

Chapter 4

Hydrophobic Interaction among Many Solute Particles

4.1. INTRODUCTION

In the previous chapter we were concerned with the HI between two solute particles. This has been considered to be the first and most important step towards the full characterization and understanding of the phenomenon of HI. It should be remembered, however, that the problem of *pairwise* HI has been isolated as a single factor that contributes to the total “driving force” of very complex biochemical processes.

At present we are still far from having a full, or even a satisfactory, knowledge of the pairwise HI phenomenon. Much is left to be done on both the experimental and the theoretical fronts before we may claim that this goal has been reached. Nevertheless, this fact alone should not hinder our efforts to study more complex processes involving HI. The next step that we have in mind is the study of the HI among many simple solute particles in a solvent. This step serves as a bridge leading from the simplest pairwise HI to the enormously more complex biochemical processes.

This chapter is devoted to surveying the various experimental sources from which we can obtain information on HI among many solute particles. As in the case of pairwise HI we shall find that information on this subject is rather fragmentary and much more should be done before any reasonably clear view of this field emerges.

We shall also devote some space to discussing processes such as micelle formation and conformational changes in biopolymers. All of these certainly involve, in one way or another, the concept of HI. However, care must be exercised to make a distinction between two classes of processes. On one hand we have those processes from which we can *extract* information on HI, and hence contribute to our store of knowledge in this field. On the other hand we have the more complex processes in which many factors besides HI combine to determine their driving force. Here we *use* our knowledge on HI in an attempt to understand the mechanism and the relative importance of the various factors that govern the overall process.

For example, there exists a vast amount of experimental data on the properties of micelles in aqueous solutions. It is clear that HI plays an important role in their formation. It is also clear that there are other factors involved, such as charge-charge interaction and the solvation of polar groups in water. What is not clear is how to extract information on HI from any given piece of information on these systems. This point will be further elaborated upon in Section 4.8.

In our introductory discussion of the pairwise HI, we have pointed out that the solute-solute interaction may be considerably modified when we proceed from the vacuum (or the direct) interaction to the HI. For example we mentioned the temperature and pressure dependence of the HI that may be quite outstanding even when we assume that the direct interaction is temperature and pressure independent. We also noted that these peculiar features of the HI stem from the fact that the HI is an average quantity, the averaging process being carried out over all the possible configurations of the solvent molecules (see also Chapter 5 for further treatment of this subject).

In proceeding to the study of the HI among many particles, there is a new feature that should be recognized from the very outset. This is the non-additivity effect, sometimes also referred to as the cooperative effect of the HI, and its possible dependence on the configuration of the interacting solutes (or nonpolar groups).

It is true, though, that at present we know almost nothing about the extent of the nonadditivity effect of the HI. Nevertheless, it is appropriate at this stage to introduce a precise definition of this concept, hopefully paving the way for future investigation in this field.

Consider for simplicity the case of three simple solute particles at some close configuration, as indicated in Figure 4.1. Let \mathbf{R}_i be the position vector of the center of the i th solute particle, and $R_{ij} = |\mathbf{R}_j - \mathbf{R}_i|$ be the scalar distance between the i th and the j th particles. If these three

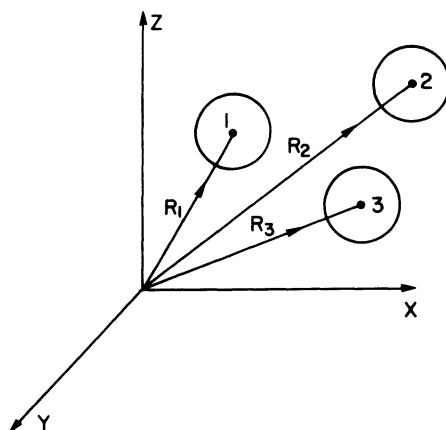


Figure 4.1. Three solutes at a configuration $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3$.

particles are in vacuum then $U(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3)$ will designate the work required to bring these particles from fixed positions at infinite separation from each other (i.e., $R_{ij} = \infty$ for $i, j = 1, 2, 3$) to the final configuration $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3$. This work will be referred to as the *direct* interaction among the three solutes particles for the configuration $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3$.

For simple solutes, such as argon or methane molecules, $U(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3)$ is approximately pairwise additive in the sense that it can be written as a sum of the interactions between each of the pairs i, j , namely,

$$U(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) = U(\mathbf{R}_1, \mathbf{R}_2) + U(\mathbf{R}_2, \mathbf{R}_3) + U(\mathbf{R}_1, \mathbf{R}_3) \quad (4.1)$$

For hard-sphere (HS) particles the last property may be considered as part of our definition of the HS. For real molecules we shall assume that this is a good approximation (in fact most of the progress in the theory of simple liquids has been based on the assumption of pairwise additivity of the total potential energy (Hill, 1956; Hansen and McDonald, 1976). There are known cases where large nonadditivity effects do exist—an example might be water molecules. However, in all the forthcoming discussions we shall assume that relation (4.1) strictly holds for all the configurations $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3$. The reason for doing so is twofold: In the first place we shall be interested in simple solutes for which (4.1) is indeed a good approximation. More important, however, is our desire to stress a new feature of the HI that may appear independently of the assumption of pairwise additivity of the direct interaction.

Next we consider the same process as described above, but now the interparticle space is filled by a solvent. The process is carried out while maintaining a constant temperature and pressure in the system. The total

work associated with this process is given by the change of the Gibbs free energy, namely,

$$\Delta G(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) = G_3(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) - G_3(\infty) \quad (4.2)$$

where $G_3(\infty)$ stands for the free energy of the system with the three solutes being at fixed positions at infinite separation from each other. Similarly $G_3(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3)$ is the free energy of the system with the solutes being at the configuration $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3$ (the thermodynamic variables T, P are omitted to simplify the notation). The work required to carry out a similar process involving two particles is

$$\Delta G(\mathbf{R}_1, \mathbf{R}_2) = G_2(\mathbf{R}_1, \mathbf{R}_2) - G_2(\infty) \quad (4.3)$$

The quantities defined in (4.2) and in (4.3) are known in the literature as the potentials of average force. We prefer, in the context of this book, to refer to these quantities as free energy changes for the described processes.

The question that may now be asked is to what extent the work $\Delta G(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3)$ may be written as a sum of pairwise terms, in analogy with (4.1). This assumption has indeed been used in the theory of simple fluids and it is known as the Kirkwood superposition approximation (Kirkwood, 1935; Hill, 1956). Nowadays it is generally recognized that this is a poor approximation even for simple fluids, and one can suspect that this is also true for a solution of, say, argon in water. Therefore, we define the extent of nonadditivity in the work $\Delta G(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3)$ by the difference

$$\begin{aligned} \phi(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) &= \Delta G(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) \\ &\quad - [\Delta G(\mathbf{R}_1, \mathbf{R}_2) + \Delta G(\mathbf{R}_2, \mathbf{R}_3) + \Delta G(\mathbf{R}_1, \mathbf{R}_3)] \end{aligned} \quad (4.4)$$

In a similar fashion one can extend the definition of nonadditivity for any number of particles. (We discuss here only nonadditivity with respect to *pairs*. One can also define higher-order nonadditivities, but these will not concern us here.)

In classical statistical mechanics one can always split the total work involved in the processes described above into two terms, the *direct* and the *indirect* parts, i.e.,

$$\Delta G(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) = U(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) + \delta G^{\text{HI}}(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) \quad (4.5)$$

$$\Delta G(\mathbf{R}_1, \mathbf{R}_2) = U(\mathbf{R}_1, \mathbf{R}_2) + \delta G^{\text{HI}}(\mathbf{R}_1, \mathbf{R}_2) \quad (4.6)$$

where the indirect part is being referred to as the HI part, since we shall be mainly interested in water as a solvent.

Using the assumption of the additivity of the direct work (4.1) and relations (4.4), (4.5), and (4.6) we find that the nonadditivity defined in (4.4) may be expressed in terms of the indirect parts of the work, namely,

$$\phi(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) = \delta G^{\text{HI}}(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3) - \delta G^{\text{HI}}(\mathbf{R}_1, \mathbf{R}_2) - \delta G^{\text{HI}}(\mathbf{R}_2, \mathbf{R}_3) - \delta G^{\text{HI}}(\mathbf{R}_1, \mathbf{R}_3) \quad (4.7)$$

The source of the nonadditivity in (4.7) is exactly the same as the one responsible for the peculiar features of the pairwise HI that we have discussed in Chapter 1, namely, the averaging over all possible configurations of the solvent molecules. Since our solvent of interest is water, an anomalous liquid in many respects, we may expect to find that the nonadditivity of the HI is somewhat outstanding in water as compared with other solvents. It is difficult to see exactly how the nonadditivity effect arises, or how it may be related to any known property of the solvent. We shall demonstrate, however, one very simple case of the nonadditivity effect in Section 4.2.

For any real solution we have, at present, no experimental information on the extent of the nonadditivity effect. We shall mention in Sections 4.4 and 4.6 two possible ways of studying this problem by experimental means. Other new methods are urgently needed. One potential source of "experimental" information might be the computer experiments, which may be used to study the nonadditivity effect. This has indeed been applied to the case of simple fluids, and its extension to aqueous solutions should be encouraged.

4.2. A SPECIFIC EXAMPLE FOR DEMONSTRATING THE NONADDITIVITY EFFECT

We demonstrate in this section, by a simple example, how the nonadditivity of the HI may affect the probability of occurrence of certain configurations of a group of solute particles. In a similar fashion it may also affect the preference of one particular conformation of a single complex molecule in the solvent. We shall also see that such a preference effect cannot always be ascribed to an *intramolecular* hydrophobic interaction between nonpolar groups of a single molecule such as in proteins.

Consider four simple particles at two specific configurations as depicted in Figure 4.2. In order to emphasize effects that do not originate from the *direct* interaction between these particles we assume that the total potential energy of interaction is pairwise additive and that the pair potential $U(R_{ij})$

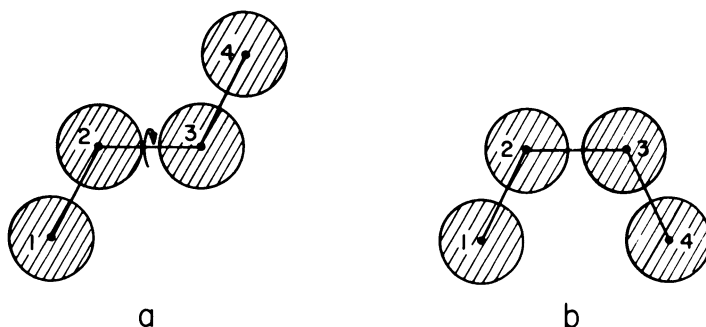


Figure 4.2. Two possible configurations of four solute particles (or groups in one molecule). The configuration *b* is obtained from *a* by rotation about the line connecting the centers of particles 2 and 3.

is of very short range. Hence for each of these configurations we write

$$U(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3, \mathbf{R}_4) = U(R_{12}) + U(R_{13}) + U(R_{23}) + U(R_{24}) + U(R_{34}) \quad (4.8)$$

Note that we have neglected $U(R_{14})$, presuming that in both configurations R_{14} is larger than the range of the direct interaction between the particles.

The two configurations *a* and *b* in Figure 4.2 are obtained from each other by rotation about the line connecting the centers of particles 2 and 3. Therefore all the distances R_{ij} except R_{14} are the same in the two configurations, hence

$$U(a) = U(b) \quad (4.9)$$

where $U(a)$ and $U(b)$ are the total interaction energies of the four particles at the configurations *a* and *b*, respectively.

A straightforward result from (4.9) is that the probability of occurrence of the configuration *a* is the same as that of *b*, provided that these are the only particles in the system, i.e.,

$$\frac{P(a)}{P(b)} = \frac{\exp[-U(a)/kT]}{\exp[-U(b)/kT]} = 1 \quad (4.10)$$

The situation becomes markedly different if the same four particles are surrounded by solvent molecules. Referring again to the same configurations *a* and *b* of Figure 4.2, and using the notation of Section 4.1, we write the HI among these solute particles as

$$\delta G^{\text{HI}}(a) = \sum_{i < j} \delta G^{\text{HI}}(R_{ij}^a) + \phi(a) \quad (4.11)$$

$$\delta G^{\text{HI}}(b) = \sum_{i < j} \delta G^{\text{HI}}(R_{ij}^b) + \phi(b) \quad (4.12)$$

where R_{ij}^a and R_{ij}^b are the interparticle distances in the configurations a and b , respectively, including R_{14} (i.e., $i, j = 1, 2, 3, 4$). $\phi(a)$ and $\phi(b)$ designate the nonadditivity of the HI for the two configurations.

In this system the ratio of the probabilities of finding the two configurations a and b is given by

$$\frac{P(a)}{P(b)} = \frac{\exp[-\Delta G(a)/kT]}{\exp[-\Delta G(b)/kT]} = \frac{\exp[-\delta G^{\text{HI}}(a)/kT]}{\exp[-\delta G^{\text{HI}}(b)/kT]} \quad (4.13)$$

The second equality on the right-hand side of (4.13) is a result of the equality of the direct potential energies in (4.9).

We shall now examine two particular cases. First we assume that the nonadditivity effects are negligible, i.e., we put $\phi(a) = \phi(b) = 0$ in (4.11) and (4.12). Since we have the equalities $R_{ij}^a = R_{ij}^b$ for all i, j except for R_{14} we obtain from (4.13)

$$\begin{aligned} \frac{P(a)}{P(b)} &= \exp\left[-\frac{\delta G^{\text{HI}}(a) - \delta G^{\text{HI}}(b)}{kT}\right] \\ &= \exp\left[-\frac{\delta G^{\text{HI}}(R_{14}^a) - \delta G^{\text{HI}}(R_{14}^b)}{kT}\right] \end{aligned} \quad (4.14)$$

This result means that in spite of the equalities of the direct potential energies of the two configurations (4.9), the ratio of the probabilities of the two configurations a and b in the *solvent* may be different from unity. In this particular case we may ascribe this new feature to the difference in the HI between particles 1 and 4, which is the only pair of particles the distance between which is different in the two configurations a and b . Clearly these two configurations may be viewed as representing two possible conformations of a single butane molecule. In the latter case we can ascribe the above result to an *intramolecular* hydrophobic interaction. However, as we shall soon demonstrate, this kind of assignment is not always possible. We recall that relation (4.14) has been based on the assumption of pairwise additivity of the HI. Clearly the same result would have been obtained if nonadditivity effects exist, but they are of equal magnitude for the two configurations a and b , i.e., $\phi(a) = \phi(b) \neq 0$.

Before turning to the more general case it should be noted that our initial assumption was that the *direct* interaction has a very short range, so that $U(R_{14})$ is practically zero in the two configurations. The possibility that the exponent in (4.14) might be nonzero is equivalent to the statement that the HI might have a larger range compared to the direct interaction. This is again a new feature of the HI that may arise from the averaging over all the configurations of the solvent molecules.

