as effective as UDP-MurNAc-L-Ala-D-Glu-L-Lys-D-Ala-D-Ala in the exchange reaction (reaction 6). Clearly a systematic modification of the pentapeptide moiety will be necessary in order to define additional features of this molecule that are necessary for activity.

Conclusion

Our knowledge of membrane function and structure is in its infancy. There is a need for basic enzymology of those enzymes that are intimately involved with the function of the membrane. A mechanistic analysis of the translocase would be greatly facilitated if the enzyme could be purified in soluble form. Although solubilization has been achieved with several diverse agents,[50] these preparations have not been successfully fractionated. With information from mechanism studies, we can begin to ask what is the relationship of this enzyme to the structure of the membrane? Does the ordered structure of the membrane have a profound effect on the activity of the enzyme? Alternately, we will ask whether this enzyme catalyzes the translocation process as part of a membrane subunit. Is the enzyme located at the point of new cross-wall formation or is it uniformly distributed throughout the plasma membrane? Is this enzyme one of the key control points? The many questions that are posed indicate that only the surface of this fascinating problem has been probed.

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It is a pleasure to acknowledge the collaboration of William G. Struve, Menard G. Heydanek, Jr., Dorothy D. Pless, Rosemary Linzer, Robert A. Stickgold, and Rabindra K. Sinha. Our work has been supported by a grant (AI-04615) from the National Institute of Allergy and Infectious Diseases and by a training grant from the Public Health Service (5T1-GM-626). The author thanks Dr. Jack L. Strominger for permission to reproduce Figure 9 and Dr. Otto W. Neuhaus for comments on the manuscript.

Some Aspects of the Theory of Liquids

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There has been much progress during the past few years in understanding the properties of liquids, but much of this work is so recent that the theory of liquids is still widely regarded as an unsolved problem.

It is interesting to note that the ideas which form the basis for the modern successful theory of liquids have been well known for almost a century. The work of van der Waals[1] in 1873 implied that the structure of a liquid is primarily determined by the repulsive forces between its molecules, so that a liquid may be regarded as a system of hard spheres with the attractive forces providing a uniform background energy. A century ago the properties of a system of hard spheres were not known. Thus van der Waals made drastic approximations to obtain the hard-sphere equation of state. It is these approximations, rather than weaknesses in his physical ideas, which are responsible for the inadequacies of his equation of state.[2]

Recently, these ideas have been revived. Zwanzig[3] and others[4,5] have shown that the effect of the attractive portion of the intermolecular potential, $u(R)$, can be obtained by means of a perturbation expansion in the strength of the attractive potential using a system of hard spheres as the unperturbed or reference system. Rowlinson[6] has shown that the effect of the repulsive portion of $u(R)$ can be obtained by means of a perturbation expansion in the inverse steepness of the repulsive potential, again using hard spheres as the reference system. Neither the Zwanzig nor the Rowlinson expansion was adequate for the liquid state. McQuarrie and Katz[7] combined these two expansions. However, their scheme had the effect of making the perturbations large and, as a result, the series did not converge at liquid temperatures and densities. An alternative scheme which is fully satisfactory has been developed by Barker and Henderson and will be treated in detail below.

We shall consider only the equilibrium properties of simple liquids in which quantum effects may be ignored and in which the potential energy results from additive contributions of intermolecular potentials which are functions only of the intermolecular separations. The physical ideas used in the theory of liquids may thus be seen without excessive complexity. Such liquids are idealizations and do not exist in nature. As a result, the thermodynamic properties and the radial distribution function (RDF), $g(R)$, which is the probability of finding a pair molecules separated by a distance R, must be obtained by computer simulation studies which are discussed in the next section.

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(3) R. W. Zwanzig, *J. Chem. Phys.*, **22**, 1420 (1954).
(4) E. B. Smith and B. J. Alder, *ibid.*, **30**, 1190 (1959).
(5) H. L. Frisch, J. L. Katz, E. Praestgaard, and J. L. Lebowitz, *J. Phys. Chem.*, **70**, 2016 (1966).
(6) J. S. Rowlinson, *Mol. Phys.*, **7**, 349 (1964); **8**, 107 (1964).
(7) D. A. McQuarrie and J. L. Katz, *J. Chem. Phys.*, **44**, 2393 (1966).

