

## Intermolecular Forces and the Nature of the Liquid State

Liquids reflect in their bulk properties the attractions and repulsions of their constituent molecules.

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The central problem in an attempt to understand the nature of a liquid from first principles is that of accounting for its bulk macroscopic properties in terms of the structure, motion, and mutual interactions of the molecules of which it may be presumed to be composed. Even leaving out of account still more difficult questions concerned with a liquid's characteristic fluidity, and asking only about those of its properties that characterize it in a state of equilibrium (its density, specific heat, compressibility, and so forth), we are yet far from having produced a fully convincing and comprehensive account of the connection between the macroscopic and microscopic levels.

There is no reason to suppose that this lack in our theoretical understanding is in any way due to the imperfection of our knowledge of the intermolecular forces. The major features of these forces [or, as I shall speak of them below, the interaction potentials ( $\phi$ ), the force being the negative of the rate at which  $\phi$  varies with increasing separation ( $r$ ) between molecular

centers] are known quite well enough; they are generally strong repulsions at short distances and weak attractions at long distances. The difficulty, rather, is in carrying out the program prescribed by statistical mechanics for relating the intermolecular forces to the bulk macroscopic properties.

Nevertheless, the broad outlines of this connection (though admittedly not its finer details) have begun to emerge as the result of recent theoretical studies. It has long been known that there are at least two qualitatively different kinds of equilibrium state in which a liquid may exist. A liquid at its triple point, where it may be simultaneously in equilibrium with its vapor and with a crystalline solid (for example, water at its freezing point in an atmosphere of its own vapor), is in a state typical of ordinary dense liquids as commonly observed; whereas a liquid at its critical point, where it and its equilibrium vapor lose their separate identities and form a single fluid phase of relatively low density, is in a unique state with properties very different from those which characterize it at its triple point. The key to our present understanding of liquids is the recognition that different aspects of the intermolecular forces, the long-range attractions in one case and the short-range repulsions in the other, are of dominant

importance in each of these two regions—the region around the triple point, where the liquid is an “ordinary” liquid, and the region around the critical point, where it is quite extraordinary.

In Fig. 1 is a typical interaction potential  $\phi(r)$  as a function of the distance ( $r$ ) between centers of a pair of interacting molecules. It is characterized by a very strong repulsion, of very short range, at small  $r$ , and by a much weaker, and much longer ranged, attraction at larger  $r$ . In Fig. 2 is a typical “phase diagram” of any simple substance, giving the ranges of pressure ( $p$ ) and temperature ( $T$ ) over which each phase is stable. It shows the triple point where the solid-liquid, solid-vapor, and liquid-vapor equilibrium lines meet and shows also the critical point at the terminus of the liquid-vapor equilibrium line. The general theme of this paper, and its major thesis, is that to understand the properties of a liquid in the neighborhood of its triple point, and, in particular, to understand the character of the liquid-solid and liquid-vapor equilibria there, one must know accurately the effects of the repulsive forces, but it is sufficient to treat quite crudely the effects of the attractive forces; while precisely the opposite is true at the critical point, where, to understand the properties of the fluid and the character of the liquid-vapor equilibrium, one must treat with great fidelity the effects of the attractive forces, though it is sufficient to take merely nominal account of the presence of repulsive forces.

Where I speak of the necessity to treat accurately the effects of the attractive or repulsive forces, I do not mean that it is important to know the corresponding part of  $\phi(r)$  with quantitative accuracy. Indeed, even if the  $\phi(r)$  of Fig. 1 were idealized as a square-well potential, as in Fig. 3, but the statistical mechanical consequences of such a potential were then determined without further approximation, there would undoubtedly result an es-

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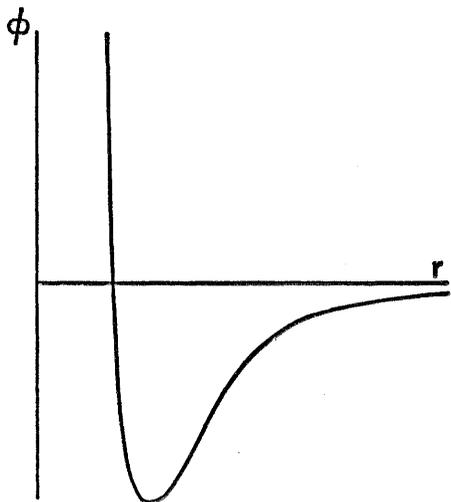


Fig. 1. Potential energy  $\phi$  as a function of distance  $r$  between centers of a pair of interacting molecules.

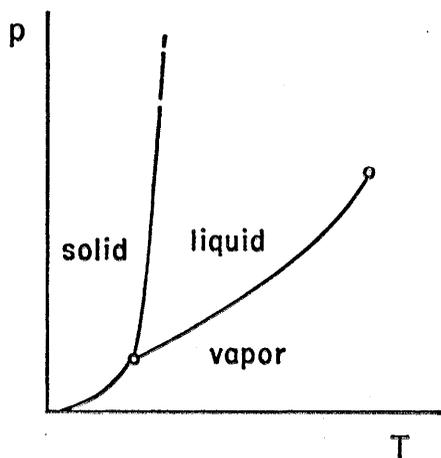


Fig. 2. Pressure-temperature phase diagram of a simple substance. The circles mark the triple point, where the three equilibrium lines meet, and the critical point, at the terminus of the liquid-vapor line.