Next we turn to the more general case where additivity of the total HI is not granted. In this case we have

$$\frac{P(a)}{P(b)} = \exp\left[-\frac{\delta G^{\text{HI}}(R_{14}^a) - \delta G^{\text{HI}}(R_{14}^b)}{kT}\right] \exp\left[-\frac{\phi(a) - \phi(b)}{kT}\right] \quad (4.15)$$

Again in order to emphasize a new feature we assume that the HI is of a short range so that the first factor in (4.15) is unity. In this case the difference in the probabilities of the occurrence of the two configurations is ascribed to the difference in the extent of the nonadditivity effect of the two configurations a and b . Since $\phi(a)$ and $\phi(b)$ are properties of the configuration of the *entire* set of solute particles, it is impossible to claim that the deviation from unity of the ratio $P(a)/P(b)$ is due to a HI between any specific pair of solute particles. This is an important observation, which should be borne in mind in any discussion of the concept of intramolecular HI between nonpolar groups hanging on a polymer. We have, for simplicity, discussed the case of four solute particles at two configurations, a and b . Clearly the same considerations would have been relevant to the case where our solutes are replaced by methylene groups and chemical bonds exist along lines 1–2, 2–3, and 3–4. In this case all our conclusions apply to the two possible conformations of a single butane molecule. Here again we may find that one of the conformations may have a higher probability than the other. To analyze the reasons for such a preference we must first examine the intramolecular potential function of the molecule, i.e., whether the same effect is also observed in the gaseous phase. If this is not the case, then we turn to the indirect free energy change for the transformation from one conformation to the other. This, in general, would involve non-additivity effects. Therefore, the reason for observing such a preference effect could not be ascribed simply to an intramolecular HI, say between the two end methyl groups of the molecule. Extending the same type of argument to biopolymers would lead to the following conclusion. Consider two conformations of a biopolymer, say the helix-coil pair. We find that one conformation is much more probable than the other. If nonadditivity effects are large, then it would be impossible to explain such a phenomenon by invoking the concept of *intramolecular* HI between pairs of nonpolar groups.

For this reason we believe that a systematic study of the nonadditivity effect, along either theoretical or experimental routes, should be given a high priority. The importance of this effect might turn out to be decisive to our understanding of the driving forces behind biochemical processes.

At this point it is instructive to present a specific example in which the ratio of the probabilities in (4.15) may be computed exactly. To do that we consider four hard-sphere (HS) solutes, in a “solvent” which consists of only *one* additional HS of a different diameter. Denoting the position vector of the “solvent” molecules by \mathbf{R}_5 , we can write the ratio of the probabilities of the two configurations as

$$\frac{P(a)}{P(b)} = \frac{\int d\mathbf{R}_5 \exp\{-[U(a) + U(5|a)]/kT\}}{\int d\mathbf{R}_5 \exp\{-[U(b) + U(5|b)]/kT\}} \quad (4.16)$$

where $U(a)$ and $U(b)$ have the same meaning as before and are presumed to be equal to each other. $U(5|a)$ is the total interaction energy between the “solvent” molecule at \mathbf{R}_5 and the four solute molecules at the configuration a . A similar meaning applies to $U(5|b)$. The integrations in (4.16) extend over the entire volume V of our system. This integration is the simplest example of an average over all the configurations of the “solvent” molecules.

Let σ_1 and σ_2 be the diameter of the solute and the solvent molecules, respectively. The integrand in (4.16) has the obvious property

$$\exp\left[-\frac{U(5|a)}{kT}\right] = \begin{cases} 0 & \text{if at least one distance} \\ & |\mathbf{R}_5 - \mathbf{R}_i| < (\sigma_1 + \sigma_2)/2 \\ & \text{for } i = 1, 2, 3, 4 \\ 1 & \text{if all distances} \\ & |\mathbf{R}_5 - \mathbf{R}_i| > (\sigma_1 + \sigma_2)/2 \end{cases} \quad (4.17)$$

In words, the integrand is zero whenever the “solvent” particle penetrates into the excluded volume $V_{\text{ex}}(a)$ produced by the solute molecules, and is unity everywhere else. The two excluded volumes are depicted in Figure 4.3.

The property (4.17) renders possible the immediate integration of the two integrals in (4.16). The result is

$$\frac{P(a)}{P(b)} = \frac{V - V_{\text{ex}}(a)}{V - V_{\text{ex}}(b)} \quad (4.18)$$

Thus the configuration that produces the larger excluded volume will have the smaller probability of occurrence. In our particular example it is evident from Figure 4.3 that

$$V_{\text{ex}}(a) > V_{\text{ex}}(b) \quad (4.19)$$

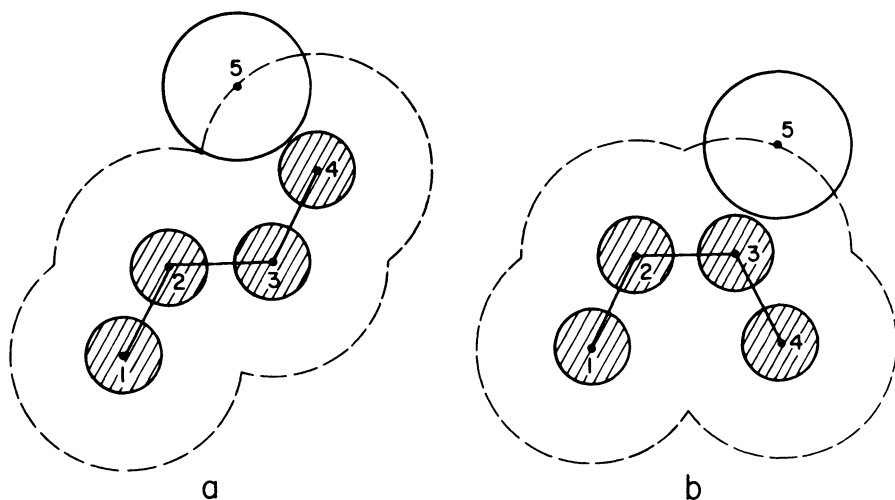


Figure 4.3. The excluded volume of four hard spheres for the two configurations *a* and *b* in Figure 4.2. A hard sphere “solvent” cannot penetrate into the region bounded by the dashed line.

Hence

$$P(a) < P(b) \quad (4.20)$$

Clearly the excluded volume of a given configuration is a property of the configuration of the entire set of the solutes (or the set of groups in a single molecule such as butane). For this reason an inequality of the form (4.20) may not be interpreted in terms of a pairwise HI between any specific pair of solutes (or groups in a single molecule).

In the above discussion we have made a distinction between the effect of the long range of the HI and its nonadditivity. Such a distinction was made only to stress two aspects of the same phenomenon. The important quantity is always the *total* HI among the set of solute molecules. In general, it is not clear under which conditions one can assume complete pairwise additivity of this quantity. Hence the distinction between the two effects may not be possible in practical examples.

The above illustration was made for a very simple “solvent.” It is obvious that the situation becomes more complicated if the “solvent” consists of many molecules and far more so when the solvent is liquid water. For such cases it is impossible to predict, even in a qualitative fashion, which configuration might be favored by any real solvent. This problem forms an interesting, though difficult, challenge for future work.

Comments

The reader may wonder, at this point, on the usefulness of the general strategy of studying HI as outlined in Section 1.1. There we started with a very complex process of a conformational change of a biopolymer. This process involves several factors that combine to determine its overall driving force. As a first step in the study of such complex processes we have decided to separate the various factors and study each of them in isolation, by using simple model systems. One of these factors is the pairwise HI, to which we have devoted an entire chapter in this book.

The present section raises some doubts about the way the various factors cooperate in the complex process. It is, in principle, possible that, if nonadditivity effects are large, all our information on pairwise HI might become totally irrelevant to the understanding of the complex process. We have stressed here the nonadditivity of the HI only. Clearly, different factors such as HI and charge-charge interaction might also combine in a nonadditive manner.

In spite of the above somewhat discouraging comment, we believe that the study of each of the factors separately is unavoidably the best strategy we can adopt before we can even hope to understand the mechanism of real biochemical processes. Besides, whatever the relevance of the pairwise HI to real processes is, we can always view this topic as one aspect of the properties of aqueous solutions. This in itself is sufficient reason for pursuing further the study of pairwise HI, as well as any other single factor that contributes to the more complicated processes.

4.3. THE RELATION BETWEEN HI AND THE STANDARD FREE ENERGY OF AGGREGATION

In anticipation of the discussion of micellization processes in Section 4.8, we present here a general relation between the HI among m solute particles and what is conventionally referred to as the standard free energy of aggregation.

Consider a system consisting of m simple solutes in a solvent at a given T and P . As before, we are interested in the process of bringing these solute particles from some fixed positions at infinite separation from each other (a configuration that will be symbolically denoted by $\mathbf{R}^m = \infty$) to some close configuration $\mathbf{R}^m = \mathbf{R}_1, \dots, \mathbf{R}_m$. The process is carried out within the solvent, keeping the temperature and pressure fixed.

The free energy change associated with this process is

$$\Delta G(\mathbf{R}^m) = G_m(\mathbf{R}^m) - G_m(\infty) \quad (4.21)$$

Clearly, this process cannot be carried out as an actual experiment in the laboratory. Its importance stems from the fact that the free energy change associated with this process is directly related to the probability density of observing the configuration \mathbf{R}^m , namely,

$$P(\mathbf{R}^m) = C \exp[-\Delta G(\mathbf{R}^m)/kT] \quad (4.22)$$

where C is a normalization constant. This fact establishes the relevance of $\Delta G(\mathbf{R}^m)$ to the general problem of HI.

As we have done in Sections 1.3 and 4.1 we can split $\Delta G(\mathbf{R}^m)$ into two contributions; the direct and the indirect parts, namely,

$$\Delta G(\mathbf{R}^m) = U(\mathbf{R}^m) + \delta G^{\text{HI}}(\mathbf{R}^m) \quad (4.23)$$

Generalizing the idea of the thermodynamic cycle of Section 1.3 we can first transfer all the m solute particles to the gaseous phase. Then we bring the solutes to the configuration \mathbf{R}^m , in the gaseous phase. Finally we transfer the aggregate, as a single entity, from the gas into the liquid. From the equality of the free energy change of the process along the two routes (see Figure 4.4), we obtain the generalized relation for $\delta G^{\text{HI}}(\mathbf{R}^m)$

$$\delta G^{\text{HI}}(\mathbf{R}^m) = \Delta\mu_A^\circ - m \Delta\mu_M^\circ \quad (4.24)$$

where $\Delta\mu_M^\circ$ is the standard free energy of transferring a single solute M from a fixed position in the gas to a fixed position in the liquid. Similarly, $\Delta\mu_A^\circ$ refers to the process of transferring the aggregate A as a single entity from the gas to the liquid. The last relation may be obtained either by the use of a generalized thermodynamic cycle as we have done in Section 1.3 or directly by using statistical mechanical arguments (Ben-Naim, 1974).

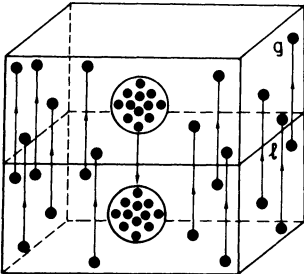


Figure 4.4. A thermodynamic cycle involving m solute particles. Instead of bringing the m solute particles from infinite separation from each other to a close configuration, we first transfer all the particles to the gaseous phase, then we bring them to the close-packed configuration, and finally we transfer the entire aggregate from the gas into the liquid.

Next we consider an experimental system consisting of the same solvent as before, at the same T and P , but now there is a chemical equilibrium between the monomers and the aggregates of m monomers (for simplicity we assume here the existence of one kind of aggregate, with the interparticle distances between its monomers the same as in \mathbf{R}^m). We assume that we have an experimental means by the use of which we can determine the concentration of the monomers ϱ_A . If the solute is very dilute in the solvent we may write the equilibrium condition

$$\mu_A = m\mu_M \quad (4.25)$$

in the form

$$\Delta G_A^\circ \equiv \mu_A^\circ - m\mu_M^\circ = -kT \ln[\varrho_A/\varrho_M^m]_{\text{eq}} \quad (4.26)$$

where μ_A° and μ_M° are the standard chemical potentials of A and M , respectively. Thus from the knowledge of the concentrations of A and M at equilibrium, we can determine the corresponding standard free energy of aggregation ΔG_A° .

The question we pose now is how the experimental quantity ΔG_A° is related to the quantities of interest $\Delta G(\mathbf{R}^m)$ or $\delta G^{\text{HI}}(\mathbf{R}^m)$ in our study of HI.

To do this we must use the statistical mechanical expressions for the chemical potentials of A and M . These are (for details, see Appendixes A.1 and A.7)

$$\mu_A = W(A | \text{sol}) + kT \ln \Lambda_A^3 q_A^{-1} \varrho_A = \mu_A^\circ + kT \ln \varrho_A \quad (4.27)$$

$$\mu_M = W(M | \text{sol}) + kT \ln \Lambda_M^3 q_M^{-1} \varrho_M = \mu_M^\circ + kT \ln \varrho_M \quad (4.28)$$

where $W(A | \text{sol})$ is the coupling work of A against the solvent and a similar meaning is assigned to $W(M | \text{sol})$. Λ_A^3 and Λ_M^3 are the momentum partition functions of A and M , respectively, and q_A and q_M are the remaining parts of the internal partition functions of A and M . For simplicity we assume that the solutes are structureless particles, and that the aggregate as an entity has a rigid structure (no internal motions of the monomers in A), hence we take

$$q_M = 1, \quad q_A = q_{\text{rot}} \exp[-U(\mathbf{R}^m)/kT] \quad (4.29)$$

where q_{rot} is the rotational partition function of A .

In an ideal gas system containing A and M , the coupling work in (4.27) and in (4.28) are evidently zero, hence we have

$$\mu_A^{\circ g} = kT \ln \Lambda_A^3 q_A^{-1} \quad (4.30)$$

$$\mu_M^{\circ g} = kT \ln \Lambda_M^3 q_M^{-1} \quad (4.31)$$

Combining the expressions for the standard chemical potentials in (4.27), (4.28), (4.30), and (4.31) we obtain

$$\begin{aligned} \Delta G_A^{\circ} &= \mu_A^{\circ} - m\mu_M^{\circ} = \Delta\mu_A^{\circ} - m\Delta\mu_M^{\circ} + \mu_A^{\circ g} - m\mu_M^{\circ g} \\ &= \delta G^{\text{HI}}(\mathbf{R}^m) + kT \ln(\Lambda_A^3 q_A^{-1} / \Lambda_M^{3m}) \\ &= U(\mathbf{R}^m) + \delta G^{\text{HI}}(\mathbf{R}^m) + kT \ln(\Lambda_A^3 q_{\text{rot}}^{-1} / \Lambda_M^{3m}) \\ &= \Delta G(\mathbf{R}^m) + kT \ln(\Lambda_A^3 q_{\text{rot}}^{-1} / \Lambda_M^{3m}) \end{aligned} \quad (4.32)$$

This is the required relation between the standard free energy of aggregation ΔG_A° and the free energy of the process described at the beginning of this section. The physical meaning of this relation is quite simple. The standard free energy of aggregation consists of the free energy of bringing m solutes from fixed positions at infinite separation to some close configuration \mathbf{R}^m . In addition, in the real process of aggregation we “lose” m times the momentum partition function of the monomers, and we “gain” one momentum partition function and one rotational partition function of the aggregate. This is essentially the meaning of the second term on the right-hand side of Equation (4.32).