For simplicity we shall restrict our attention to the Lennard-Jones 12–6 potential (eq 1). We refer to the

$$u(R) = 4\epsilon[(\sigma/R)^{12} - (\sigma/R)^6] \qquad (1)$$

fluid with this pair potential as "the 12–6 fluid." For this fluid it is convenient to use the reduced density, $\rho^* = N\sigma^3/V$, and the reduced temperature, $T^* = kT/\epsilon$.

Computer-Simulation Methods

Recent developments in computer-simulation methods have permitted explicit demonstration of the fact that statistical mechanics contains a complete description of the equilibrium properties of classical solids, liquids, and gases and of the phase equilibria between them. There are two important simulation methods, the Monte Carlo method, due originally to Metropolis, *et al.*,[8] and the method of molecular dynamics, due to Alder and Wainwright.[9] Since there have been excellent recent reviews[10–13] we shall give only a brief account of these methods.

In both of these methods a direct attack is made on the evaluation of many-body averages. A fixed number of molecules (typically from several tens to several hundreds) in a cubic box is studied by the computer. To minimize surface effects a "periodic boundary condition" is used, so that the whole of space is imagined to be filled by periodic reproductions of the basic cell.

In the Monte Carlo method the molecules are moved one at a time according to certain rules which ensure that, in the chain of configurations so generated, individual configurations appear with probability proportional to $e^{-U/kT}$, where U is the potential energy. Thus by averaging over the configurations of long chains one can evaluate averages in the Gibbs canonical ensemble. The thermodynamic energy can be calculated by averaging U, and the pressure, p, can be calculated by averaging the "virial of intermolecular forces" according to eq 2, in which the vector $\mathbf{r}_i$ specifies the position

$$pV = NkT - {}^1/_3\langle\sum_{i=1}^{N}\mathbf{r}_i\cdot(\partial U/\partial\mathbf{r}_i)\rangle \qquad (2)$$

of the ith atom and the angular brackets indicate averaging in the canonical ensemble. Of course the statistical accuracy depends on the length of the chain of configurations, and the accuracy with which an effectively infinite system is modelled depends on the number of molecules, but it turns out that satisfactory accuracy can be attained with reasonable amounts of computer time.

In the method of molecular dynamics the successive configurations of the system are found by solving by finite difference methods the Newtonian equations of motion, with appropriate random initial velocities being assigned. The quantities of interest are determined by time averaging, the temperature being determined from the average kinetic energy.

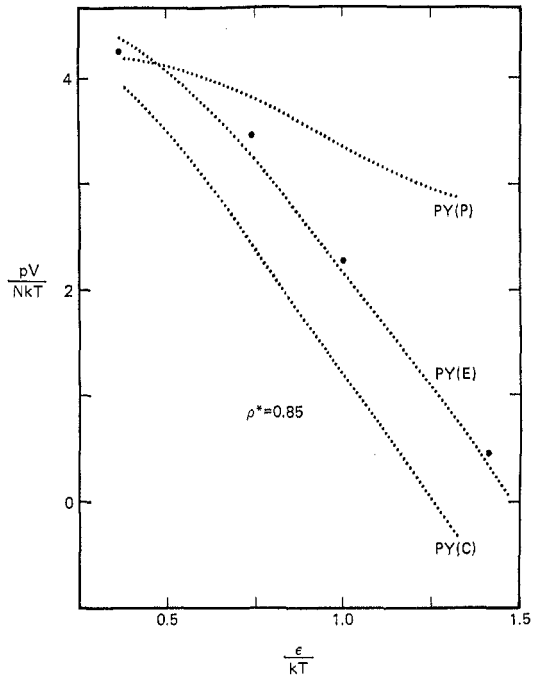

Figure 1. Equation of state of the 6:12 fluid. The three curves marked C, P, and E give the PY results using the compressibility, pressure, and energy equations, respectively. The points give the results of simulation studies.