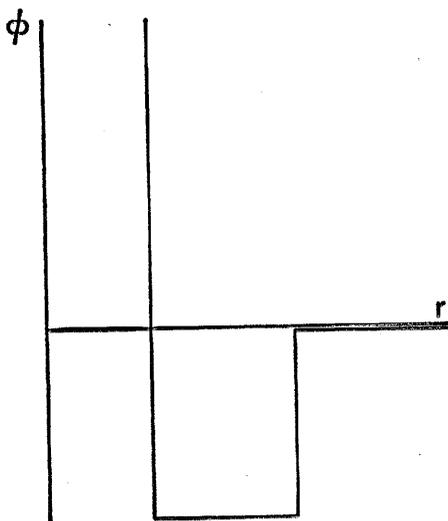


Fig. 3. The square-well potential, an idealization of the more realistic potential in Fig. 1.

essentially correct description of all the macroscopic properties of matter throughout a vast region of the  $p, T$  plane, including the neighborhoods of the triple and critical points. Thus, what matters is not the quantitative accuracy of the assumed  $\phi(r)$ , but rather the qualitative accuracy of the resulting spatial correlations of molecular positions; the triple and critical points are distinguished by having the relevant qualitative features of this correlation, and the nature of its propagation through the fluid, determined primarily by the short-range repulsive forces between molecules, or by the longer ranged attractive forces, respectively.

### Properties of a Fluid Near Its Critical Point

The classical description of a critical point by the van der Waals equation of state,

$$p = NkT/(V - Nb) - a(N/V)^2, \quad (1)$$

is well known. Here the fluid of volume  $V$  consists of  $N$  molecules, with  $a$  and  $b$  characteristic molecular constants and  $k$ , Boltzmann's constant. The variation of pressure with volume at fixed temperature, which is implied by Eq. 1 near the critical point, is shown in Fig. 4. The highest lying of the three isotherms shown is a typical one for a temperature above the critical temperature,  $T > T_c$ ; the next is the critical isotherm,  $T = T_c$ , characterized by vanishing slope at its point of inflection, which is the critical point; and the lowest of those shown is a typical one for a temperature below the critical temperature,  $T < T_c$ . The latter, which as determined from Eq. 1 is a smooth curve with loops, is to be reinterpreted by use of Maxwell's equal-areas construction, as shown; and the loops are then to be discarded in favor of the horizontal line segment, which represents the behavior of the system when a liquid and a vapor phase are both present. The dashed curve, known as the coexistence curve, is the locus of the end points of the horizontal line segments, and thus outlines the two-phase region of the  $p, V$  plane. Its maximum is at the critical point, where it is tangent to the critical isotherm.

Of the numerous features which characterize the van der Waals equation of state of that type, I shall call particular

attention to three: (i) The critical isotherm is a cubic curve in the neighborhood of the critical point; that is, on the critical isotherm the deviation of  $p$  from its value  $p_c$  at the critical point is proportional to the cube of the deviation of  $V$  from the critical volume  $V_c$ ,

$$p - p_c \sim -(V - V_c)^3, \quad (2)$$

for small values of  $V - V_c$ . (ii) The coexistence curve is parabolic in the neighborhood of the critical point; that is, on the coexistence curve the deviation of  $p$  from  $p_c$  is proportional to the square of the deviation of  $V$  from  $V_c$ ,

$$p - p_c \sim -(V - V_c)^2, \quad (3)$$

for small values of  $V - V_c$ . (iii) For any fixed volume  $V$ , including the critical volume  $V_c$ , the heat capacity at constant volume,  $C_v$ , suffers a simple discontinuity when the coexistence curve is crossed. More specifically, as shown in Fig. 5, it increases discontinuously from one finite value to another when the two-phase region is entered from the one-phase region through any point of the coexistence curve, even the critical point. The horizontal axis in the figure could just as well have been labeled with  $p$  as with  $T$ , and the discontinuity occurs at that value of  $T$  (or, equivalently, of  $p$ ) that corresponds, on the coexistence curve, to the given volume.

Each of these three features, com-

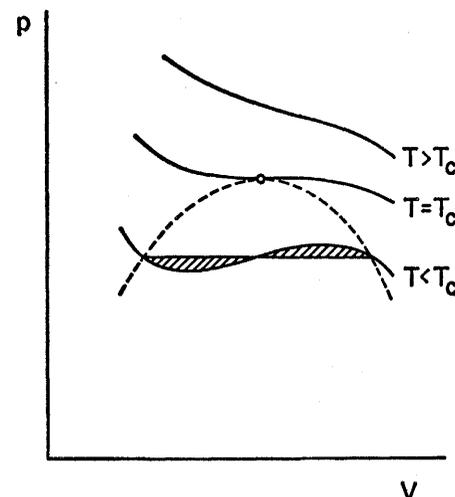


Fig. 4. Pressure-volume isotherms from the van der Waals equation of state. The horizontal line-segment on the  $T < T_c$  isotherm is drawn so as to make the shaded areas equal. The dashed curve is the coexistence curve, which is the locus of the end points of such horizontal line segments. The circle marks the critical point.

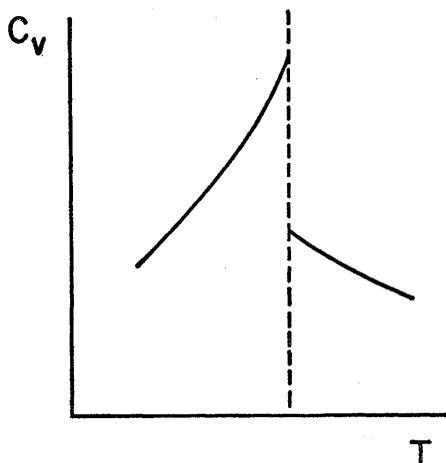


Fig. 5. Heat capacity  $C_v$  as a function of temperature, at a fixed volume, for a fluid satisfying any of the "classical" equations of state of the type of the van der Waals equation. The diagram is qualitatively the same whatever the fixed volume  $V$ , even if it is the critical volume  $V_c$ . The discontinuity occurs at the phase transition temperature that corresponds to the fixed volume in question. For the van der Waals equation itself the high-temperature branch of the curve, representing  $C_v$  in the one-phase region, would be horizontal at the constant value  $3Nk/2$ .