In other words, in order to form a *free* aggregate from m *free* solutes, we may first “freeze in” the translational degrees of freedom of the solutes, form the aggregate at a *fixed* configuration, and then release translational and rotational freedom of the aggregate.

From relation (4.32) it is evident that more information is required in order to extract information on HI from experimental data. One simple way of supplementing this information is to measure, if possible, the standard free energy of aggregation of the same aggregate in the gaseous phase. If this is possible, then the corresponding standard free energy of aggregation is

$$\Delta G_A^{\circ g} = U(\mathbf{R}^m) + kT \ln(\Lambda_A^3 q_{\text{rot}}^{-1} / \Lambda_M^{3m}) \quad (4.33)$$

Hence from (4.32) and (4.33) we may obtain

$$\Delta G_A^{\circ} - \Delta G_A^{\circ g} = \Delta G(\mathbf{R}^m) - U(\mathbf{R}^m) = \delta G^{\text{HI}}(\mathbf{R}^m) \quad (4.34)$$

which is the required measure of the HI.

In practice, the above procedure is not useful. The reason is that in real cases even if aggregates are formed in two phases, they would usually have different configurations in each phase. We have seen in Section 3.7 that even the structure of the dimers of carboxylic acids in two phases are different. The situation is, of course, far more complicated for larger aggregates.

Finally, we note that in our treatment of the aggregates in this section we have ignored, for simplicity, internal motions in the aggregate (such as vibrations and internal rotations). In real examples the corresponding partition functions should also be taken into account in relations such as (4.32) and (4.33).

This complication renders the whole procedure outlined above useless from the practical point of view. For this reason we shall devote the next four sections to other routes by way of which we may obtain information on the HI among m solute particles. We shall then return to micellization processes for which ΔG_A° may be determined experimentally. It is true that many attempts have been made to extract information on HI from such experimental data. Unfortunately, these procedures are not well founded. We shall elaborate further on these difficulties in Section 4.8.

4.4. APPROXIMATE MEASURE OF THE HI AMONG m SOLUTE PARTICLES

In this section we present a straightforward generalization of the method of Section 3.3 to devise a measure of the HI among a large number of solute particles. As in Section 3.3 our treatment here is based essentially on thermodynamics. A more detailed statistical mechanical treatment may be found in Ben-Naim (1971b, 1974). The nature of the approximation that we shall use in this section is the same as the one we have used in Section 3.3. However, in the following section we shall show how to improve upon this approximation to obtain more reliable measurements of the HI at more realistic configurations.

Consider again the process of bringing m solute particles from fixed positions, at infinite separation from each other, to some close configuration that we denote by $\mathbf{R}^m = \mathbf{R}_1, \dots, \mathbf{R}_m$. As in the previous sections we write the free energy change associated with this process as

$$\Delta G(\mathbf{R}^m) = U(\mathbf{R}^m) + \delta G^{\text{HI}}(\mathbf{R}^m) \quad (4.35)$$

where the two terms on the right-hand side of (4.35) are referred to as the

direct and the *indirect* parts of the free energy change. The *indirect* part is also referred to as the HI among the m solute particles at the configuration \mathbf{R}^m .

Using the same thermodynamic cycle as in Section 4.3 (see Figure 4.4), we may express $\delta G^{\text{HI}}(\mathbf{R}^m)$ as

$$\delta G^{\text{HI}}(\mathbf{R}^m) = \Delta\mu_A^\circ - m \Delta\mu_M^\circ \quad (4.36)$$

which is a generalization of relation (3.13) of Section 3.3. Here, $\Delta\mu_M^\circ$ is the experimental standard free energy of solution of the monomers M , and $\Delta\mu_A^\circ$ is the standard free energy of transferring the aggregate A from the gas to the liquid. The latter is not a measurable quantity, since A is not a molecular entity. Therefore, we seek an approximate version of relation (4.36) which leads to an experimentally determinable quantity. To this end, we exploit the fact that the quantity $\delta G^{\text{HI}}(\mathbf{R}^m)$ is a smooth function of the configuration \mathbf{R}^m even for configurations that are experimentally inaccessible. Specifically, suppose we start with three methane molecules as the monomers, and we bring these solutes to a configuration in which the centers of the monomers occupy the same relative positions as the centers of the three carbon atoms in propane.

We recall that $\Delta\mu_A^\circ$ depends essentially on the binding energy of A with the solvent. More specifically, the binding energy of A is defined by

$$B_A = \sum_{j=1}^3 \sum_{i=1}^N U(\mathbf{R}_j, \mathbf{X}_i) \quad (4.37)$$

where $U(\mathbf{R}_j, \mathbf{X}_i)$ is the interaction energy between the j th solute at \mathbf{R}_j and the i th solvent molecule at a given configuration (location and orientation) \mathbf{X}_i . The standard free energy of solution $\Delta\mu_A^\circ$ is given by

$$\Delta\mu_A^\circ = -kT \ln \langle \exp[-B_A/kT] \rangle_0 \quad (4.38)$$

where the symbol $\langle \rangle_0$ stands for an average over all the configurations of the solvent molecules.

Our approximation involves the replacement of B_A , the binding energy of the three methane molecules, by the binding energy of *one* propane molecule, which we denote by B_{Pr} , i.e., we assume

$$B_A \approx B_{\text{Pr}} \quad (4.39)$$

If (4.39) is a good approximation for all the configurations of the solvent molecules that contribute to the average in (4.38), then we have the following

approximate replacement:

$$\Delta\mu_A^\circ \approx \Delta\mu_{\text{Pr}}^\circ \quad (4.40)$$

and hence, instead of (4.36) we write the approximate relation

$$\delta G_3^{\text{HI}} = \Delta\mu_{\text{Pr}}^\circ - 3\Delta\mu_{\text{Me}}^\circ \quad (4.41)$$

where $\Delta\mu_{\text{Pr}}^\circ$ and $\Delta\mu_{\text{Me}}^\circ$ are the standard free energies of solution of propane and methane, respectively. What we have achieved by this approximation is a relation between HI at some particular configuration of three methane molecules and experimentally determinable quantities. As in Section 3.3 we note again that our generalized measure of HI among three or more solute particles is not related to any realizable configuration of a real system. Therefore, the main use of these quantities is not to estimate the absolute magnitude of the HI but to compare the relative strength of the HI in different solvents. We also note here that all of the δG_m^{HI} values for molecules that have internal rotations should be understood as averages over all possible conformations of the molecules (see also Appendix A.7 for more details).

In Figures 4.5 and 4.6 we present some values of δG_m^{HI} for m methane particles in water and in methanol. The final configuration at which the HI is measured is indicated next to each of the curves. Two important features should be noted. In the first place the absolute magnitude of the HI, at any specific configuration, in water is larger than in methanol. Second, the temperature dependence of δG^{HI} is distinctly more pronounced and negative in water as compared with the corresponding curves in methanol. These two features have already been observed in the behavior of the pair-wise HI, reported in the previous chapter.

In Tables 4.1 and 4.2 we present some further values of δG_m^{HI} for various m , at one temperature, $t = 25^\circ\text{C}$. Perhaps the most interesting aspect of the results of these tables is the following. Let m_B be the number of the nearest-neighbor carbon atoms in the final configuration (i.e., the number m_B is equal to the number of chemical bonds in the molecule which is used to replaced the m methane molecules in the final configuration). If we divide δG_m^{HI} by m_B , we obtain a measure of the HI per pair of nearest neighbors. This quantity seems to tend to an almost constant value of about -1.88 kcal/mol for all the reported data in Tables 4.1 and 4.2. Does this indicate some kind of additivity of the HI? It is difficult to answer this question affirmatively. One reason for this is that the data on which the results of these tables are based are not sufficiently accurate to draw

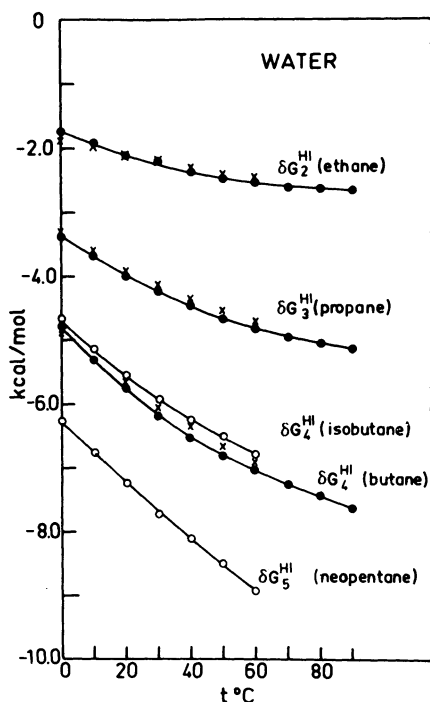


Figure 4.5. Values of δG_m^{HI} in water for various numbers of methane molecules brought to the final configuration as indicated next to each curve. Based on data from Morrison and Billet (1952) and from Wetlaufer *et al.* (1964).

such a conclusion. More important, however, is the observation that the constant value of $\delta G_m^{\text{HI}}/m_B \approx -1.88$ kcal/mol is considerably different from the pairwise HI, i.e., $\delta G_2^{\text{HI}} = -2.16$ kcal/mol. Therefore, even if we trust the data on which these results are based, we cannot conclude that δG_m^{HI} is pairwise additive in the sense that it is a sum of m_B times the pairwise HI, δG_2^{HI} . It is also difficult to imagine that in such close-packed

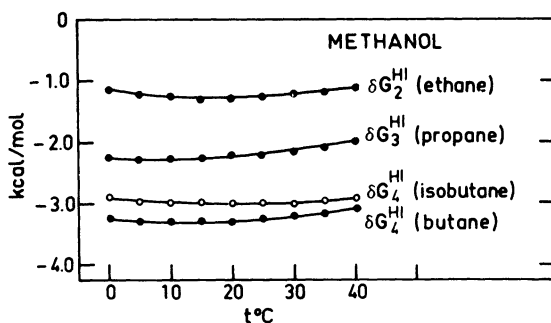


Figure 4.6. Values of δG_m^{HI} for the same configurations as in Figure 4.5, but in methanol.

Table 4.1

Values of δG_m^{HI} (in kcal/mol at 25°C) for the Interaction of m Methane Molecules Brought to a Final Configuration Similar to an Existing Molecule Containing m Carbons^a

| Hydrocarbon | m | $-\delta G_m^{\text{HI}}$ | $-\delta G_m^{\text{HI}}/m_B$ |
|------------------------|-----|---------------------------|-------------------------------|
| Ethane | 2 | 2.16 | 2.16 |
| Propane | 3 | 4.01 | 2.00 |
| <i>n</i> -Butane | 4 | 5.87 | 1.96 |
| Isobutane | 4 | 5.70 | 1.90 |
| <i>n</i> -Pentane | 5 | 7.53 | 1.88 |
| Isopentane | 5 | 7.59 | 1.89 |
| 2,2-Dimethylpropane | 5 | 7.34 | 1.83 |
| <i>n</i> -Hexane | 6 | 9.43 | 1.88 |
| 2-Methylpentane | 6 | 9.48 | 1.89 |
| 3-Methylpentane | 6 | 9.41 | 1.88 |
| 2,2-Dimethylbutane | 6 | 9.39 | 1.88 |
| <i>n</i> -Heptane | 7 | 11.34 | 1.89 |
| 2,4-Dimethylpentane | 7 | 11.07 | 1.85 |
| <i>n</i> -Octane | 8 | 13.08 | 1.87 |
| 2,2,4-Trimethylpentane | 8 | 13.10 | 1.87 |

^a In the last column, m_B is the number of chemical bonds (or nearest neighbors) in the hydrocarbon. [Computations based on data from Wen and Hung (1970) and McAuliffe (1966).]

Table 4.2

Values of δG_m^{HI} (in kcal/mol, at 25°C) for Cyclic Molecules^a

| Cycloparaffin | m | $-\delta G_m^{\text{HI}}$ | $-\delta G_m^{\text{HI}}/m_B$ |
|--------------------------------------|-----|---------------------------|-------------------------------|
| Cyclopropane | 3 | 3.49 | 1.16 |
| Cyclopentane | 5 | 8.80 | 1.76 |
| Cyclohexane | 6 | 10.72 | 1.78 |
| Cycloheptane | 7 | 13.17 | 1.88 |
| Cyclooctane | 8 | 15.13 | 1.89 |
| Methylcyclopentane | 6 | 10.37 | 1.73 |
| Methylcyclohexane | 7 | 12.25 | 1.75 |
| 1- <i>cis</i> -2-Dimethylcyclohexane | 8 | 14.40 | 1.80 |

^a Here $m = m_B$. (From Ben-Naim, 1972a.)

configurations only the "nearest-neighbor" pairs contribute to the total HI. We note that the second nearest neighbors are at a distance of about 2.51 Å and this cannot be regarded as large compared to the possible range of the HI.

Perhaps the best example that may be used to study the extent of additivity (or nonadditivity) of the HI is provided by the example of cyclopropane, for which we find

$$\delta G_3^{\text{HI}} = -3.49 \text{ kcal/mol} \quad (4.42)$$

If we assume that each C–C bond in cyclopropane is of the same length as the C–C bond of ethane, then we may estimate the extent of nonadditivity of the HI by

$$\begin{aligned} \phi(\text{cyclopropane}) &= \delta G_3^{\text{HI}}(\text{cyclopropane}) - 3 \times \delta G_2^{\text{HI}}(\text{ethane}) \\ &= -3.49 + 3 \times 2.16 = 2.99 \text{ kcal/mol} \end{aligned} \quad (4.43)$$

Thus, if our figures for δG_3^{HI} and δG_2^{HI} are reliable, we can conclude that the nonadditivity of the HI is positive and quite large (having the same order of magnitude of the HI itself).

The above example was presented mainly to illustrate the possibility of studying the nonadditivity effect of the HI by experimental means. Of course, more accurate and detailed data are needed in order to reach any significant conclusions from such measurements. Clearly one can extend the method for studying nonadditivity effects in higher cycloparaffin molecules. We believe, however, that this should be postponed until better experimental data become available.

Comment

We believe that more extensive and accurate data on the solubilities of various simple hydrocarbons in water and in other solvents should be sought. Such data could well be used to study the extent of nonadditivity of the HI and its dependence on configuration (e.g., the comparison between the butane and the isobutane configurations).

Similar data may be used to study the effect of a polar group on the HI. For example, the following expression

$$\delta G^{\text{HI}} = \Delta\mu^\circ[\text{CH}_3-(\text{CH}_2)_n\text{-P}] - \Delta\mu^\circ[\text{H}-(\text{CH}_2)_n\text{-P}] - \Delta\mu^\circ(\text{CH}_4) \quad (4.44)$$

is a measure of the indirect work required to bring a methane molecule to one end of a hydrocarbon, which has on its other end a polar group P. Thus, with a given group P (say, halogen or carboxylic groups) one can study the range of the HI by varying n . The question is how large n must be so that the above work becomes independent of P. A second study could be to fix n and examine the relative effects of different groups P on the HI.

