, Ohio, 1958, p. 2760.

(247) Tiller, W. A., in "Growth and Perfection of Crystals," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 332.
(248) Tiller, W. A., *J. Iron Steel Inst.* (London), **192**, 338 (1959).
(249) Tiller, W. A., *J. Appl. Phys.*, **33**, 3106 (1962).
(250) Tiller, W. A., *J. Appl. Phys.*, **34**, 2757 (1963).
(251) Tiller, W. A., in "The Art and Science of Growing Crystals," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 276.
(252) Trainor, A., and Bartlett, B. E., *Solid-State Electron.*, **2**, 106 (1961).
(253) Tunnicliff, D. D., and Stone, H., *Anal. Chim. Acta*, **17**, 1 (1957).
(254) Ubbelohde, A. R., *Anal. Chim. Acta*, **17**, 1 (1957).
(255) Ueda, H., *J. Phys. Soc. Japan*, **16**, 61 (1961).
(256) U. S. Army Quartermaster Research and Engineering Command, *Chem. Eng.*, **66**, 80 (1959).
(257) "The United States Pharmacopeia. VI." The United States Pharmacopeia Convention, Inc., 1960.
(258) "U. S. P. Reference Standards Booklet," New York, N. Y., 1951.
(259) Vela, M. A., U. S. Patent 2,839,411 (1958).
(260) Vold, R. D., and Vold, R. H., in "Techniques of Organic Chemistry," Vol. I, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1949, Part 1, Chapter 7.
(261) Von Euler, U. S., *Can. Med. Assoc. J.*, **86**, 981 (1962).
(262) Walton, D., Tiller, W. A., Rutter, J. W., and Winegard, W. C., *Trans. AIME*, **203**, 1023 (1955).
(263) Walter, W. G., "Purification of Some Organic Medicinal Compounds by Zone Melting," Ph.D. Thesis, University of Connecticut, Storrs, Conn., 1962.
(264) Weedman, J. A., U. S. Patent 2,868,830 (1959).
(265) Weisberg, L. R., and Rosi, F. D., *Rev. Sci. Instr.*, **31**, 206 (1960).
(266) Weissberger, A., Proskauer, E. A., *et al.*, in "Techniques of Organic Chemistry," 2nd Ed., Vol. VII, Interscience Publishers, Inc., New York, N. Y., 1955.
(267) Western Electric Co., British Patent 909,257 (1962).
(268) Westwater, J. W., and Thomas, L. J., (motion picture) "Microscopic Study of Solid–Liquid Interfaces during Melting and Freezing," University of Illinois, Urbana, Ill., 1962.
(269) White, W., *J. Phys. Chem.*, **24**, 393 (1920).
(270) Wilcox, W. R., "Fractional Crystallization from Melts," Ph.D. Thesis, University of California, Berkeley, Calif., 1960; Lawrence Radiation Laboratory, Berkeley, Calif., UCRL-9213, 1960.
(271) Wilcox, W. R., Patent Applied for by Atomic Energy Commission, Case No. 2-24,938 (RL-2922), 1960.
(272) Wilcox, W. R., *Chem. Eng. Sci.*, **13**, 113 (1961).
(273) Wilcox, W. R., and Wilke, C. R., in "Ultrapurification of Semiconductor Materials," The Macmillan Co., New York, N. Y., 1962, p. 481.
(274) Wilcox, W. R., and Wilke, C. R., "Pure Diffusional Mass Transfer in Zone Melting," Lawrence Radiation Laboratory, Berkeley, Calif., UCRL-10433, 1962; *A.I.Ch.E. J.*, in press.
(275) Wilcox, W. R., "Incomplete Liquid Mixing in Crystal Growth from the Melt," Aerospace Corp., El Segundo, Calif., TDR-169(3240-10)TN-1, 1963; *J. Appl. Phys.*, in press.
(276) Wilcox, W. R., "Solute Redistribution During Solidification of Eutectic-Forming Mixtures," Aerospace Corp., El Segundo, Calif., TDR-169(3240-10)TN-2, 1963; to be published.
(277) Wilcox, W. R., "Zone Melting of Eutectic-Forming Mixtures," Aerospace Corp., El Segundo, Calif., ATN-64-(9236)-2, 1963; to be published.
(278) Wilcox, W. R., private communication, Aerospace Corp., El Segundo, Calif., 1963.
(279) Wilke, K. J., *Fortschr. Mineral.*, **34**, 85 (1956).
(280) William, G. A., and Firth, A., British Patent 808,176 (1959).
(281) Wilman, W. G., *Chem. Ind.* (London), 1825 (1961).
(282) Wilman, W. G., private communication, The Coal Tar Research Association, Oxford Road, Gomersal near Leeds, England, 1963.
(283) Winegard, W. C., Majka, S., Thall, B. M., and Chalmers, B., *Can. J. Chem.*, **29**, 320 (1951).
(284) Winegard, W. C., and Chalmers, B., *Trans. Am. Soc. Metals*, **46**, 1214 (1953).
(285) Wolf, H. C., *Z. Physik*, **139**, 318 (1954).
(286) Wolf, H. C., and Deutsch, H. P., *Naturwissenschaften*, **41**, 425 (1954).
(287) Wolf, H. C., German Patent 1,015,804 (1957).
(288) Wynne, E. A., *Microchem., J.*, **5**, 175 (1961).
(289) Wynne, E. A., private communication, Fisher Scientific Co., Fair Lawn, N. J., 1963.
(290) Yue, A. S., *Trans. AIME*, **215**, 871 (1959).
(291) Yue, A. S., and Clark, J. B., *Trans. AIME*, **221**, 383 (1961).
(292) Yie, A. S., *Trans. AIME*, **224**, 110 (1962).
(293) Yie, A. S., *J. Inst. Metals*, **91**, 166 (1962).
(294) Yie, A. S., *Trans. AIME*, **227**, 64 (1963).
(295) Zarchin, A., U. S. Patent 2,821,304 (1958).
(296) Zief, M., Ruch, H., and Schramm, C. H., *J. Chem. Educ.*, **40**, 351 (1963).
(297) Zief, M., private communication, J. T. Baker Chemical Co., Phillipsburg, N. J., 1963.