mon to almost all approximate equations of state, is in contradiction to the experimental facts (1). (i) In reality the degree of the critical isotherm in the neighborhood of the critical point surely exceeds 3, probably exceeds 4, and may possibly be as large as 5. Then Eq. 2 should be replaced by

$$p - p_c \sim -(V - V_c) |V - V_c|^{\delta-1} \quad (4)$$

where  $\delta$  is the algebraic degree in question, which need not be (and very likely is not) an integer, and is in any case greater than 3. (ii) Likewise, the degree of the coexistence curve in the neighborhood of the critical point is not 2, but is instead very close to 3. Then Eq. 3 should be replaced by

$$p - p_c \sim -|V - V_c|^d \quad (5)$$

where  $d$  is the algebraic degree in question, which need not be (and very likely is not) an integer, and is in any case very much closer to 3 than to 2. (iii) Finally, Fig. 5 is a correct qualitative picture of the behavior of  $C_v$  only when the fixed volume at which the temperature dependence of  $C_v$  is being depicted is far from the critical volume. In a real fluid, the closer  $V$  is to  $V_c$ , the greater are the finite values of  $C_v$  between which the discontinuous jump occurs, and these increase without limit as  $V \rightarrow V_c$ . At  $V = V_c$ , the dependence of  $C_v$  on  $T$  is like that shown

in Fig. 6. It is well established that the low-temperature branch of this curve (that is, the behavior of  $C_v$  in the two-phase region, with the system as a whole at the critical volume) is given approximately by

$$C_v = A - B \ln |T - T_c| \quad (6)$$

for  $T$  close to  $T_c$ , with  $A$  and  $B$  two constants characteristic of the substance; and that  $C_v$  on the high-temperature branch is identical, except for the replacement of  $A$  by the smaller constant  $A'$ ; so that in  $A - A'$  we have the vestigial remains of a simple discontinuity now buried beneath the logarithmic infinity. However, the data are also consistent with the possibility that the curve goes to infinity as the inverse of a small fractional power of  $T - T_c$  rather than as  $\ln(T - T_c)$ .

### Two-Dimensional Lattice-Gas Model

No equation of state of van der Waals type can account for any of these experimental facts. There is, however, a simple fluid model, known as the lattice-gas model, which has proved to be extraordinarily successful in accounting for the observed properties of a substance at its critical point. The model is a transcription, first successfully exploited by Lee and Yang (2), of the Ising model of ferromagnetism into language appropriate to a fluid. Suppose, as in Fig. 7, that the fluid volume is divided into a large number of microscopic cells each centered at one site of a lattice. The cells are not imagined to have walls which constrain the molecular motions but are rather imagined merely to provide a coordinate system in terms of which continuous distance variables may be approximated by discrete distance variables. The interaction potential between a pair of molecules at any instant is taken to depend only on the number of lattice steps separating the cells in which the molecules find themselves at that instant; but it does not depend on the precise positions of the molecules within those cells. Specifically, the potential energy of interaction of two molecules is taken to be  $+\infty$  if they are in the same cell;  $-\epsilon$  (with  $\epsilon$  a positive constant) if they are in a pair of neighboring cells, one molecule in each; and 0 if the two are neither in the same cell nor in neighboring cells but are in cells separated by two or more steps on the underlying lattice. In

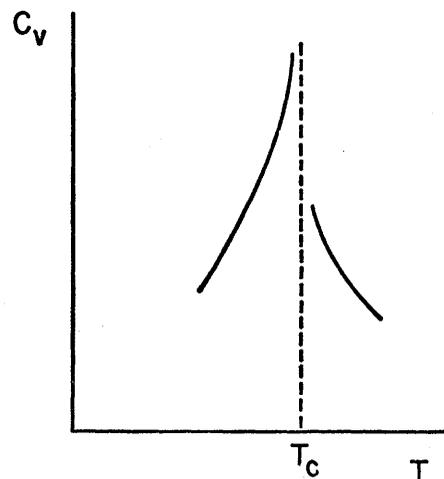


Fig. 6. Temperature dependence of  $C_v$  for a real fluid at its critical volume.

this way one imitates the strong repulsion at small  $r$ , weak attraction at intermediate  $r$ , and ultimate vanishing as  $r \rightarrow \infty$ , shown by the more realistic  $\phi(r)$  in Fig. 1. Indeed, this lattice-gas interaction appears to resemble closely the idealized  $\phi(r)$  in Fig. 3, but with " $r$ " now discrete, whereas in Fig. 3 it is an ordinary continuous distance variable. In spite of this apparent close resemblance of the lattice-gas interaction to an idealized square-well interaction in a continuum, the two differ profoundly in their account of the repulsive forces, as we shall later see.

Many of the properties of the lattice gas are known. In two dimensions, these properties follow from analytical

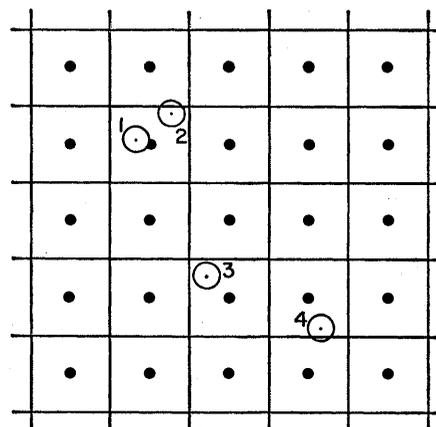


Fig. 7. The lattice-gas model, showing the fluid volume divided into cells, each centered at one site of a lattice. The lattice sites are represented by solid circles. The diagram shows four molecules represented by open circles and numbered 1, 2, 3, and 4. In this configuration the energy of interaction of the pair 1, 2 is  $+\infty$ , that of the pair 3, 4 is  $-\epsilon$ , and that of each of the four remaining pairs (1, 3; 1, 4; 2, 3; 2, 4) is 0.