4.5. AN IMPROVED APPROXIMATE MEASURE OF THE HI

The measures of the strength of the HI that were introduced in Sections 3.3 and 4.4 contain two flaws. One is the approximation, on which we have not elaborated in any detail [see Ben-Naim (1974) and Appendix A.6]. In essence, this approximation involves the neglect of the field of force produced by the two inner hydrogens of the pair of methane molecules brought to the separation $R = 1.53 \text{ \AA}$. The second is concerned with the final configuration of the solutes, which in practice have almost zero probability of occurrence.

In this section we present a modified measure of the HI which is based on essentially the same type of arguments as before but can, in principle, provide improved information on the HI. The improvement is achieved in both the nature of the approximation and the realizability of the final configuration of the solutes. The extent of the improvement depends on the availability of relevant experimental data.

As a prototype of our new measure we consider the neopentane molecule. According to the procedure of constructing a measure of the HI as discussed in Section 4.4, we can write the HI among *five* methane molecules, brought to the final configuration of a neopentane molecule (see Figure 4.7) as

$$\delta G_5^{\text{HI}}(\text{neopentane}) = \Delta\mu^\circ(\text{neopentane}) - 5\Delta\mu^\circ(\text{methane}) \quad (4.45)$$

This measure involves the same kind of approximation as indicated above.

Next we consider a different process. We start with *four* methane molecules at fixed positions at infinite separation from each other. These solutes are brought (within the solvent, keeping T and P constant) to the final configuration of the four peripheral methyl groups in neopentane. These are indicated in Figure 4.8. At this configuration we have the exact

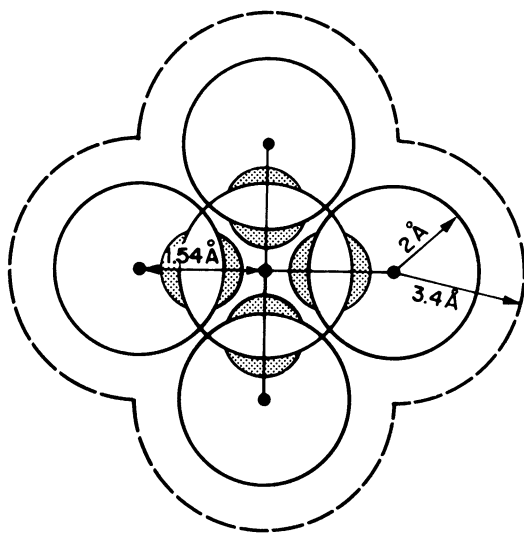


Figure 4.7. A schematic, two-dimensional description of five methane molecules in the configuration of neopentane. All the inner hydrogens are indicated by the dark areas. The boundaries of the excluded volume are indicated by the dashed curve (assuming a radius of 2 Å for the methane and 1.4 Å for the water molecule).

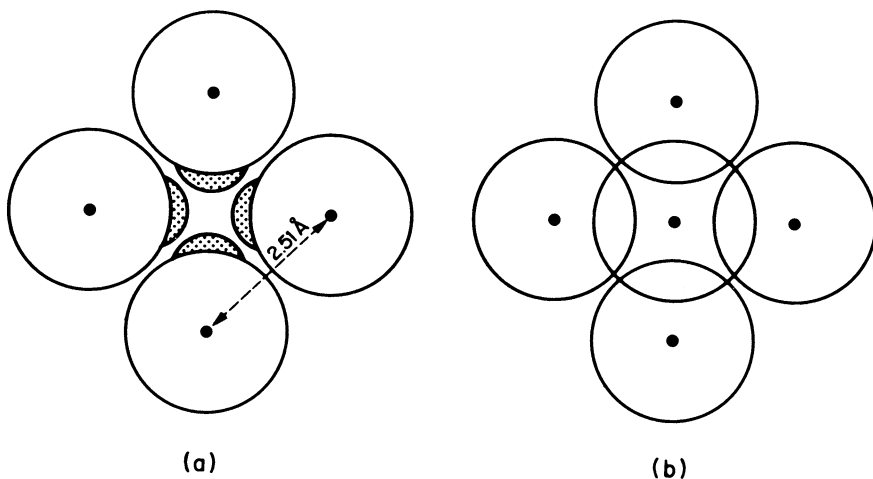


Figure 4.8. A schematic, two-dimensional description of the replacement procedure corresponding to Equations (4.50) and (4.51). (a) Four methane molecules are brought to the position of the four peripheral methyl groups of a neopentane molecule. The four hydrogens pointing towards the center are indicated by the dark areas. The distance of closest approach between any two of the methane molecules is about 2.51 Å. (b) The four methane molecules are replaced by a single neopentane molecule. A new carbon nucleus is added, which partially compensates for the loss of the four inner hydrogens.

relation

$$\delta G^{\text{HI}}(\text{agg.}) = \Delta\mu^\circ(\text{agg.}) - 4\Delta\mu^\circ(\text{methane}) \quad (4.46)$$

where $\Delta\mu^\circ(\text{agg.})$ is the standard free energy of transferring the aggregate (agg.) of Figure 4.8(a) from the gas to the liquid. Clearly, this is not a measurable quantity. The statistical mechanical expression for $\Delta\mu^\circ(\text{agg.})$ is

$$\Delta\mu^\circ(\text{agg.}) = -kT \ln \langle \exp(-B_{\text{agg.}}/kT) \rangle_0 \quad (4.47)$$

where $B_{\text{agg.}}$ is the total binding energy of the aggregate to the solvent molecules; more explicitly,

$$B_{\text{agg.}} = \sum_{j=1}^4 \sum_{i=1}^N U(\mathbf{R}_j, \mathbf{X}_i) \quad (4.48)$$

where $U(\mathbf{R}_j, \mathbf{X}_i)$ is the solute-solvent pair potential between the j th solute at \mathbf{R}_j and the i th solvent molecule at the configuration \mathbf{X}_i .

We notice that since the aggregate has a compact structure, no solvent molecule can penetrate into the interior of this aggregate. [Note, however, that the average $\langle \rangle_0$ is over *all* possible configurations of the solvent molecules. This also includes configurations for which some solvent molecules do penetrate into the region that is occupied by the solute molecules. However, for each of the configurations in which a solvent molecule penetrates into this region, $B_{\text{agg.}}$ becomes very large and positive and hence $\exp[-B_{\text{agg.}}/kT]$ becomes practically zero]. In Figure 4.7 we indicated by the dashed line the boundary of the so-called excluded volume (assuming that the solvent is water, with a molecular diameter of 2.8 Å).

Clearly, the average in (4.47) gets nonzero contributions only from those configurations for which no solvent molecules penetrate into the excluded region produced by the four solute molecules. Therefore, if we insert in the center of this aggregate any particle or a group that produces a short-range field of force—such that it is not felt outside the excluded volume, the value of the average in (4.47) will not be affected. We exploit this fact to introduce into the center of the aggregate an “agent” that binds the four solute molecules in such a way that a *real* molecule is formed and for which the standard free energy of solution is measurable.

In our particular example we replace the aggregate of *four* methane molecules by *one* neopentane molecule. This replacement is shown schematically in Figure 4.8. The approximation that is employed is

$$B(\text{agg.}) \approx B(\text{neopentane}) \quad (4.49)$$

If this is valid for all the configurations of the solvent molecules that have nonzero contribution to the average in (4.47), then we have the approximation

$$\Delta\mu^\circ(\text{agg.}) \approx \Delta\mu^\circ(\text{neopentane}) \quad (4.50)$$

Hence the exact relation (4.46) is transformed into the approximate, but more useful, relation

$$\delta G^{\text{HI}}(\text{agg.}) = \Delta\mu^\circ(\text{neopentane}) - 4\Delta\mu^\circ(\text{methane}) \quad (4.51)$$

This should be compared with (4.45), which is a measure of the HI among *five* solute particles. Here we have a measure of the HI among *four* solutes at a configuration that is more realizable than the ones we have treated in Section 4.4. Furthermore, the nature of the approximation involved in (4.51) is different from the one used in Sections 3.3 and 4.4. Here we have replaced the four inner hydrogens by one carbon center. In a sense we have partially compensated for the loss of the field of force produced by these hydrogens on the solvent. It is clear that had we started with four bulkier molecules, say four benzene molecules, and used the same procedure as above, we would have reached the relation

$$\delta G_4^{\text{HI}} = \Delta\mu^\circ(\text{TPM}) - 4\Delta\mu^\circ(\text{benzene}) \quad (4.52)$$

which measures the HI among *four* benzene molecules holding the positions of the four benzyl radicals in tetraphenylmethane (TPM). In this case the boundaries of the excluded volume are quite far from the center of the aggregate. The effect of any replacement made at the center of this aggregate on the solvent becomes negligible. Clearly, the bulkier the four molecules the better is the replacement approximation that is used in (4.49) or (4.50).

Figure 4.9 presents some values of $\delta G_4^{\text{HI}}(\text{agg.})$ defined in (4.51) as a function of the temperature. These values are compared with two other measures of the HI among *four* methane molecules at the configuration of butane and isobutane. Note that the latter are systematically more negative than the corresponding values of $\delta G_4^{\text{HI}}(\text{agg.})$. This is probably a result of the fact that the HI becomes larger as the particles come closer together in the final configuration. [For further discussion on this aspect of the HI, the reader is referred to Ben-Naim (1974).]

The quantity $\delta G^{\text{HI}}(\text{agg.})$ in (4.51) measures the HI interaction among four methane molecules: the closest distance between any pair of molecules

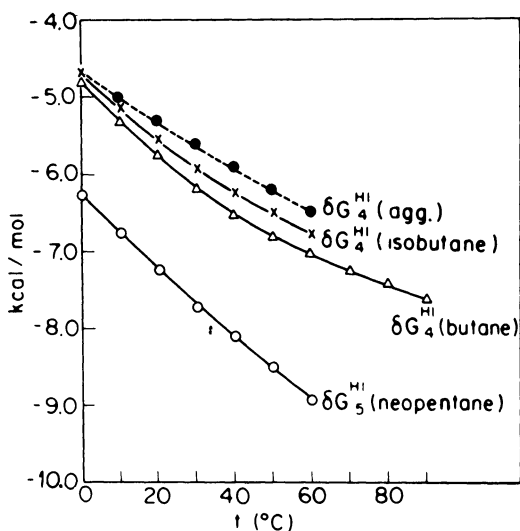


Figure 4.9. Values of δG_4^{HI} and δG_5^{HI} as a function of temperature for various configurations, as indicated next to each curve.

is about 2.51 Å, as compared to 1.5 Å between some of the pairs of methane molecules in Figure 4.7. This is an improvement towards a more realistic configuration of solute molecules in real systems. One can make further improvement in this direction by taking four bulkier molecules, such as benzene or long-chain paraffin molecules, to form tetraalkyl or tetraphenyl methane. In such cases the final configuration is very similar to an actually realizable configuration.

Also, in Figure 4.9 we have plotted values of $\delta G_5^{\text{HI}}(\text{neopentane})$ as defined in (4.45). These values are distinctly larger than the corresponding δG_4^{HI} values. The reason is that in the former case we are concerned with the HI among *five* molecules, whereas in the latter case only *four* solute molecules are involved.

Comment

We recommend the extension of the method outlined in this section to bulkier molecules. This is the only available experimental method to obtain information on HI among several solute particles at some close-packed configuration that is very close to a realizable configuration. Such information may indicate to what extent the HI is an important ingredient in the driving force for the formation of micelles in aqueous solutions.

4.6. APPLICATION OF THE SCALED-PARTICLE THEORY (SPT)

In the previous sections we presented two measures of the HI in which we made use of experimental data. In this section a partial theoretical approach to the problem of HI is described. The basic process is the same as in Section 4.3. Namely, we start with m solute particles at fixed positions but at infinite separation from each other in a solvent at some given temperature T and pressure P . We then bring these particles to a close-packed configuration. More specifically we require that the centers of all the particles be confined to a spherical region S_A , the radius of which is chosen as described below. The process is schematically written as

$$(\mathbf{R}^m = \infty) \rightarrow (\mathbf{R}^m \in S_A) \quad (4.53)$$

and the corresponding free energy change is

$$\Delta G_m = U_m + \delta G_m^{\text{HI}} \quad (4.54)$$

where U_m and δG_m^{HI} are the *direct* and the *indirect* parts of the work required to carry out the process indicated in (4.53). Using the same argument as in Section 1.3 (see also Figure 4.4), we write for the indirect, or the hydrophobic interaction, part the exact relation

$$\delta G_m^{\text{HI}} = \Delta \mu_A^\circ - m \Delta \mu_M^\circ \quad (4.55)$$

$\Delta \mu_M^\circ$ is the experimental standard free energy of solution of the monomers M , and $\Delta \mu_A^\circ$ is the standard free energy of transferring the close-packed aggregate A , viewed as a single entity, from a fixed position in the gas into a fixed position in the liquid.

In the previous sections we endeavored to find approximations for $\Delta \mu_A^\circ$ using experimental sources. Here, however, we appeal to theory to find an estimate for $\Delta \mu_A^\circ$.

In Section 2.5 we mentioned one possible application of the scaled-particle theory (SPT) to the problem of HI. Here the same theory is used in a different way to estimate the quantity $\Delta \mu_A^\circ$. This application is based on a recent work by Ben-Naim and Tenne (1977). In Appendix A.4 we present some details on the elements of the SPT. We feel that applicability of the SPT to liquid water is somewhat dubious. Therefore we shall be using this theory only to compute $\Delta \mu_A^\circ$, whereas $\Delta \mu_M^\circ$ is taken from experimental sources. In this way we base our calculations of the HI only partially on this theory.

The procedure of estimating $\Delta\mu_A^\circ$ by the SPT is the following. First we split $\Delta\mu_A^\circ$ into two terms

$$\Delta\mu_A^\circ = \Delta\mu_A^\circ(\text{cav}) + \Delta\mu_A^\circ(\text{soft}) \quad (4.56)$$

where the first term on the right-hand side of (4.56) is the work required to create a cavity of a suitable size (see below) in the solvent. The second term is due to the "turning on" of the "soft" (or the attractive) part of the interaction between the aggregate A and the solvent. Such a split of $\Delta\mu_A^\circ$ into two terms may be carried out in a rigorous fashion by using a consecutive double-charging process for introducing A into the solvent [for details see Ben-Naim (1974)].