Calculations made by both methods using the 12–6 potential with parameters determined from gas properties lead to excellent qualitative and good quantitative agreement with the properties of solid, liquid, and gaseous argon. In its quantitative aspect this is somewhat fortuitous, since the approximation of pair-additive 12–6 interactions is not a good one for argon. However, calculations with more realistic pair and triplet potentials by these methods lead to excellent agreement with experiment. Some simulation results for the 12–6 fluid[14–17] are displayed in Figures 1–4.

It is conventional to describe simulation calculations as "computer experiments," but it should be realized that they are valid "experiments" only because the laws of statistical mechanics (for the Monte Carlo method) and kinetic theory (for molecular dynamics) are correctly formulated. In fact, the agreement of such calculations with experiment provides an experimental test of statistical mechanics and kinetic theory.

Percus–Yevick Theory

One theory which has been widely applied to liquids

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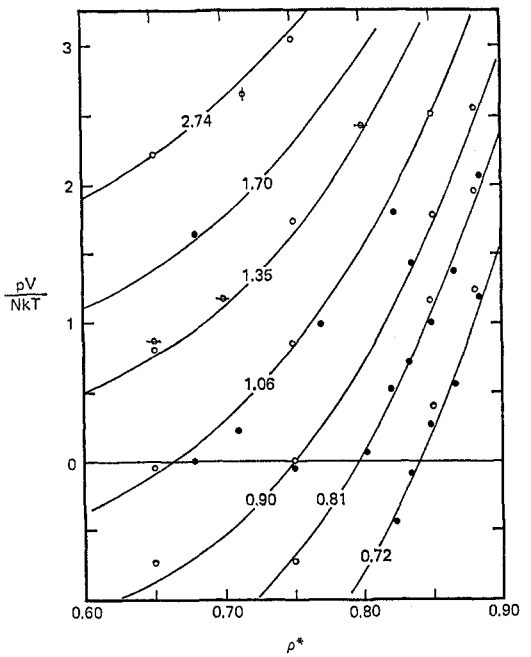

Figure 2. Equation of state of 12–6 fluid. The solid curves are isotherms given by the BH theory and the points give the results of simulation studies.

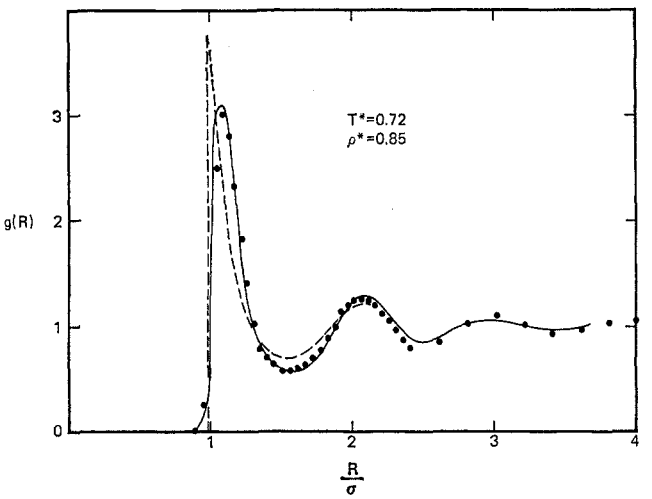

Figure 3. RDF of the 12–6 fluid. The curves give the results of the BH theory and the points give the results of simulation studies.

is that of Percus and Yevick[18] (PY). In this theory an integral equation for $g(R)$ is developed. Once this integral equation has been solved, the thermodynamic properties can be obtained by first calculating the compressibility, the pressure, or the energy and then calculating the other thermodynamic properties. We refer to these methods as the *compressibility*, the *pressure*, and the *energy* methods. Each of these methods yields the same result if an exact $g(R)$ is used. However, the PY $g(R)$ is not exact and as a result the three methods yield different results. That is, the PY theory is not thermodynamically consistent.