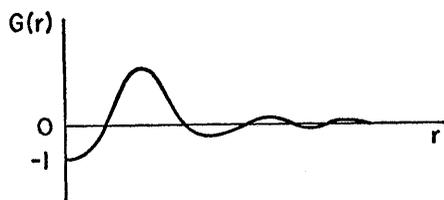


Fig. 8. A typical pair-correlation function in a liquid. It is a measure of the extent to which the average density at a distance  $r$  from the center of any molecule deviates from the mean density of the fluid.

results derived by Onsager (3) and Yang (4) for the corresponding Ising model, and from some later developments (5); while, in three dimensions, they are known largely from extensive numerical analysis by Domb, Fisher, Sykes, and their co-workers (6). The following are properties of the two-dimensional lattice gases: (i) The critical isotherm is of the 15th degree, so that  $\delta = 15$  in Eq. 4. (ii) The coexistence curve is of the 8th degree, so that  $d = 8$  in Eq. 5. (iii) When  $V = V_c$ , the heat capacity  $C_v$  has a symmetrical logarithmic infinity at  $T = T_c$ , so that Eq. 6 holds, but with  $A' = A$ ; that is, there is no finite discontinuity superimposed on the logarithmic singularity. These are, of course, not the experimentally observed properties; but remember that so far we are looking only at a two-dimensional model. Nevertheless, even these results are noteworthy, for they mean that at last a theory has been discovered which does not comply with those of van der Waals type, that is, a theory which does not inevitably give rise to a cubic critical isotherm, a parabolic coexistence curve, and a  $C_v$  which is finite, albeit discontinuous, at the critical point. Furthermore, these results apply exclusively to a two-dimensional system, so they show, for the first time, that the dimensionality of the system is important in determining the qualitative nature of

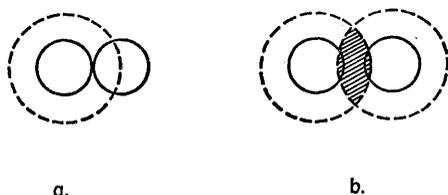


Fig. 9. (a) The solid circles represent two hard spheres in contact. The dashed circle is the exclusion sphere of the hard sphere with which it is concentric; that is, it is the sphere from which the center of the second hard sphere is excluded. (b) Two hard spheres with overlapping exclusion spheres. The region of overlap is shaded.

the critical point. This essential idea was missing from all the earlier theories, which took account, at most, only of certain trivial aspects of dimensionality.

### Three-Dimensional Lattice-Gas Models

We turn, then, to the three-dimensional lattice-gas models, with the well-founded expectation that their properties will account for the experimental observations in real fluids, and this hope is fully realized. If there are residual differences between the behavior of three-dimensional lattice gases and real continuum fluids at the critical point (and slight differences are indeed indicated), the agreement is in any event very much closer than with any of the classical theories of van der Waals type: (i) The critical isotherm of a three-dimensional lattice gas has a degree close to 5; (ii) the coexistence curve has a degree close to 3; and (iii), when  $V = V_c$ , the heat capacity  $C_v$  in the neighborhood of  $T = T_c$  is given approximately by Eq. 6, with different constants  $A$  and  $A'$  on the high- and low-temperature branches; though, as with the real experimental results, the data are also consistent with the possibility that  $C_v$  becomes infinite as the inverse of a small fractional power of  $T - T_c$ , rather than as  $\ln(T - T_c)$ .

Granting that the lattice-gas model provides an essentially correct description of a fluid in the neighborhood of its critical point, we must now inquire into the different ways in which the effects of the repulsive and attractive forces propagate through the model fluid. If  $\epsilon$ , the magnitude of the attractive interaction potential between molecules in neighboring cells, were 0, there would remain as molecular interaction only the infinite repulsion between molecules in the same cell. In this limiting case, if it is known that a particular cell is occupied then it is certain that no second molecule is in that same cell, but the probability of any other cell in the volume being occupied is simply  $N/C$ , where  $N$  is the total number of molecules, and  $C$  is the total number of cells, in the model fluid. Thus, in the lattice-gas model, when the attractive component of the intermolecular potential vanishes, the equilibrium condition of the fluid is one in which the cells are occupied entirely at random, subject only to the restriction of no multiple occupancy. The repulsive component of the intermolecular po-

tential does not by itself lead to correlations in molecular positions extending beyond a single cell. Any longer ranged correlations in the lattice gas must then be due entirely to the attractive component of the potential. The repulsive component merely establishes a scale of distance, that is, the edge-length of the cell, or the spacing of the underlying lattice, but it is the attractive component which determines through how many multiples of this unit of distance the correlation of molecular positions may propagate.

### Real Continuum Fluids

It is the propagation of such correlations through great distances which is the single most significant feature of the critical point at the molecular level. Turn now from the lattice-gas model to a real continuum fluid. Define the radial distribution function  $g(r)$  to be that function of distance  $r$  which, when multiplied by the average density  $\rho$  of the fluid, yields the average local density at a distance  $r$  from the center of an arbitrarily chosen molecule in the fluid. Thus it is the deviation of  $g(r)$  from 1 which measures the extent of the correlation between molecular positions, that is, the quantity  $G(r)$  defined by

$$G(r) = g(r) - 1$$

is the pair correlation function and describes the correlating effect of the presence of any one molecule on the position of any second molecule. A typical  $G(r)$  is shown in Fig. 8. At very small distances  $r$ , the correlation is large and negative because the strong intermolecular repulsion at short distances makes it extremely unlikely that any other molecule will be found so close to the arbitrarily chosen central molecule. At somewhat larger distance  $G(r)$  becomes positive, for at such distances from the central molecule there is a greater than average chance of finding another molecule. Such a molecule, in turn, would repel strongly molecules that are near it, so at still larger distances from the central molecule the local density becomes less than the average density; that is,  $G(r)$  again goes negative, and so forth. At each stage, however, molecular positions are determined only with some probability, not with certainty, so the information about the presence of the central molecule is gradually lost,  $G(r)$  decays to 0 at large  $r$ , and the local density becomes indistinguish-

able from the overall average density.