We further assume that m is a large number, that the solute monomers are simple (e.g., argon, methane), and that the aggregate A has a spherical shape and consists of closely packed monomers. Following these assumptions we expect that the soft part of the field of force of A will originate essentially from those molecules that are in direct contact with the solvent, i.e., the molecules that form the surface of the aggregate A . If the number of monomers m is large, the contribution of $\Delta\mu_A^\circ(\text{soft})$ to $\Delta\mu_A^\circ$ becomes small compared to $\Delta\mu_A^\circ(\text{cav})$. Thus for sufficiently large m we use the approximation

$$\Delta\mu_A^\circ \approx \Delta\mu_A^\circ(\text{cav}) \quad (4.57)$$

where $\Delta\mu_A^\circ(\text{cav})$ may be computed from the SPT. Note that for hard-sphere solutes $\Delta\mu_A^\circ(\text{soft})$ is zero and (4.57) is an equality. We therefore expect that for a simple solute such as methane, (4.57) is a good approximation.

To proceed we must now estimate the size of the appropriate cavity in which the aggregate is to be accommodated. Let σ_M be the effective hard-core diameter of methane, which we take as equal to the Lennard-Jones diameter of methane $\sigma_M = 3.82 \text{ \AA}$. If m solutes of diameter σ_M are packed compactly in such a way that they form a sphere of diameter σ_A , it is well known that the ratio of the volume of the m particles to the volume of the sphere S_A is

$$\frac{m\pi\sigma_M^3/6}{\pi\sigma_A^3/6} = 0.7405 \quad (4.58)$$

From which we may eliminate σ_A :

$$\sigma_A = (m\sigma_M^3/0.7405)^{1/3} \quad (4.59)$$

Let the diameter of the solvent molecules be σ_S , then the radius of the cavity produced by the aggregate A is given by

$$R_{\text{cav}} = (\sigma_A + \sigma_S)/2 \quad (4.60)$$

The situation is schematically depicted in Figure 4.10. Once we have the radius R_{cav} , the molecular diameter, and the number density of the solvent, we can use the SPT to estimate $\Delta\mu_A^\circ(\text{cav})$. Here we present only some results of these calculations. For more details on the SPT see Appendix A.4, and for the calculation procedure see Ben-Naim and Tenne (1977).

Thus, in essence we have replaced the exact result in (4.55) by the approximate relation

$$\delta G_m^{\text{HI}} \approx \Delta\mu_A^\circ(\text{cav}) - m \Delta\mu_M^\circ \quad (4.61)$$

where $\Delta\mu_M^\circ$ is taken from experimental sources, and $\Delta\mu_A^\circ(\text{cav})$ is computed from the SPT.

As we have noted in Section 4.3, the process described in the beginning of this section is not a *real* process, i.e., one cannot carry out such a process of aggregation in the laboratory. The relevance of the quantity δG_m^{HI} to real processes is through its relationship to the probability of finding such an aggregate made up of m free solute particles in a solvent (see Section 4.3). It is only in the latter sense that the quantity δG_m^{HI} might be of relevance to the process of micelle formation, which will be discussed in Section 4.8.

In the following numerical examples we always use methane, with a molecular diameter of $\sigma_M = 3.82 \text{ \AA}$, as our monomer. The solvents that

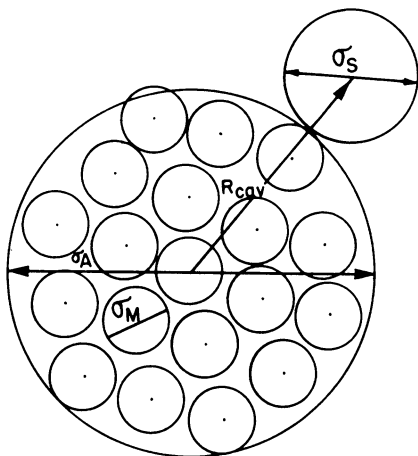


Figure 4.10. A cavity of radius R_{cav} is formed by an aggregate of diameter σ_A in a solvent; the diameter of the solvent molecules is σ_S .

are used in these illustrations are water (and heavy water) with $\sigma_S = 2.90 \text{ \AA}$, methanol with $\sigma_S = 3.69 \text{ \AA}$, ethanol with $\sigma_S = 4.34 \text{ \AA}$, and cyclohexane with $\sigma_S = 5.63 \text{ \AA}$. All the "effective" hard-core diameters are taken from the literature [see, for example, Reiss (1966) and Wilhelm and Battino (1971)]. It should be borne in mind, however, that for nonspherical molecules σ_S has no clear-cut physical meaning, as in the case of simple spherical molecules.

In addition to the effective molecular diameter, the solvents are characterized by their number densities at the given temperature and pressure. This information is sufficient for the computation of the free energy change associated with the formation of a cavity $\Delta\mu_A^\circ(\text{cav})$, and hence the computation of the HI through relation (4.61).

In order to compute the entropy and the enthalpy changes that correspond to δG_m^{HI} we use the following relations:

$$\delta S_m^{\text{HI}} = - \frac{\partial \delta G_m^{\text{HI}}}{\partial T} = \Delta S_A^\circ(\text{cav}) - m \Delta S_M^\circ \quad (4.62)$$

and

$$\delta H_m^{\text{HI}} = \delta G_m^{\text{HI}} + T \delta S_m^{\text{HI}} = \Delta H_A^\circ(\text{cav}) - m \Delta H_M^\circ \quad (4.63)$$

where again we use the SPT to compute $\Delta S_A^\circ(\text{cav})$ and $\Delta H_A^\circ(\text{cav})$ but use experimental sources for ΔS_M° and ΔH_M° . The latter are the standard entropy and enthalpy changes corresponding to the process of transferring a monomer from a fixed position in the gas to a fixed position in the liquid. These are different from the conventional standard quantities as used in the literature. [For more details see Section 5.2, and Ben-Naim (1974) and (1978a)].

In using the SPT to compute $\Delta S_A^\circ(\text{cav})$ and $\Delta H_A^\circ(\text{cav})$ we must also consider the temperature dependence of the effective hard-core diameter of the solvent molecules. (Only for hard-sphere particles is the molecular diameter, by definition, strictly temperature independent.) As we have noted above, the effective diameter, especially for nonspherical molecules, is not a uniquely defined quantity, and clearly the same is true for its temperature dependence. There are several procedures that have been suggested in the literature to obtain this temperature dependence, but none is satisfactory from the theoretical point of view. This fact is another quite serious flaw of the SPT when applied to complex solvents such as water, methanol, ethanol, etc.

Finally we note that δS_m^{HI} as defined in (4.62) is the same as the *total* entropy change for the process indicated in (4.53). On the other hand,

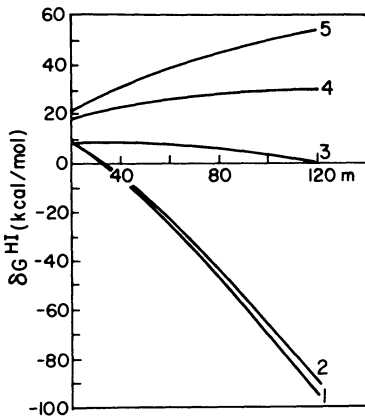


Figure 4.11. Values of δG_m^{HI} as a function of the number of monomers m for different solvents. The solute is methane and the solvents are (1) H_2O ; (2) D_2O ; (3) methanol; (4) ethanol; and (5) cyclohexane. All values are for atmospheric pressure at $t = 30^\circ\text{C}$.

δH_m^{HI} is only the indirect part of the enthalpy change that corresponds to this process. The relation between the total and the indirect enthalpy changes is

$$\Delta H_m[(\mathbf{R}^m = \infty) \rightarrow (\mathbf{R}^m \in S_A)] = U_m + \delta H_m^{\text{HI}} \quad (4.64)$$

which should be compared with relation (4.54).

In Figures 4.11 and 4.12 we present some computed values of δG_m^{HI} as a function of m , the number of monomers, for two temperatures, 30°C and 60°C . It is quite clear that as m becomes large enough (say $m \gtrsim 100$) the values of δG_m^{HI} in water (and heavy water) become large and negative. In methanol, ethanol, and cyclohexane the corresponding values are either positive or slightly negative. As we have noted above, we do not particularly

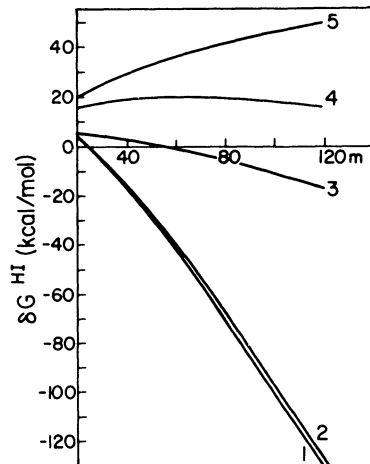


Figure 4.12. Same as Figure 4.11 but for $t = 60^\circ\text{C}$.

trust the absolute results of δG_m^{HI} for each solvent, but we believe that the difference between such values between two solvents is a more reliable quantity. Such differences may be easily transformed into ratios of probabilities as we have discussed in Section 4.3. To be more precise, suppose we take two solvents, say water and methanol, both at the same temperature T and pressure P . Also we assume that the solute M forms a very dilute solution in these two solvents, in such a way that the number density ϱ_M is the same in the two solvents, i.e., $\varrho_M(\text{in water}) = \varrho_M(\text{in methanol})$. (ϱ_M is the number of solute molecules per unit volume of the solvent.) In such a solution we may ask what the probability is of finding a close-packed aggregate containing m solute molecules. Clearly, if we have given a precise configuration $\mathbf{R}^m = \mathbf{R}_1, \dots, \mathbf{R}_m$ to these particles, then the probability of its occurrence is zero (since one point in a continuous space of events has a zero measure). However, the ratio of such probabilities in two solvents is a *finite* quantity, which provides information on the difference in the solvation properties of the two solvents.

This ratio is given by

$$\xi = \frac{P_m(\text{water})}{P_m(\text{methanol})} = \exp \left[- \frac{\delta G_m^{\text{HI}}(\text{water}) - \delta G_m^{\text{HI}}(\text{methanol})}{kT} \right] \quad (4.65)$$

Note that this ratio should be understood as a limit of a ratio of two *finite* quantities, namely,

$$\lim_{d\mathbf{R}_1 \cdots d\mathbf{R}_m \rightarrow 0} \left\{ \frac{\text{Pr}[l \text{ in } d\mathbf{R}_1 \text{ at } \mathbf{R}_1 \cdots m \text{ in } d\mathbf{R}_m \text{ at } \mathbf{R}_m (\text{in water})]}{\text{Pr}[l \text{ in } d\mathbf{R}_1 \text{ at } \mathbf{R}_1 \cdots m \text{ in } d\mathbf{R}_m \text{ at } \mathbf{R}_m (\text{in methanol})]} \right\} \quad (4.66)$$

where $\text{Pr}[]$ means the probability of finding the event specified in the square brackets.

As an example we choose $m = 100$ and compute the ratio ξ at three temperatures. The results are

$$\xi(t = 10^\circ\text{C}) \approx 4 \times 10^{32}, \quad \xi(t = 30^\circ\text{C}) \approx 5 \times 10^{53}, \quad \xi(t = 60^\circ\text{C}) \approx 2 \times 10^{57} \quad (4.67)$$

These results indicate that, in a dilute solution of the monomers M , as described above, the probability of finding a close-packed aggregate in water is far larger than the corresponding probability in methanol. Furthermore, this ratio becomes *larger* as the temperature increases in the range of temperatures of say, $0 \lesssim t \lesssim 80^\circ\text{C}$. (One would have expected to find that, as the temperature increases, water would tend to become more "normal" and hence $\xi \rightarrow 1$. This may be true at higher temperatures.

There is evidence that indicates that the opposite effect is true at around room temperature. This aspect will be further discussed in Chapter 5, where we shall also present a qualitative molecular reason for this kind of behavior.)

Another interesting aspect of the results reported in Figures 4.11 and 4.12 is the difference between light and heavy water. In spite of our reservation about the applicability of the SPT to liquid water, we believe that whatever the nature of the approximation introduced in these calculations, they are likely to be of the same order of magnitude in light and heavy water. If this reasoning is sound, we should trust the difference in δG_m^{HI} between the two solvents, rather than the magnitude of each of these in a single solvent.

We have seen in Section 3.4 that the pairwise HI between methane molecules is stronger in H_2O as compared to D_2O . We also noted that conclusions to the contrary have been reached from other sources (see Sections 3.8 and 3.9). From Figures 4.11 and 4.12 we see that the HI among m solute particles in D_2O is weaker than in H_2O , in conformity with the behavior of pairwise HI. At present there is no molecular interpretation to this finding. However, in Section 5.8 we shall present a qualitative rationalization of this result, which will depend on a particular definition of the concept of the "structure of water." We shall also see that in some sense the replacement of H_2O by D_2O has an effect similar to that of decreasing the temperature of H_2O .

Next we turn to assessing the relative extent of the contribution of the two terms in (4.61). The question that we pose is the following: We have used a theoretical source for the computation of $\Delta\mu_{A^{\circ}}(\text{cav})$ and an experimental source for $\Delta\mu_{M^{\circ}}$. Which of the two terms is the dominating one?

Figure 4.13 shows the variation with m of the three quantities involved in (4.61). We see that for small m the values of $\Delta\mu_{A^{\circ}}(\text{cav})$ and $m\Delta\mu_{M^{\circ}}$ are of comparable magnitude. As m increases it is clear that the term $m\Delta\mu_{M^{\circ}}$ becomes the dominating one. This means that for large values of m our computed results rest more heavily on the experimental rather than on the theoretical source. This conclusion may also be understood on intuitive grounds. To see this, let us make a distinction between two kinds of monomers that build up our aggregate; let m_s be the number of solute monomers that form the surface of the aggregate (i.e., those that are in contact with the solvent) and m_l be the number of solute monomers that are in the interior of the aggregate (i.e., those that are surrounded by other solute monomers only).

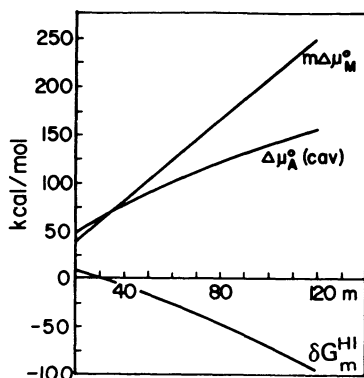
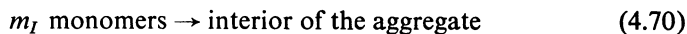
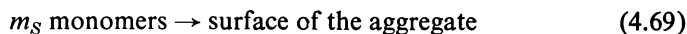


Figure 4.13. Values of δG_m^{HI} , $\Delta \mu_A^{\circ}(\text{cav})$ and $m\Delta \mu_M^{\circ}$ as a function of the number of monomers m in water at $P = 1$ atm and $t = 30^{\circ}\text{C}$.

Thus the overall process of aggregation



may be viewed as being split into two parts:



Clearly, for very large aggregates, the number of surface particles may be neglected with respect to the number of interior particles. This means that the “reaction” (4.70) will dominate the overall process (4.68). Hence the free energy change of the overall process will be determined by the free energy of transferring m_I monomers from the solvent into the interior of the aggregate. Furthermore, since we have eliminated the *direct* solute–solute interaction in the definition of δG_m^{HI} (see 4.54), the process (4.70) is the same as transferring m_I solutes from the liquid to the gas. Hence, this process is approximately represented by $-m \Delta \mu_M^{\circ}$.