As is well known,[19,20] the PY equation has an exact

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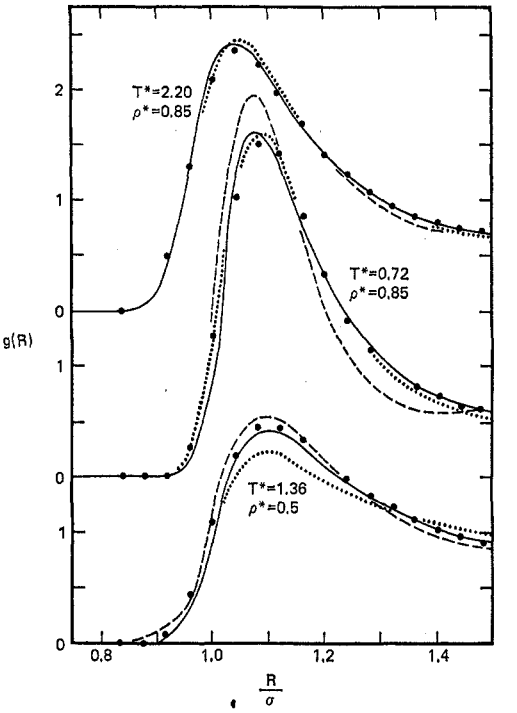

Figure 4. RDF of the 12–6 fluid. The curves marked - - -, ——, · · ·, give the results of the PY theory, the BH theory, and the WCA theory, respectively. The points give the results of simulation studies.

solution for the hard-sphere potential. Comparison with simulation studies shows the PY $g(R)$ and the resulting thermodynamic properties to be quite good.

For other potentials the PY equation must be solved numerically. The results for the 12–6 liquid have only recently been obtained. Some representative results are shown in Figures 1 and 4. The pressure and compressibility results[21,22] are rather poor. However, the energy equation results[23] are in good agreement with the simulation results. The agreement, however, is not as good as that obtained from the Barker–Henderson perturbation theory which we now consider.

Perturbation Theory of Barker and Henderson

In this theory we assume that certain properties of the hard-sphere fluid are known, and we use these properties with a perturbational technique to derive properties of a real fluid with attractive forces and steep but not infinitely steep repulsive potential.

For a fluid with intermolecular potential $u(R)$ we define[24] a modified potential $v(R)$ by eq 3, where $d' =$

$$\exp[-\beta v(R)] = \{1 - H(d' - \mu)\} \exp[-\beta u(d')] + H(d' - \mu) + H(R - \mu)\{\exp[-\gamma\beta u(R)] - 1\} \quad (3)$$

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(20) E. Thiele, *J. Chem. Phys.*, **39**, 474 (1963).
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(24) J. A. Barker and D. Henderson, *J. Chem. Phys.*, **47**, 2856, 4714 (1967).

$d + (R - d)/\alpha$ and $H(x)$ is the Heaviside step function, equal to zero for $x < 0$ and 1 for $x > 0$; d is the hard-sphere diameter, so far unspecified; μ is usually taken to be equal to σ; and α and γ are "inverse steepness" and "depth" parameters, respectively. For α and γ equal to 0, $v(R)$ becomes equal to the hard-sphere potential, and with $\alpha = \gamma = 1$, $v(R)$ becomes equal to $u(R)$. Our procedure is to make a double Taylor series expansion of the Helmholtz free energy, A, in α and γ about the point $\alpha = \gamma = 0$. The result, if terms of order $\alpha\gamma$, α^2, γ^3, and all higher order terms are neglected, can be written in the form

$$\frac{A}{NkT} = -\left(\frac{1}{N}\right) \ln \left\{\frac{\lambda^{-3N}}{N!}\int \cdots \int \exp\left[-\beta\sum_{i<d} u(R_{ij})\right] d\mathbf{r}_1 \ldots d\mathbf{r}_N\right\} = \frac{A_0}{NkT} - \alpha 2\pi\rho d^2 g_0(d) \times \left(d - \int_0^\sigma \{1 - \exp[-\beta u(z)]\}\, dz\right) + \frac{\gamma}{NkT}\langle U_1\rangle_0 - \frac{1}{2}\frac{\gamma^2}{N(kT)^2}[\langle (U_1)^2\rangle_0 - (\langle U_1\rangle_0)^2] \quad (4)$$

in which

$$U_1 = \sum_{i<j} w(R_{ij})$$

where $w(R_{ij})$ is equal to $u(R_{ij})$ for $R_{ij} > \sigma$ and to zero for $R_{ij} < \sigma$; thus U_1 is the total attractive part of the interaction. The brackets $\langle\ \rangle_0$ mean "average over the configurations of hard-sphere system of diameter d," and A_0 is the free energy of the hard-sphere system. Detailed derivation of this result is given elsewhere.[24]