Now, by a fundamental theorem of Ornstein and Zernike (7), the isothermal compressibility  $\chi$  is closely connected to the integral of the pair-correlation function; in a three-dimensional fluid,

$$\rho kT\chi = 1 + 4\pi\rho \int_0^\infty G(r)r^2 dr, \quad (7)$$

where  $\rho$  is the average density measured in number of molecules per unit volume. The integral, as the average of the correlation function, determines the density fluctuations in the fluid, which in turn are related by statistical mechanical theory to the compressibility  $\chi$ . Equation 7 results from equating those two expressions for the density fluctuations. Near the critical point in the one-phase region the  $p, V$  isotherms are almost horizontal (Fig. 4), and at the critical point itself  $(\partial p/\partial V)_T = 0$ . The compressibility  $\chi$ , which is  $-V^{-1} \cdot (\partial V/\partial p)_T$ , is then very large near, and infinite at, the critical point. Therefore, the integral in Eq. 7 converges in the one-phase region, but more and more slowly as the critical point is approached, finally diverging at the critical point. The reason is that the effective range of the correlations—that is, the distance within which the correlations are still significant but beyond which  $G(r)$  decays rapidly—itself becomes infinite at the critical point. Thus, macroscopically a fluid in the neighborhood of its critical point is characterized by a very great compressibility, and this is a manifestation of what we have now seen, at the molecular level, to be a very great correlation range. This correlation length determines the average linear size of the density inhomogeneities, and hence also of the inhomogeneities in the index of refraction, that arise from spontaneous density fluctuations. Sufficiently close to the critical point, the correlation length becomes as large as the wavelength of visible light, which these inhomogeneities then scatter strongly, thus manifesting themselves in the “critical opalescence” that Debye’s recent researches have done so much to elucidate (8).

We may summarize, as follows, the position we have now reached in our argument. The repulsive forces in the lattice-gas model serve merely to establish a unit of distance but do not otherwise contribute to the propagation of correlations through the fluid. This is not a general feature of repulsive forces—quite the contrary, as we shall see—but merely an artificiality of the model;

yet the model is phenomenally successful in accounting for the properties of real fluids near their critical points. It must be, then, that it is fundamentally the propagation of those correlations that are due to the attractive component of the intermolecular interaction, and not of those due to the repulsive component, that determines the character of the critical phenomenon. This was the first half of the thesis I proposed in my introductory remarks. The second half may now be stated thus: It is fundamentally the molecular correlations that are due to the repulsive component of the intermolecular forces, and not those that are due to the attractive component, that determine the properties of a fluid at its triple point; and a model which idealizes the attractive forces in such a way as to ascribe to them no correlating effect whatever, yet treats the correlating effect of the repulsive forces with high accuracy, is just as successful in accounting for the character of the triple point as the lattice-gas model is in describing the critical point.

### Molecules as Hard Spheres

The first clue to the importance of the repulsive forces in determining the nature of liquid-solid equilibrium is provided by the lattice-gas model itself—by its utter failure to show any sign of the appearance of a solid phase. A crystalline solid would be characterized by a pair-correlation function  $G(r)$  which, unlike that in Fig. 8, was not asymptotically zero, but rather approached more and more closely a function which oscillated with undiminished amplitude, and strict periodicity, at large distances  $r$ . A solid, then, unlike a fluid, has long-range order. Even at the critical point of a fluid,  $G(r)$  is damped to zero, though the damping is then much slower and of a character qualitatively different from that in a fluid of finite compressibility. The liquid-solid equilibrium line in Fig. 2 separates sharply those states of the system, in which long-range order is absent, from those in which it is present. The lattice-gas model, however, has only one two-phase equilibrium line in its entire  $p, T$  plane, a single analytic curve emerging from the origin and ending in a critical point. At no finite  $p$ , however large, and at no positive  $T$ , however small, is there any state of the lattice gas with long-range order. Thus the lattice gas fails as a model near the

triple point as spectacularly as it succeeds near the critical point. We already know that in that model the attractive forces produce correlations that can propagate beyond the range of the forces themselves, but that the repulsive forces do not; and it is in the latter feature of the model that we must then seek the origin of the failure of the lattice gas to account for crystallization.

If  $v_0$  is the volume of one cell in the lattice-gas model, then this is the volume from which any one molecule excludes the center of any other. A pair of molecules, one in each of two different cells, excludes the center of any third molecule from a volume  $2v_0$ . In general,  $n$  molecules, whatever their relative positions, exclude an  $(n+1)$ th molecule from a total volume  $nv_0$ . Thus, the repulsive forces in the lattice gas lead to exclusion volumes which are additive. Contrast this with the exclusions of impenetrable spheres in a continuum, that is, with the exclusions that result from the repulsive portion of a potential such as that in Fig. 3, where  $r$  is a continuous distance variable. A hard sphere excludes the center of a second identical sphere from a sphere of twice its own diameter, which I shall call the exclusion sphere (Fig. 9a). While the physical spheres may not overlap, their exclusion spheres may (Fig. 9b), with the result that exclusion volumes are not additive: the volume from which two spheres exclude the center of a third may be less than simply twice the volume from which one sphere excludes the center of a second; and the deviation from additivity, that is, the extent of overlap of the exclusion spheres, depends on the molecular configuration. It is through this configuration-dependent deviation from additivity of exclusion volumes that short-range repulsive forces produce longer ranged correlations in molecular positions, so that a continuum fluid of hard spheres has a pair-correlation function  $G(r)$  not qualitatively different from that in Fig. 8, but very different indeed from the  $G(r)$  of the lattice gas without attraction.