The above considerations are valid for very large m 's, in which case δG_m^{HI} becomes essentially equal to m times $-\Delta \mu_M^{\circ}$. As we see from Figure 4.13, for m of the order of 100, both terms in (4.61) contribute to δG_m^{HI} , hence for such a size of aggregate we are still far from the limiting behavior that we mentioned above. This means that δG_m^{HI} , with m of the order of 100, is more relevant to an aggregation process rather than to a mere reversal of the solubility of the monomer.

In the above examples we have used a mixture of experimental and theoretical sources to compute δG_m^{HI} . It is worth noting that similar quantities may, in principle, be obtained by either purely theoretical or purely experimental sources.

First, consider m hard-sphere solutes of diameter σ_M brought to a compact configuration to form a sphere of diameter σ_A . We can apply the SPT to compute *both* $\Delta\mu_A^\circ(\text{cav})$ and $\Delta\mu_M^\circ(\text{cav})$ and define

$$\delta G_m^{\text{HI}} = \Delta\mu_A^\circ(\text{cav}) - m \Delta\mu_M^\circ(\text{cav}) \quad (4.71)$$

Figure 4.14 compares the results obtained from (4.61) with those of (4.71) for water and cyclohexane. It is clear that though the magnitude of δG_m^{HI} changes significantly from one method of computation to the other, the values of δG_m^{HI} in water are systematically lower than in cyclohexane in both methods.

The second, purely experimental, way of computing δG_m^{HI} is noted here, though no relevant computations have been carried out. Suppose that we could find a *real* compact polymer which has a roughly spherical shape, and for which the interaction energy with the solvent is similar to the interaction between our aggregate of m solutes and the solvent. In such a case we could write the approximate relation

$$\delta G_m^{\text{HI}} = \Delta\mu_P^\circ - m \Delta\mu_M^\circ \quad (4.72)$$

where $\Delta\mu_P^\circ$ is the experimental standard free energy of solution of the polymer P . This relation relies only on experimental results for estimating δG_m^{HI} . It might be interesting to explore the practicability of this method in the future.

In Figure 4.15 we present further results computed by the mixed method of relation (4.61) for the system of water and ethanol. These

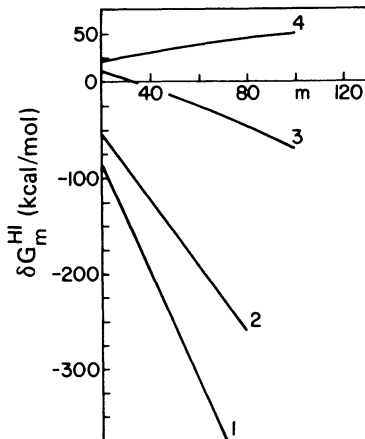


Figure 4.14. Comparison between the results obtained from equations (4.71) and (4.61). (1) Water, using only SPT. (2) Cyclohexane, using only SPT. (3) Water, using partial experimental data. (4) Cyclohexane, using partial experimental data. All values are for $P = 1$ atm at $t = 30^\circ\text{C}$.

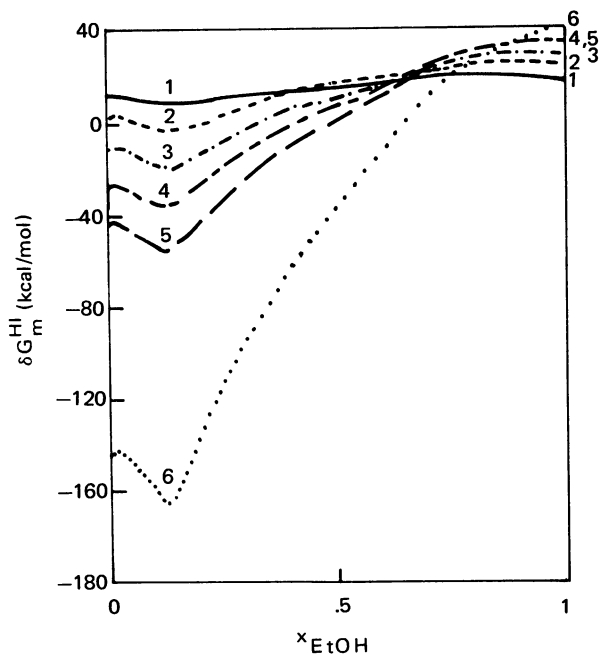
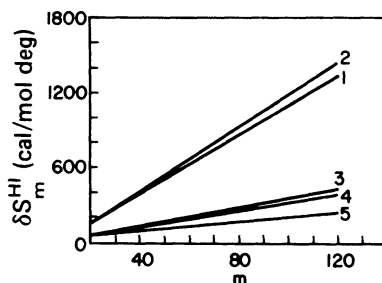


Figure 4.15. Values of δG_m^{HI} as a function of the mole fraction of ethanol in mixtures of water and ethanol. The various curves correspond to different values of m : (1) $m = 20$; (2) $m = 40$; (3) $m = 60$; (4) $m = 80$; (5) $m = 100$; (6) $m = 200$. All values are for $P = 1$ atm and $t = 10^\circ\text{C}$.

calculations are based on an extension of the SPT to a mixture of solvents (Lebowitz *et al.*, 1965; Tenne and Ben-Naim, 1977). The interesting trend that we observe in Figure 4.15 is that as m increases to the order of 100 particles the HI, as measured by δG_m^{HI} , has a behavior very similar to the one we have found in Section 3.4. Namely, when we add ethanol, the HI becomes initially *weaker* than in water; thereafter there is a pronounced increase in the strength of the HI, and finally (above, say, $x_{EtOH} \approx 0.2$) the HI gradually decreases to its limiting value in pure ethanol. We believe that this behavior is due mainly to our use of experimental data through $\Delta\mu_M^\circ$. It has been demonstrated that the SPT alone, as used in a relation of the form (4.71) *does not* show the characteristic dependence of the HI on the composition of the solvent that we have mentioned above. [Details are to be found in Tenne and Ben-Naim (1977).] We therefore believe that the SPT, as devised to deal with a mixture of simple solvents (say two kinds of hard spheres), is not applicable, as it stands, to a mixture of complex fluids such as water and ethanol.

Figure 4.16. Values of δS_m^{HI} as a function of m , at $P = 1$ atm and $t = 30^\circ\text{C}$, in different solvents: (1) H_2O ; (2) D_2O ; (3) methanol; (4) ethanol; (5) cyclohexane. In all the calculations the molecular diameter of the solvent is taken to be temperature independent.



Next we turn to the temperature dependence of the HI as it is computed by the mixed method (4.61) through the relations (4.62) and (4.63). Figures 4.16 and 4.17 present the values of δS_m^{HI} and δH_m^{HI} as a function of the number of monomers m . These computations are based on the assumption that the diameter of the solvent molecules is temperature independent (see below).

The curves clearly indicate that both the entropy and the enthalpy associated with the process of aggregation are larger than the corresponding values in methanol, ethanol, and cyclohexane. These results are in complete agreement with the results obtained for $\delta G_2^{\text{HI}}(\sigma_1)$ using the model of Section 3.3.

It must be noted, however, that the question of which temperature dependence for the molecular diameter one must employ in these computations is not yet settled. It is obvious that only for hard spheres is the diameter of the particles a well-defined quantity and temperature independent (by definition!). For simple fluids, say argon, methane, etc., one may reasonably argue that the effective hard-core diameter should be a decreasing function

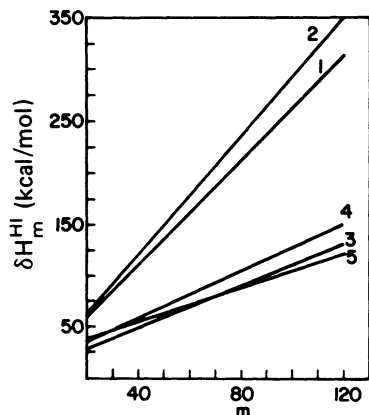


Figure 4.17. Values of δH_m^{HI} as a function of m , at $P = 1$ atm and $t = 30^\circ\text{C}$, in different solvents as in Figure 4.16.

of the temperature. The physical idea is that as one increases the temperature, the kinetic energy of the particles increases. Hence, on the average, interparticle collisions would lead to more extensive penetration into the repulsive region of the pair potential for the two particles.

In fact, it has been demonstrated that if such a negative temperature dependence of σ_s is adopted, then one can obtain a good agreement between the prediction from the SPT and experimental results.

The situation is far more complicated for nonspherical, or more complex, solvent molecules. In the first place the very concept of a hard-core diameter is not a well-defined quantity. For water, for instance, one may conveniently *choose* the effective diameter of the water molecule as the location of the first peak in the radial distribution function $g(R)$ for pure water. If we adopt this definition, we find that there exists a small *positive* temperature dependence of the molecular diameter of water. The rationalization of this behavior is quite simple. It is known that in liquid water at room temperature most of the water molecules are engaged in hydrogen bonds. The optimal distance for a hydrogen bond is about 2.76 Å, which is well within the effective hard-core diameter assigned to a water molecule, about 2.9 Å. Now as we increase the temperature we should consider at least two competing effects. On the one hand, we have the kinetic effect that was described above, which tends to *decrease* the effective hard-core diameters of *free* water molecules. On the other hand, hydrogen-bonded pairs are broken as we increase the temperature: hence fewer pairs of molecules will be found at the relatively short distance of 2.76 Å. This tends to *increase* the effective hard-core diameters of the bonded molecules. We believe that in water at room temperature the second effect mentioned above is the dominant one. This belief rests on two findings. In the first place the location of the first peak of the radial distribution function increases by about 0.005 Å as the temperature is raised by 10°C. Second, we have recently found (Ben-Naim and Tenne, 1977) that if one takes a positive temperature dependence for σ_M the computed results from the SPT are more consistent with experimental findings.

In any event the question of the sign or the extent of the temperature dependence of the diameter of a water molecule is far from being resolved. What is usually done is to choose a $\partial\sigma_s/\partial T$ that leads to the best fit between the computed and the experimental result. This kind of approach clearly is equivalent to feeding the theory with quantities that are characteristic of the solvent (in addition to the solvent density and its temperature dependence, which are to be supplied from experimental sources). In this sense the results of the computation of the entropies and the enthalpies based

on the SPT should not be considered as emerging from a pure molecular theory of liquids.

Similarly when extending the applicability of the SPT to a mixture of solvents, such as water and ethanol, one must consider the possibility that the effective hard-core diameter of both molecules be composition dependent (at a given temperature). The results exhibited in Figure 4.15 were computed on the assumption of a *fixed* molecular diameter for both water and ethanol molecules. This choice is inevitable since we have no information to guide us in the choice of the composition dependence for these diameters. We believe that this is the major reason for the failure of the theory to predict the “correct” trend of the dependence of δG_m^{HI} on the composition of the solvent at small values of m . However, for large m , the term $-m \Delta\mu_M^\circ$ becomes dominant and the results of the computations rely more on the experimental than the theoretical sources. This is the reason for the more plausible results obtained for the larger m 's in Figure 4.15.

Finally, we turn briefly to the pressure dependence of δG_m^{HI} . We use again Equation (4.61), where $\Delta\mu_A^\circ(\text{cav})$ is estimated from the SPT and $\Delta\mu_M^\circ$ is estimated as follows. We use the relation

$$\frac{\partial \Delta\mu_M^\circ}{\partial P} = \bar{V}_M^\circ \quad (4.73)$$

where \bar{V}_M° is the *local* standard partial molar volume of the solute at infinite dilution. [This is different from the conventional standard partial molar volume. For more details see Section 5.2 and Ben-Naim (1978a).]

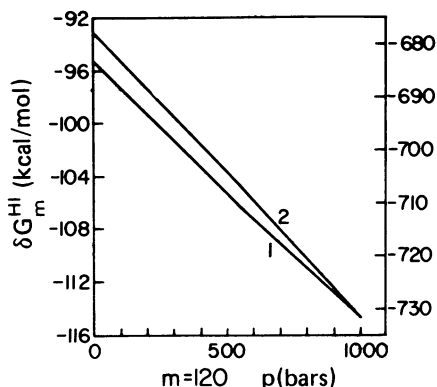
Assuming that \bar{V}_M° is approximately constant over a certain range of pressures, we write

$$\Delta\mu_M^\circ(P) \approx \Delta\mu_M^\circ(P = 1 \text{ atm}) + (P - 1)\bar{V}_M^\circ \quad (4.74)$$

This quantity is used in Equation (4.61) to compute the pressure dependence of δG_m^{HI} . Two sets of results are shown in Figure 4.18. One is based on the method described above. The second is based solely on the SPT, i.e., both $\Delta\mu_A^\circ$ and $\Delta\mu_M^\circ$ are computed by the SPT. We note again that some kind of pressure dependence of σ_S should be included in such calculations, but because of lack of any reliable information on this we have simply taken a constant value for σ_S .

The two sets of results presented in Figure 4.18 are considerably different in their magnitude. In both cases, however, the general result is that the strength of the HI increases with pressure. We shall further discuss the pressure dependence of the HI in Chapter 5.

Figure 4.18. The dependence of δG_m^{HI} , with $m = 120$, on the pressure in water at $t = 30^\circ\text{C}$. Curve (1) was obtained by using only the SPT (4.71). Curve (2) was obtained by using the combination of experimental data and the SPT as in (4.61). The right and left scales refer to curves (1) and (2), respectively.



Comments

In spite of our general reservation on the applicability of the SPT to complex solvents such as water, methanol, and the like, we believe that the procedure outlined in this section provides reasonable information on the HI among a large number of solute particles. One should also be aware of the fact that, at present, we have no other source that provides information of this kind.

Of course, if m is very large, then the results obtained from these calculations are equivalent to the standard free energy of solution of the monomers. In this respect our process of aggregation provides the same information as the reversal of the dissolution process. This is not the case, however, for m of the order of 100, in which both $\Delta\mu_A^\circ$ and $m\Delta\mu_M^\circ$ are of comparable magnitude. In the future, when δG_2^{HI} at contact distance $R \approx \sigma_M$ between two solutes may be available, one could use the computed values of δG_m^{HI} to estimate the extent of nonadditivity of the HI. A further possible application of the SPT is to compute δG_m^{HI} for configurations other than spherical, and therefore to gain some idea of the dependence of the HI on the configuration of the aggregate.

4.7. A DIRECT MEASURE OF INTRAMOLECULAR HI

In Section 3.3 we introduced a quantity, $\delta G^{\text{HI}}(\sigma_1)$, that measures the HI between two simple solutes at a very small distance $R = \sigma_1$. It was stressed there that this quantity should be useful for comparing the HI in different solvents, and not for estimating the strength of the HI in any specific solvent. The derivation of the relation between $\delta G^{\text{HI}}(\sigma_1)$ and ex-

perimental quantities also involved an approximation. It is, therefore, desirable to construct a new measure of HI that does not involve such an approximation.

We now present a new, and exact, relation between a quantity that conveys information on HI and experimental quantities. Furthermore, this relation provides information on the HI between two alkyl groups at realistic configurations. Perhaps these configurations are not the ones that nonpolar groups are actually found in in real biopolymers, but we certainly are making a step forward towards that end.