The best choice for μ is the one for which A is insensitive to variations in μ. At liquid densities, the choice $\mu = \sigma$ has this property. At very high densities, such a choice gives $\mu < \sigma$. This has the effect of making d density dependent at high densities.[25]

We choose d so that the second term in the second form of (4) is zero, and setting $\alpha = \gamma = 1$ to give the approximate A for the real system, we find

$$\frac{A}{NkT} = \frac{A_0}{NkT} + \frac{\langle U_1\rangle_0}{NkT} - \frac{1}{2N(kT)^2}[\langle (U_1)^2\rangle_0 - (\langle U_1\rangle_0)^2] \quad (5)$$

Thus the softness of the repulsive potential has been dealt with by our choice of d, and the second and third terms in (5) describe the effects of the attractive potential. To discuss these terms further we subdivide the range of intermolecular distances $R > d$ into intervals R_1 to R_2, R_2 to R_3, etc., sufficiently narrow so that the potential may be regarded as effectively constant within each range, and we denote by u_i the value of the potential in the ith interval and by N_i the number of intermolecular distances lying in that interval. In our numerical work we use the subdivision $R_{i+1} = d(1 + 0.07i)^{1/2}$. Then (5) may be rewritten

$$\frac{A}{NkT} = \frac{A_0}{NkT} + \frac{\sum_i \langle N_i\rangle_0 u_i}{NkT} - \frac{1}{2N(kT)^2}\sum_{i,j}(\langle N_i N_j\rangle_0 - \langle N_i\rangle_0\langle N_j\rangle_0)u_i u_j \quad (6)$$

In earlier work[24] we used approximate values for the averages of N_i derived from the PY equation, and we proposed semimacroscopic approximations for the covariances of N_i and N_j and found reasonable agreement with experimental and simulation results.

More recently we have performed extensive Monte Carlo calculations of these averages and covariances for a wide range of hard-sphere densities. An account of the methods used has been given previously,[25] and preliminary results of these calculations have been used elsewhere,[26,27] but these were slightly in error at the highest densities because of inadequate equilibration. In the present calculations we took special care on this point, generating up to 2,000,000 preliminary configurations to ensure that no effect of the initial configuration remained.

Once A has been determined using (6), other thermodynamic quantities such as energy and pressure may be calculated by differentiation with respect to temperature and pressure. In Figure 2 we compare values of pV/NkT calculated in this way (called BH) with those derived from simulation calculations.[14-17] It will be seen that the agreement is excellent. The calculated free energies also agree almost exactly with those derived from simulation studies; we compare pressures rather than free energies because this is a more sensitive test of the BH perturbation theory. It appears that the neglected higher order terms are very small indeed.

It is also of interest to use the BH theory to calculate $g(R)$. By an argument similar to that leading to (6) it can be shown that, to first order in the depth parameter γ, the average value of N_i in the actual system with attractive forces is given by eq 7. From this one can

$$\langle N_i\rangle = \langle N_i\rangle_0 - \beta\sum_j u_j(\langle N_i N_j\rangle_0 - \langle N_i\rangle_0\langle N_j\rangle_0) \quad (7)$$

calculate $g(R)$ by relation 8, in which R_i' is a mean

$$g(R_i') = 3\langle N_i\rangle/[2\pi N\rho(R_{i+1}^3 - R_i^3)] \quad (8)$$

value of R in the interval R_i to R_{i+1}, for which we chose the arithmetic mean of R_i and R_{i+1}. In Figure 3 we show the results of such a calculation for a temperature and density corresponding roughly to the triple point. To take into account the softness of the repulsive potential we assumed that, for $R < R_2$, $g(R)$ has the form $Ae^{-\beta u(R)}$, with the normalization constant A chosen so that the appropriate integral of $g(R)$ up to R_2 reproduced the correct value of $\langle N_1\rangle$. This is consistent with the philosophy of our approach which is based on the fact that $e^{-\beta u(R)}$ is varying very rapidly near $R = d$.