If exclusion volumes were strictly additive, so that  $n$  molecules excluded the center of any other from a volume  $nv_0$ , with  $v_0$  a fixed constant, then in the absence of attractive forces the equation of state of an assembly of  $N$  such impenetrable molecules in a volume  $V$  would be (9)

$$p = -(kT/v_0)\ln(1 - Nv_0/V),$$

whatever the dimensionality of the system. In particular, this is also the equation of state of the lattice gas when  $\epsilon = 0$ . It is an analytic function of density for all densities up to that of complete filling,  $N/V = 1/v_0$ , and therefore shows no phase transition. When, as in a continuum fluid of hard spheres, exclusion volumes are not additive, the equation of state depends sensitively on the dimensionality of the system. In one dimension the equation of state of hard spheres  $hs$  (that is, rigid rods) without attraction is

$$p_{hs} = NkT/(V - Nb) \text{ (one-dimensional)} \quad (8)$$

where  $b$  is the sphere diameter (rod length). This, too, shows no phase transition. In two and three dimensions, the equations of state of hard spheres are not known analytically, but the computer studies of Alder and Wainwright and of Wood and Jacobson provide strong evidence that in each of these cases there is a first-order phase transition between a less dense phase without crystalline order and a more dense phase with crystalline order (10).

That the attractive forces between molecules are relatively weak and long ranged compared to the very steep repulsive forces suggests that, in a fluid as dense as a liquid is at its triple point, the attractive forces exerted on any molecule by its neighbors largely cancel, while the negative potentials largely add, so that each molecule in such a liquid may be thought of as a hard sphere in a deep but uniform (that is, without gradients) negative background potential. The depth of this background potential is proportional to the number of molecules contributing to it, and hence to the density of the fluid, so that the total potential energy  $U$  in the fluid of  $N$  molecules is

$$U = -aN \cdot N/V \quad (9)$$

where  $a$  is a positive proportionality constant. Because the background potential has no gradient, it leads to no forces on the hard spheres which are immersed in it, and the equilibrium configurations of the latter are identical to what they would be in a fluid of hard spheres at the same density but without a background potential. If  $S_{hs}$  is the configurational entropy of the latter system, then the configurational entropy  $S$  of the model fluid with the background potential is identical:

$$S = S_{hs} \quad (10)$$

Then from Eqs. 9 and 10 the equation of state of the model system is

$$p = [\partial(TS - U)/\partial V]_T = p_{hs} - a(N/V)^2 \quad (11)$$

where  $p_{hs}$  is the pressure of a hard-sphere fluid without a background potential which is at the same density and temperature as the model fluid. The effect of the uniform negative background potential on the equation of state of the hard-sphere system is therefore merely to lower the pressure by an amount proportional to the square of the density (9, 11, 12).

This is now the model which I anticipated earlier. The positional correlations in it are due entirely to the repulsive forces, idealized as those between hard spheres. The attractive forces, which are imagined to give rise merely to a uniform background potential, do not in any way influence the molecular configurations. My original thesis will then be fully established if Eq. 11 proves to account well for the properties of a liquid near its triple point.

It is essential to take  $p_{hs}$  in Eq. 11 to be the correct pressure of a three-dimensional hard-sphere system, just as it was essential in the application of the lattice-gas model to the study of the critical phenomenon to evaluate accurately the partition function of the three-dimensional model. If, only for the moment, we identify  $p_{hs}$  with what

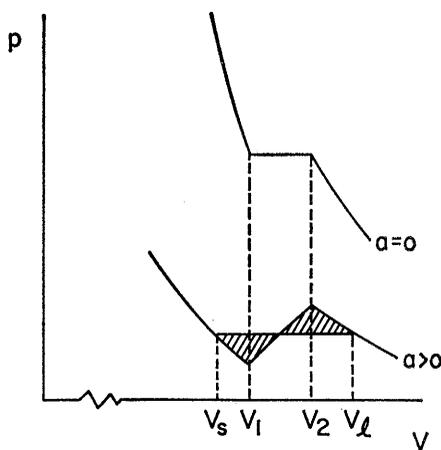


Fig. 10. A pressure-volume isotherm of a fluid of hard spheres with no background potential ( $a = 0$ ), and an isotherm at the same temperature for the same hard-sphere fluid with a background potential ( $a > 0$ ). The latter has been reinterpreted by an equal-areas construction and shows a first-order phase transition from a solid of volume  $V_s$  to a liquid of volume  $V_l$ . The phase transition in the former case ( $a = 0$ ) occurs between a state of volume  $V_1$ , with crystalline order, and a state of volume  $V_2$ , with no long-range order.

we know it to be in one dimension, Eq. 8, then the equation of state of the model, as given by Eq. 11, becomes the van der Waals equation (11, 12), Eq. 1. Thus, except for the fact that we must use the true three-dimensional  $p_{hs}$ , rather than its one-dimensional form, our model fluid is a van der Waals "gas." An interesting and curious inversion has therefore occurred. The van der Waals equation was originally introduced into physical science to represent the behavior of imperfect gases and to treat liquid-vapor equilibria, in particular the critical phenomenon. Those applications have now been discredited; but I claim that, instead, what is in essence still the van der Waals equation, though with the three-dimensional  $p_{hs}$  replacing the original one-dimensional  $p_{hs}$ , is the basis of a correct theory of dense liquids and of the liquid-solid equilibrium in the neighborhood of the triple point.