The method described below starts from the recognition of the fact that pairwise HI in a single biopolymer is an *intramolecular* phenomenon. Referring to Figure 1.1 we realize that in the process of a conformational change two alkyl groups are brought from a large to a small separation. In both of these conformations the two alkyl groups are anchored on the same molecular backbone. Having this prototype process in mind, we now replace the biopolymer, as a carrier for the alkyl groups, by a relatively simple molecule. By doing that, we have freed ourselves from the formidable complexities of the real biopolymer. We are thus left with a simple process of transferring an alkyl group between two states of a small carrier. Hence, the term *intramolecular* HI seems to be appropriate for this process.

We now turn to describe the theoretical background of the method. The idea is very similar to the one described in Section 3.3. The reader should realize that for a full appreciation of the method described below, it is essential to appeal to some statistical mechanical arguments. The final result is indeed a relation between thermodynamic quantities, but its derivation relies on statistical mechanics.

Consider a molecule such as 1,4-dialkylbenzene, which we shall denote by ϕ_{14} . Suppose that we “cut” this molecule into four groups as indicated schematically in Figure 4.19. The exact location of the “cut” is of no importance since in our final expression we shall deal with the whole molecule. For convenience, however, we assume that the “cut” is done at

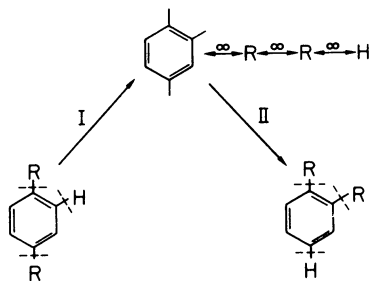


Figure 4.19. I is a schematic process of breaking 1,4-dialkylbenzene into four radicals: benzyl ring ϕ , two alkyl groups R, and a hydrogen atom H. These radicals are recombined in process II to form the new molecule 1,2-dialkylbenzene. In the intermediate stage all the radicals are at fixed configurations and at infinite separation from each other.

the center of the C–C and of the C–H bond. Also for simplicity we assume that the molecule as a whole is rigid.

We now consider the following process: We start with a single solute ϕ_{14} at some fixed configuration (location and orientation) in a solvent at a given temperature T , pressure P , and total number of molecules N . We “cut” the molecule into four radicals and remove them to fixed configurations but at infinite separation from each other. This process is indicated by I in Figure 4.19.

The Gibbs free energy change for this process is written, in the T, P, N ensemble, as

$$\Delta G(\text{I}) = kT \ln \left[\frac{\Delta(T, P, N; \phi_{14})}{\Delta(T, P, N; \phi, H, R, R)} \right] \quad (4.75)$$

where in the numerator and in the denominator we wrote the partition functions of the system at the initial and the final states considered above. Dividing the numerator and the denominator by the partition function of the pure solvent $\Delta(T, P, N)$ we obtain

$$\Delta G(\text{I}) = kT \ln \frac{\langle \exp[-\beta B(\phi_{14})] \rangle_0 \exp[-\beta U(\phi_{14})]}{\langle \exp[-\beta B(\phi) - \beta B(H) - \beta B(R) - \beta B(R)] \rangle_0} \quad (4.76)$$

where $B(A)$ represents the “binding energy” of the solute (or radical) A to the rest of the system which is at a fixed configuration \mathbf{X}^N . $\beta = (kT)^{-1}$ with k the Boltzmann constant, and the average $\langle \rangle_0$ is over all the configurations and volumes of the pure solvent. More specifically the binding energy of A is defined by

$$B(A) = \sum_{i=1}^N U(\mathbf{X}_A, \mathbf{X}_i) \quad (4.77)$$

where $(\mathbf{X}_A, \mathbf{X}_i)$ represents the configuration of the solute A and of the i th solvent molecule. By $U(\phi_{14})$ we denote the total *direct* interactions between the four radicals at the final configuration of the molecule ϕ_{14} . Alternatively, $-U(\phi_{14})$ is the total work required to perform the same process, as described above, but in the absence of a solvent. The two alkyl groups R are identical (i.e., methyl, ethyl, etc.). However, in (4.76) they are understood to be at infinite separation from each other.

Since we have assumed that the radicals ϕ, H, R, R are at infinite separation from each other we may factor the average in the denominator on the right-hand side of (4.76) into a product of four average quantities, namely,

$$\begin{aligned} & \langle \exp[-\beta B(\phi) - \beta B(H) - \beta B(R) - \beta B(R)] \rangle_0 \\ &= \langle \exp[-\beta B(\phi)] \rangle_0 \langle \exp[-\beta B(H)] \rangle_0 \langle \exp[\beta B(R)] \rangle_0^2 \end{aligned} \quad (4.78)$$

Using this factorization we rewrite (4.76) as (see also Appendix A.1)

$$\Delta G(\text{I}) = -U(\phi_{14}) - \Delta\mu^\circ(\phi_{14}) + \Delta\mu^\circ(\text{H}) + \Delta\mu^\circ(\phi) + 2\Delta\mu^\circ(\text{R}) \quad (4.79)$$

where $\Delta\mu^\circ(A)$ is the free energy change for transferring the solute (or radical) A from a fixed configuration in the gaseous phase to a fixed configuration in the liquid. Of course in (4.79) the only directly measurable quantity is $\Delta\mu^\circ(\phi_{14})$. All the other terms will now be eliminated by the following considerations. First we define the indirect part of the total work $\Delta G(\text{I})$ by

$$\delta G^{\text{HI}}(\text{I}) = \Delta G(\text{I}) + U(\phi_{14}) \quad (4.80)$$

i.e., we define the excess work for process I in the liquid relative to the gaseous phase. This quantity has been referred to as the *indirect*, or the *hydrophobic interaction* (HI), part of the total work. From (4.80) and (4.79) we obtain

$$\delta G^{\text{HI}}(\text{I}) = -\Delta\mu^\circ(\phi_{14}) + \Delta\mu^\circ(\text{H}) + \Delta\mu^\circ(\phi) + 2\Delta\mu^\circ(\text{R}) \quad (4.81)$$

Similarly for the process indicated as II in Figure 4.19 we write the indirect part of the total work as

$$\delta G^{\text{HI}}(\text{II}) = \Delta\mu^\circ(\phi_{12}) - \Delta\mu^\circ(\text{H}) - \Delta\mu^\circ(\phi) - 2\Delta\mu^\circ(\text{R}) \quad (4.82)$$

Adding (4.81) to (4.82) we obtain

$$\begin{aligned} \delta G^{\text{HI}}[(1,4) \rightarrow (1,2)] &= \delta G^{\text{HI}}(\text{I}) + \delta G^{\text{HI}}(\text{II}) \\ &= \Delta\mu^\circ(\phi_{12}) - \Delta\mu^\circ(\phi_{14}) \end{aligned} \quad (4.83)$$

Thus, on the right-hand side of (4.83) we have two measurable quantities: the standard free energies of solution of the two dialkylbenzene molecules. All the “standard free energies” of the solution of the radicals in (4.81) and (4.82) have been canceled out. On the left-hand side of (4.83) we have the indirect part of the work required to transfer an alkyl group from position 4, where it does not “see” the alkyl group at position 1, to position 2, where it is close to the group at position 1.

The quantity defined by (4.83) also has an important probability interpretation. Suppose we have a single dialkylbenzene in a solvent in such a way that one alkyl group at position 1 is fixed, whereas the second alkyl group may attain one of the two positions: 2 or 4. We assume that the alkyl group is free to move between these two states. The ratio of the

probabilities of finding the second alkyl group in the two states is given by

$$\frac{\text{Pr}(2)}{\text{Pr}(4)} = \exp[-\beta U(\phi_{12}) + \beta U(\phi_{14})] \exp\{-\beta \delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]\} \quad (4.84)$$

The first factor on the right-hand side of (4.84) is the probability ratio in vacuum, i.e., in the absence of the solvent. The second factor is due to the presence of the solvent. This factor determines the probability ratio in a system in which the direct interactions $U(\phi_{12})$ and $U(\phi_{14})$ have been "switched off." Alternatively, if we take two phases a and b in which the direct interactions do exist but are not affected by the solvent, we obtain

$$\left[\frac{\text{Pr}(2)}{\text{Pr}(4)} \right]_a / \left[\frac{\text{Pr}(2)}{\text{Pr}(4)} \right]_b = \frac{\exp\{-\beta \delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]\}_a}{\exp\{-\beta \delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]\}_b} \quad (4.85)$$

and in particular if a is a liquid and b is an ideal gas we have

$$\frac{y(2)}{y(4)} \equiv \left[\frac{\text{Pr}(2)}{\text{Pr}(4)} \right]_l / \left[\frac{\text{Pr}(2)}{\text{Pr}(4)} \right]_g = \exp\{-\beta \delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]\}_l \quad (4.86)$$

which is the probability interpretation of the quantity defined in (4.83). We have denoted the ratio of the two probabilities of the same state in the two phases by $y(2)$ and $y(4)$. This quantity has a significance similar to $y(R)$ introduced in Section 1.4. Before turning to some numerical illustrations we note that relation (4.83) is an exact relation and does not involve an approximation similar to the one used in Section 3.3. Furthermore, the quantity $\delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]$ means essentially the difference between the HI in the 1,4 relative to the 1,2 configuration. Both of these configurations are "realistic" ones and do not involve extensive penetration of one group into the other, as was the case in $\delta G^{\text{HI}}(\sigma_1)$.

We will now describe some illustrative examples of the application of relations (4.83) and (4.86).

The solubilities and partition coefficients of dialkylbenzene solutes between water and n -hexane were measured spectroscopically (Ben-Naim and Wilf, 1979). From these measurements one may easily calculate the various standard free energies of transfer of the solutes from the gas to water, $\Delta\mu^\circ(G \rightarrow W)$, from n -hexane to water, $\Delta\mu^\circ(H \rightarrow W)$, and from the gas to n -hexane, $\Delta\mu^\circ(G \rightarrow H)$. These values are reported in Table 4.3.

From the standard free energies of solution we compute the quantities $\delta G^{\text{HI}}[(1,4) \rightarrow (1,2)]$ as defined in (4.83). These are shown in Table 4.4. It is clearly seen from this table that in n -hexane the values of δG^{HI} are either positive or very small and probably within the limits of the ex-

Table 4.3

Standard Free Energies of Transfer between the Gas and Water, between *n*-Hexane and Water, and between the Gas and *n*-Hexane for Different Solutes at Two Temperatures and 1 atm^a

| Solute | <i>t</i> (°C) | $\Delta\mu^\circ(G \rightarrow W)$ (kcal/mol) | $\Delta\mu^\circ(H \rightarrow W)$ (kcal/mol) | $\Delta\mu^\circ(G \rightarrow H)$ (kcal/mol) |
|---------------------|---------------|--|--|--|
| Benzene | 10 | -1.175 | 2.862 | -4.038 |
| | 20 | -0.981 | 2.868 | -3.849 |
| Methylbenzene | 10 | -1.224 | 3.632 | -4.856 |
| | 20 | -0.974 | 3.741 | -4.715 |
| Ethylbenzene | 10 | -1.232 | 3.678 | -4.910 |
| | 20 | -0.956 | 3.754 | -4.710 |
| 1,2-Dimethylbenzene | 10 | -1.478 | 4.189 | -5.667 |
| | 20 | -1.243 | 4.321 | -5.564 |
| 1,4-Dimethylbenzene | 10 | -1.240 | 4.496 | -5.736 |
| | 20 | -0.943 | 4.593 | -5.536 |
| 1,2-Diethylbenzene | 10 | -1.908 | 3.926 | -5.834 |
| | 20 | -1.540 | 3.727 | -5.267 |
| 1,4-Diethylbenzene | 10 | -1.305 | 4.888 | -6.193 |
| | 20 | -0.924 | 4.788 | -5.712 |

^a Data from Ben-Naim and Wilf (1979).

Table 4.4

Values of the Indirect Part of the Work Required to Transfer an Alkyl Group from Position 4 to Position 2 at Two Temperatures

| Alkyl group | <i>t</i> (°C) | $\delta G^{HI}[(1,4) \rightarrow (1,2)]$ (cal/mol) in water | $\delta G^{HI}[(1,4) \rightarrow (1,2)]$ (cal/mol) in <i>n</i> -hexane |
|-------------|---------------|--|---|
| Methyl | 10 | -238 | +69 |
| | 20 | -300 | -28 |
| Ethyl | 10 | -603 | +359 |
| | 20 | -616 | +445 |

perimental error. However, in water we find negative values of δG^{HI} which seem to increase with the chain length of the alkyl group.

It should be noted that the HI reported in Table 4.4 are not *pairwise* HI in the sense of Chapter 3 (this is why this method belongs to this chapter). The reason is that we have started our considerations with the HI among *four* radicals, and by taking differences we have ended up with a quantity that measures the indirect part of the work of transferring an alkyl group from position 4 to position 2; the process is carried out in the *presence of the benzene ring*. This is the reason for referring to δG^{HI} as a measure of the *intramolecular* HI. This process should therefore be clearly distinguished from the process of bringing two alkyl groups from infinite separation to some close configuration in the solvent. Here, the proximity of the benzene ring must have some effect on the structure or properties of the medium in which the two alkyl groups “see” each other. We believe that this is one reason for finding small values of δG^{HI} between two methyl groups in water. In this case the two groups are very close to the benzene ring and hence their surroundings greatly differ from that of pure water. Once we take a longer alkyl group, such as ethyl (or longer chains), the medium for the HI between the two groups is farther away from the benzene rings and hence closer to that of pure liquid water.

We also note that the values of $|\delta G^{\text{HI}}|$ in water are slightly larger at 20°C compared to 10°C. This is in agreement with our previous conclusions on the temperature dependence of the HI. However, we believe that in this particular example the difference is well within the experimental error involved in the estimation of δG^{HI} .

It is now instructive to translate the same data reported in Table 4.4 into the language of probabilities. This reinterpretation is contained in Equation (4.86). The relevant situation is the following.

Suppose we have a dialkylbenzene molecule at some fixed configuration in the solvent. Let us fix one alkyl group at position 1 and assume that the second group can attain either position 2 or position 4. We may now ask: what is the ratio of the probabilities of finding this group in the two positions? The answer to this question requires a knowledge of the direct interaction between the alkyl groups as well as the HI part. Since we are interested only in the latter part we may assume that the direct interactions are being “switched off,” hence the quantity $y(2)/y(4)$ defined in (4.86) gives the ratio of the two probabilities in such a system.

We see from Table 4.5 that the entries for *n*-hexane are either of the order of unity or smaller than unity, indicating a preference for the 1,4 configuration. On the other hand, in water there is a clear-cut preference

Table 4.5

Ratios of the (Solvent-Induced) Probabilities of Finding an Alkyl Group in Positions 2 and 4 in a Molecule with a Fixed Alkyl Group at Position 1

| Alkyl group | t (°C) | $y(2)/y(4)$ in water | $y(2)/y(4)$ in n -hexane |
|-------------|----------|----------------------|----------------------------|
| Methyl | 10 | 1.527 | 0.885 |
| | 20 | 1.675 | 1.049 |
| Ethyl | 10 | 2.924 | 0.528 |
| | 20 | 2.878 | 0.465 |

for the 1,2 configuration. This is another way of describing the phenomenon of HI.