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(27) D. Henderson and J. A. Barker in ref 13, Vol. 8, Chapter 6.

The dashed line in Figure 3 is the zero-order distribution function determined by hard-sphere packing, and the solid line is the first-order result. It is basically the attractive potential which produces the rounding of the peak; the effect of the softness of the repulsive potential is apparent only for $R < 1.03\sigma$, where $g(R)$ has fallen to about 1.5.

A more detailed comparison for the region of the first peak is shown for three thermodynamic states in Figure 4. In this case the solid line is our first-order result while the dashed line represents results calculated from the PY equation. It is clear that at low temperatures the BH theory gives a considerably more accurate radial distribution function than does the PY theory.

Thus it appears that part of the success (relative to the PY theory) of our perturbation theory is due to the fact that our procedure for calculating thermodynamic properties is more similar to the energy method than to the pressure or compressibility methods but that part is also due to the fact that the perturbation theory gives a more accurate $g(R)$.

Other Perturbation Theories

Recently, two theories similar to the BH perturbation theory have been developed. The first is that of Mansoori and Canfield[28] and Rasaiah and Stell,[29] who show that the perturbation series of Zwanzig,[3] when truncated after first order, is an upper bound on A. They choose d to minimize this upper bound. This approach gives fairly good results at low temperatures, but the results become worse as the temperature is increased because the finite steepness of the repulsive portion of the potential has not been adequately treated.

Very recently, Weeks, Chandler, and Andersen[30] (WCA) have proposed an interesting perturbation theory which uses a reference fluid whose potential is given by eq 9, where R_m is the value of R for which

$$u_0(R) = \begin{cases} u(R) + \epsilon & (R < R_m) \\ 0 & (R > R_m) \end{cases} \quad (9)$$

$u(R)$ is a minimum. For the 12–6 potential $R_m = 2^{1/6}\sigma$.

The difficulty with the WCA theory is that the properties of their reference fluid are not well known. To overcome this, they introduce a number of untested approximations. As may be seen from Figure 4, they obtain very good results at high densities. In order to examine their theory, we have made some Monte Carlo studies of their reference fluid and have found that the RDF which they propose as an approximation to that of the reference fluid is actually a better approximation to that of the 12–6 fluid than to that of the reference fluid. This results from the use of the PY hard sphere RDF. If accurate values for this function are used their RDF approximates well that of the reference fluid but less closely that of the 12–6 fluid. Their approach is promising.

Summary

In this review we have briefly considered three treatments of the equilibrium properties of the liquid state: computer-simulation methods, the PY theory, and perturbation theory. The computer-simulation methods are exact treatments and provide valuable quasiexperimental data for model systems. However, they have the disadvantage of requiring large amounts of computing time and they often provide little intuitive insight. The PY theory requires moderate amounts of computing time and, if used with the energy equation, gives satisfactory results for the thermodynamic properties. However, it yields even less insight than do the simulation studies. On the other hand, the BH perturbation theory requires very little computing time, gives excellent results, and provides considerable insight into the factors determining the structure of liquids.

This work has been supported in part by a grant from the Department of the Interior, Office of Saline Waters.

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Persistence of Atomic Orbitals in Complexes and Other Compounds

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Orbitals are, strictly speaking, the wave functions of stationary states of systems containing one electron. From the point of view of quantum mechanics it is by no means obvious that atoms or monatomic ions containing more than one electron can be described in terms of *electron configurations* in which each electron is assigned to an orbital, with no more than two electrons in any orbital. Yet the "buildup" or Aufbau of the periodic table is based on this very picture. It is perhaps even more surprising that the ground state and the low-lying excited levels of molecules and polyatomic ions can be classified spectroscopically in terms of one-electron con-