The upper curve in Fig. 10, labeled  $a = 0$ , represents schematically the three-dimensional  $p_{hs}$  as a function of volume, at a single temperature, as it might be estimated from the computer studies (10) of the hard-sphere system. Because the only forces are then infinitely strong repulsions, it follows that, at any fixed volume, the pressure is necessarily proportional to the absolute temperature, so a  $p_{hs}$  isotherm at any other temperature would differ from the one shown only by a vertical scale factor. The horizontal portion of the isotherm shows the first-order phase transition occurring between a "liquid" of volume  $V_2$  and a "solid" of volume  $V_1$ . The lower curve, labeled  $a > 0$ , represents schematically the  $p$  given by Eq. 11 at the same temperature as that for which the upper curve is drawn; so that it is constructed from the upper curve by subtracting from the latter a quantity inversely proportional to  $V^2$ . Over the range of volumes where the  $a = 0$  isotherm has its horizontal portion, the  $a > 0$  isotherm is an increasing function of  $V$  and so represents mechanically unstable states of the model system. Outside the range  $V_1 < V < V_2$ , the pressure  $p_{hs}$  on the upper curve falls sufficiently rapidly with increasing  $V$  so that the resulting  $p$  on the lower curve also decreases with increasing  $V$  outside that range. The  $a > 0$  isotherm must next be reinterpreted by an equal-areas construction, as shown in Fig. 10, with the result that the model system, at the temperature for which its  $p, V$  isotherm

Table 1. Properties at the triple-point. First column, ratio of liquid to solid volume. Second column, logarithm of  $pV_l/NkT$ , with  $V_l/N$  the volume per molecule in the liquid phase. Third column, entropy of fusion per molecule,  $\Delta S/N$ , in units of Boltzmann's constant  $k$ . Fourth column, potential energy per molecule,  $U_l/N$ , in the liquid, in units of  $kT$ .

System	$V_l/V_s$	$\ln(pV_l/NkT)$	$\Delta S/Nk$	$U_l/NkT$
Model				
liquid	1.19	-5.86	1.64	-8.6
Argon	1.144	-5.88	1.69	-8.53

is shown, undergoes a phase transition between a crystalline solid of volume  $V_s$  and a liquid of volume  $V_l$ .

We may read directly from the figure the equilibrium pressure  $p$  at the temperature of the depicted isotherm, for it is the value of  $p$  at which the horizontal line segment is drawn in the equal-areas construction. Moreover, this may be done at any  $T$ , so in this way we derive the solid-liquid equilibrium line in the  $p, T$  plane, like that in Fig. 2. Furthermore, applying known thermodynamic formulas to the low-density branch of any isotherm, we may also calculate the common value of the activity  $z$  of the liquid and the solid when they are in equilibrium at that temperature. Let  $z$  be normalized in such a way as to be asymptotic, say, to the number density  $\rho = N/V$  in the ideal gas limit which is approached at low density. Suppose that at every temperature  $T$  the solid-liquid equilibrium pressure  $p$  and activity  $z$  have been derived in the manner I have just outlined, and that  $p/kT$  and  $z$  are then compared. In general these two quantities will differ, but at one temperature they will be equal and that is the triple-point temperature of the model fluid, which I show as follows: At the triple-point of any liquid to which this theory might reasonably be applied, the vapor which is in equilibrium with the condensed phases is so dilute as to be effectively an ideal gas; therefore, by the stated normalization of the activity  $z$ , the equality  $p/kT = z$  must hold in this vapor; but, at the triple point,  $p$  has

Table 2. Dimensionless forms of the coefficient of thermal expansion  $\alpha$ , the isothermal compressibility  $\chi$ , and the heat capacity at constant volume  $C_v$  in the liquid phase at the triple-point.

System	$T\alpha$	$NkT\chi/V$	$C_v/Nk$
Model			
liquid	0.50	0.058	1.50
Argon	.366	.0495	2.33

the same value in all three phases, as do  $T$  and  $z$ , so that at the triple-point the equality  $p/kT = z$  must hold also in the condensed phases. Indeed, the condition that this equality hold with the  $p$  and  $z$ , which are the liquid-solid equilibrium  $p$  and  $z$  for the given  $T$ , then uniquely identifies the triple-point.

All the thermodynamic properties of the model have now been derived or are readily accessible; but, so far, they still depend on two parameters, namely, the constant  $a$  in Eq. 11 and the sphere diameter  $b$  which is implicit in  $p_{hs}$ . However, if we content ourselves with calculating only dimensionless quantities, and these evaluated only at the triple-point, then the results are invariant characteristics of the model, independent of  $a$  and  $b$ . In Table 1, I quote what amount to the free energy and its first derivatives, in dimensionless form and evaluated at the triple-point. In the first row are the consequences of this model (12, 13) and in the second row are the experimental results for argon (14). Because only dimensionless quantities appear, the experimental results apply not only to argon but also to any substance which obeys with argon a law of corresponding states; thus, these experimental results are, with considerable accuracy, the same also for krypton and xenon, and with slightly less accuracy are the same for a very much wider class of substances.

In the first column of Table 1 is the ratio of liquid to solid volume at the triple-point,  $V_l/V_s$ . In comparing the theoretical and experimental results for  $V_l/V_s$ , we must recognize that the 1 preceding the decimal point is a significant figure. The theory is absolute and without parameters, containing no data beside the single curve giving  $p_{hs} \times b^3/kT$  as a function of  $V/Nb^3$ , which is provided by the computer calculations of the equation of state of a three-dimensional hard-sphere system. That  $V_l$  and  $V_s$  are nearly equal, so that 1 precedes the decimal point in  $V_l/V_s$ , is therefore a significant (if hardly surprising) result of the theory. In the second column is the logarithm of  $pV_l/NkT$  at the triple-point, with  $V_l/N$  the volume per molecule in the liquid phase. In the third column is the entropy of fusion per molecule,  $\Delta S/N$ , in units of Boltzmann's constant  $k$ , evaluated at the triple-point, while in the fourth column is the potential energy  $U_l$  of the liquid (the negative of the energy of vaporization) in units of

$NkT$ , again at the triple-point. The agreement between theory and experiment in Table 1 is sufficiently close so that we may conclude that the model of hard spheres in a uniform background potential provides an essentially correct description of a liquid at its triple-point.

The second and higher derivatives of the free energy, however, are finer probes than are the quantities in Table 1, and they show the extent to which the model is an oversimplification. Because, in the model, the background potential is independent of the temperature, while the interactions of the hard spheres with each other contribute no potential energy to the system, the model has no configurational specific heat, and  $C_v$  is just  $3Nk/2$ , arising only from the kinetic energy of the spheres. But in a real liquid there is a configurational  $C_v$ , of magnitude about half that contributed by the momenta. The other second derivatives of the free energy, namely the coefficient of thermal expansion  $\alpha$  and the isothermal compressibility  $\chi$ , also reflect the artificialities of the model, though to a somewhat lesser extent. I quote in Table 2 dimensionless forms of these three quantities, all evaluated in the liquid phase at the triple-point, both for the model liquid and for argon.

That in a liquid near its triple-point the correlations due to the short-ranged repulsive forces are more significant than those due to the longer-ranged attractive forces, and that in a fluid near its critical point precisely the opposite is true, may be viewed as inevitable consequences of the fact that at the triple-point the density of a liquid is close to that of the corresponding solid, while typically the critical density is only one-third that. Nevertheless, the extreme sharpness with which the distinction appears is most striking and unexpected. I believe it fair to conclude, in any event, that both halves of the thesis are now established, and that we can claim to know, if only in broad outline, the ways in which intermolecular forces manifest themselves in the macroscopic properties of simple liquids.

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## Prostaglandins: Members of a New Hormonal System

These physiologically very potent compounds of ubiquitous occurrence are formed from essential fatty acids.

Sune Bergström

In 1930 two New York gynecologists, Kurzrok and Lieb (1), reported that the human uterus could react with either strong contractions or relaxation on instillation of fresh human semen. We now know that these effects were due to the prostaglandins present in the seminal plasma, but not until a few years later was it clearly recognized that the effect was due to the presence of these then-unknown compounds.

Goldblatt (2) in England and von Euler (3) in Sweden independently discovered and studied the strong activity in seminal plasma that stimulates smooth muscle. The seminal plasma of several species was investigated by von Euler, who found similar effects in the seminal fluid of only monkey, sheep, and goat and in extracts of vesicular glands of male sheep. He prepared lipid extracts of these glands and found the activity to be associated with the fraction containing the lipid-soluble acids. He named the active factor prostaglandin and made extensive studies of the physiologic and pharmacologic effects of these extracts (3).

### Isolation and Structure

At the suggestion of von Euler in 1947, I started work on the purification of a concentrate prepared (4) from glands of Icelandic sheep. With the

small amount of material available, using primarily the Craig countercurrent procedure, I showed that the activity was associated with a fraction containing unsaturated hydroxy acids. Our present knowledge shows that the best concentrates consisted predominantly of a mixture of prostaglandins (5). However, for technical and personal reasons, the project was laid aside until 1956 when a program for the collection of frozen glands of sheep was organized in several countries in the Northern Hemisphere.

The bioassay used for the isolation work utilized the smooth muscle-stimulating activity of the prostaglandins on rabbit duodenum—a sensitive but rather unspecific test. With this method of assay, an improved isolation procedure (6) led to the isolation of two prostaglandins, PGE<sub>1</sub> and PGF<sub>1α</sub>, in pure crystalline form (7). They both showed high physiologic activity (higher than 10<sup>-9</sup> gram per milliliter) on smooth muscle, but the former was the more active in reducing blood pressure in the rabbit (8).

Analysis of the first few milligrams by ultramicroanalysis and mass spectrometry proved that these substances were C<sub>20</sub> compounds possessing a unique structure (Table 1). An early observation that proved very important was that PGE<sub>1</sub> was of ketonic nature and that reduction with borohydride yielded two isomeric trihydroxy com-

pounds, one of which was identical with the isolated natural PGF<sub>1α</sub> (7, 9).

Prostaglandin PGE<sub>1</sub> was very sensitive to alkali, which rapidly destroyed the biologic activity, with formation of a compound absorbing at 278 nanometers. With more dilute alkali, an intermediate was first formed that absorbed at 217 nanometers. The structure finally elucidated by oxidative ozonolysis of PGE<sub>1</sub>, dihydro-PGE<sub>1</sub>, and the above-mentioned compounds absorbing at 217 and 278 nanometers. The reaction products were resolved by gas-liquid chromatography and identified directly by mass spectrometry (10).

These studies showed the PGE<sub>1</sub> molecule to contain a five-membered ring, with one of the hydroxyls β to the keto group, which fact explains the lability to alkali. The second hydroxyl and the *trans* double bond were located in a side chain (Fig. 1). Treatment of PGE<sub>1</sub> with weak base yields the α, β-unsaturated ketone absorbing at 217 nanometers, PGA<sub>1</sub>, (PGE<sub>1</sub>-217), that then rearranges to the doubly conjugated ketone PGB<sub>1</sub> (PGE<sub>1</sub>-278).

The stereochemistry was then elucidated by complete x-ray analysis of the bromo- and iodobenzoates of PGF<sub>1β</sub> (11). The correct absolute stereochemical configuration has been obtained by redetermination of the optical activity of the 2-hydroxy-heptanoate formed by oxidative ozonolysis (Fig. 2) (12).

Two more compounds, PGE<sub>2</sub> and PGE<sub>3</sub>, were subsequently isolated from the sheep glands. Mass spectrometry and nuclear magnetic resonance yielded most of the complete structure (13). They were identical with PGE<sub>1</sub> except that they contained, respectively, one and two additional *cis* double bonds (Fig. 2). The corresponding PGF<sub>2α</sub> and PGF<sub>3α</sub> were first isolated from sheep and bovine lung tissues, respectively (14). As to the structures of the six "primary" prostaglandins, the numbering system of the basic "prostanic acid" is indicated (Fig. 2) and a general system of nomenclature is explained (Fig. 2, legend).

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