Another way of processing the data presented in Table 4.3 follows. Consider the disproportionation “reaction” depicted in Figure 4.20. This is not a “real” reaction, but one in which the solute molecules are devoid of their translational and rotational degrees of freedom. We start with two monoalkylbenzenes $\phi-R$ at fixed configurations and at infinite separation from each other in the solvent. Next we exchange the alkyl group R of one molecule with the hydrogen atom at position 2 of the second molecule. As a result of this exchange we obtain a 1,2-dialkylbenzene molecule ϕ_{12} and a benzene molecule B . This process is indicated by a in Figure 4.20.

The corresponding indirect part of the free energy change is

$$\delta G^{\text{HI}}(a) = \Delta\mu^\circ(\phi_{12}) + \Delta\mu^\circ(B) - 2\Delta\mu^\circ(\phi - R) \quad (4.87)$$

and similarly for the “reaction” b in Figure 4.20 we obtain

$$\delta G^{\text{HI}}(b) = \Delta\mu^\circ(\phi_{14}) + \Delta\mu^\circ(B) - 2\Delta\mu^\circ(\phi - R) \quad (4.88)$$

Values of $\delta G^{\text{HI}}(a)$ and $\delta G^{\text{HI}}(b)$ were computed from the data in Table 4.3 and are presented in Table 4.6.

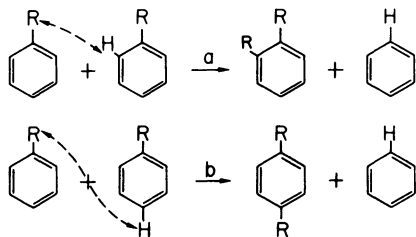


Figure 4.20. Two disproportionation reactions: In (a) two monoalkylbenzenes are used to form a 1,2-dialkylbenzene and a benzene molecule. In (b) a 1,4-dialkylbenzene and benzene are formed from the same initial molecules.

Table 4.6

Values of $\delta G^{\text{HI}}(a)$ and $\delta G^{\text{HI}}(b)$ (in kcal/mol) as Defined in Equations (4.87) and (4.88), Respectively

| Alkyl group | t (°C) | In water | | In <i>n</i> -hexane | |
|-------------|----------|---------------------------|---------------------------|---------------------------|---------------------------|
| | | $\delta G^{\text{HI}}(a)$ | $\delta G^{\text{HI}}(b)$ | $\delta G^{\text{HI}}(a)$ | $\delta G^{\text{HI}}(b)$ |
| Methyl | 10 | -0.205 | +0.033 | +0.007 | -0.062 |
| | 20 | -0.276 | +0.024 | +0.040 | +0.068 |
| Ethyl | 10 | -0.619 | -0.016 | -0.160 | -0.411 |
| | 20 | -0.609 | +0.007 | +0.304 | -0.141 |

The values of $\delta G^{\text{HI}}(a)$ and $\delta G^{\text{HI}}(b)$ may be assigned a probability meaning similar to the one given by relation (4.86). Briefly, we look at the two sides of the "chemical reactions" in Figure 4.20 as being two states of the system (i.e., the solvent with the two solutes at infinite separation from each other). We may ask about the relative probabilities of these two states. Excluding, as before, the direct interaction energies, we can focus only on the solvent effect on the relative probabilities of finding these two states of the system, which is given by $\exp[-\beta\delta G^{\text{HI}}]$. Thus, from Table 4.6 we see that for the two "ethyls in water," the *right-hand* side of "reaction" *a* will be about 3 times more probable (at 20°C) than the *left-hand* side. On the other hand, the opposite is true for "reaction" *b*, namely, the *left-hand* side is about 1.3 times more probable than the *right-hand* side. This is clearly another manifestation of the HI between the two ethyl groups at the positions 1,2—an aspect that bears important relevance to the role of HI in chemical reactions.

Finally, we note that the HI, as measured by the quantity defined in (4.83), seem to be larger in H₂O as compared with D₂O (Wilf and Ben-Naim, 1979), a result that is consistent with the conclusion arrived at in Section 3.4.

Comment

We believe that the extension of the method described in this section will provide important information on the intramolecular HI and on its dependence on temperature, on pressure, and on the addition of solutes. Furthermore, by changing the "carrier molecule," one can gain some

ideas about the effect of the carrier on the HI. Hopefully, one could eventually extrapolate to real carriers, such as proteins or nucleic acids, in order to understand the role of HI in biopolymers.

4.8. HI IN AQUEOUS MICELLAR SOLUTIONS

In this and in the following section we present a very brief discussion of some properties of more complex aqueous systems. In all of these systems the concept of HI has been involved, in one way or another, in order to explain some of their outstanding properties. The point we shall emphasize here is that though HI certainly plays a role in the determination of the properties of these systems, it is impossible, at present, to extract information on HI from the study of such systems. In this sense we deviate here from the prevailing attitude maintained in this book. The reader should realize that each of the topics touched upon in these two sections consists of a large field of research in its own right. We mention here only a few points that bear some relevance to the problem of HI.

Aqueous micellar solutions may be viewed as intermediate systems bridging the gap between the simple aqueous solutions that we have discussed before, on the one hand, and the more complex biological systems, on the other. In this sense, the study of micelles provides an excellent model through which one can infer, and perhaps understand, the more complex biological solutions. The literature on micelles is quite voluminous; some general reviews are Winsor (1954), Mukerjee and Mysels (1971), Krescheck (1975), and Mittal (1977).

The basic experimental observation is quite simple. A surface-active molecule usually contains a polar "head" group and a nonpolar "tail." These molecules are known to reduce the surface tension when they are added to water—hence the term "surface-active" or "surfactants." The main reason for their doing so is ascribed to the tendency of these molecules (more precisely, the nonpolar part of them) to avoid contact with water and to seek, as far as possible, a nonaqueous environment. It is here that the concept of "hydrophobicity," in the sense of Chapter 2, enters into this field.

When the concentration of the surfactant is gradually increased, one observes systematic deviations from the behavior of ideal dilute solutions. This phenomenon may be ascribed to the formation of small aggregates of solute molecules. This is a common phenomenon shared by many concentrated solutions. What makes aqueous surfactant solutions so

remarkable is that at some small concentration range one finds an abrupt change in the properties of the solution. The concentration (or better the range of concentration) at which this “turning point” occurs is referred to as the “critical micelle concentration” (CMC).

There are many physical properties that may be followed in order to determine the CMC. The most common ones are surface tension and conductivity of the solution.

As an illustrative example, consider the equivalent conductance of aqueous solutions of sodium dodecylsulfate. At very small concentrations of the surfactant there is almost no change in Λ as a function of $c^{1/2}$ (where c is the concentration of the surfactant). Beyond a certain concentration one finds a sharp decrease of the equivalent conductance as a function of $c^{1/2}$. This behavior is demonstrated in Figure 4.21. By drawing the two asymptotes to this curve one determines the CMC from their intersection. As is clear from Figure 4.21, the experimental points do not indicate a well-defined point but a range of concentrations, which is referred to as the CMC.

It is not uncommon to find in the literature statements referring to the “discontinuity” at the CMC. However, though in some cases there is a remarkably sharp transition at the CMC, the function and its derivatives are quite continuous. [See, also, Mukerjee and Mysels (1971), who stressed this point.]

Instead of the conductivity of the solution, one may follow other physical properties of the solution. In all of these the determination of the CMC gives almost the same value of the CMC within 3–5%. This observation indicates that the solution undergoes some fundamental changes in this concentration range. It is now well established that at the CMC large aggregates of surfactant molecules having compact shapes are formed. These are called micelles. A typical structure of a spherical micelle is depicted in Figure 4.22. The main feature of the mode of packing of the

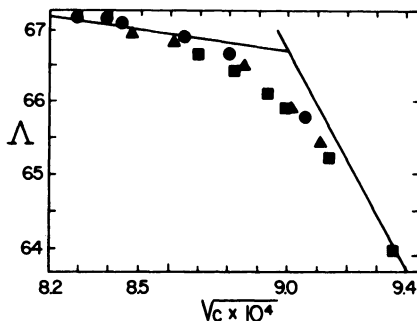


Figure 4.21. Equivalent conductance of aqueous solutions of sodium dodecylsulfate as a function of the square root of the surfactant concentration [reproduced with changes from Mukerjee and Mysels (1971)].

solute molecules in the micelle is that the nonpolar “tails” occupy the interior of the micelle, whereas the “head” groups are exposed to the aqueous environment.

The qualitative rationalization for the formation of this particular structure of the micelle is based on the idea that the nonpolar groups tend to avoid the aqueous environment. By clustering together they obviously achieve that end. Here, again, we have a phenomenon akin to the HI.

Experimental evidence indicates that below the CMC micelles are not formed (or at least are undetectable by all experimental means). Above the CMC it has been established that most of the added surfactant is used to build up micelles. The concentration of the monomeric solute remains fairly constant. If it was exactly constant, then, as was suspected by several authors, we would have a phenomenon similar to a phase transition at the CMC. However, to the best of the author’s knowledge, there exists no experimental evidence to support the phase-separation contention. The very fact that the CMC is not a singular point but rather a small range of concentration, at which the properties of the solution change smoothly precludes the possibility of the existence of a phase transition. In fact, Mukerjee and Mysels (1971) have stressed that the very term “CMC” might be misleading, because of its implication that there exists such a singular point—which is not the case, however. Further discussion of the various theories of micelle formation may be found in a review by Hall and Pethica (1967). We shall demonstrate below that by using a quite simple “mass-action” model for micelle formation one can simulate the characteristic change in the monomer concentration as a function of the total concentration of the surfactant.

Regarding the nature of the interior of the micelles, there is experimental evidence showing that it has the character of both a nonpolar and a water mixture. We present here some evidence that is based on NMR chemical shifts and nuclear spin–lattice relaxation times.

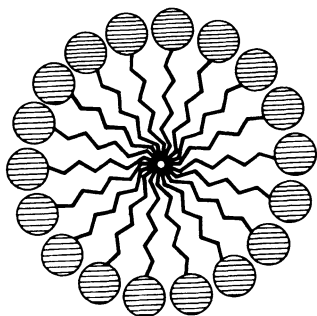


Figure 4.22. Schematic structure of a micelle in aqueous solution.

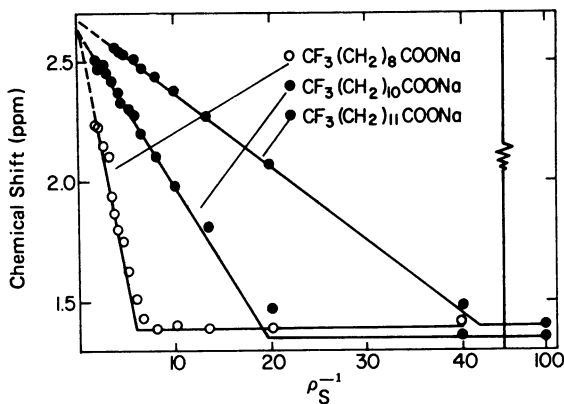


Figure 4.23. Fluorine chemical shifts as a function of ρ_S^{-1} , where ρ_S is the surfactant concentration (in mol/liter). The three surfactant molecules are indicated. [Reproduced with changes from Muller and Birkhahn (1967).]

Muller and Birkhahn (1967) measured the chemical shift of fluorine in solutes of the form $\text{CF}_3(\text{CH}_2)_n\text{COONa}$. We reproduce some of their results in Figure 4.23. From this figure one observes several characteristic features of micellar solutions. In the first place the sharp transition at the CMC is demonstrated. Secondly, we find, as is commonly found by other experimental means, that the larger the alkyl chain the smaller the CMC. In fact, there exists a general correlation between the ability of the surfactant to reduce the surface tension of the solution, and the tendency to form micelles at lower concentration. For a given homologous series, the larger the alkyl group, the more “anxious” the molecules are to form micelles, hence the lower their CMC.

Finally, it is seen from Figure 4.23 that the fluorine chemical shift in very dilute aqueous solutions is the same and about 1.38 for the three solutes and it is almost unchanged as a function of concentration. At the CMC the chemical shift changes abruptly and reaches the value of about 2.66 for the three solutes. The interesting finding is that the latter value of the chemical shift is about midway between that of water and that of pure hydrocarbon. This suggests that the interior of the micelles has the character of a water and hydrocarbon mixture.[†]

Similar data on shorter alkanates have been reported by Ödberg *et al.* (1972) and by Henriksson and Ödberg (1976). We present one of

[†] Of course one should note that the C–F bond is quite polar and therefore it is likely to drag water molecules into the micelle. Hence, from such measurements spurious conclusions may be drawn about water penetration in simple hydrocarbon micelles.

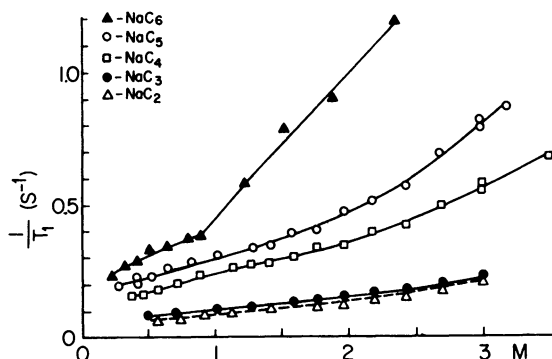


Figure 4.24. Proton spin-lattice relaxation rate for sodium alkananoate as a function of the solute concentration [reproduced with changes from Ödberg *et al.* (1972)].

their results in Figure 4.24. Here, the proton spin-lattice relaxation rate of sodium alkananoate in D_2O solutions was followed as a function of the solute concentration. For the first two alkananoates there is a very slight concentration dependence of T_1^{-1} . For butyrate and valerate, the dependence is more pronounced, indicating the formation of small aggregates. It is only for the caproate solution that a clear-cut CMC is observed. The steep increase of the relaxation rate beyond the CMC is clearly a result of the proximity and high concentration of the protons of the alkyl chains that form the micelles.

We now turn briefly to the thermodynamic description of surfactant solutions, to see where HI might be involved and why it is not a simple matter to extract information on HI from the study of these systems.

First we note that if the micelles are viewed as a separate phase, then the chemical potential of the surfactant S in the two phases is (assuming ideality of the aqueous solution)

$$\mu_S(\text{in micelle}) = \mu_S(\text{in water}) = \mu_S^{\text{oe}} + kT \ln \varrho_S \quad (4.89)$$

If $\mu_S(\text{in micelle})$ is treated as the chemical potential of a “pure” phase, then one would have predicted that ϱ_S is constant and equal to the CMC. Hence, one often writes an equation in the form

$$\Delta G^\circ = \mu_S(\text{in micelle}) - \mu_S^{\text{oe}} = kT \ln(\text{CMC}) \quad (4.90)$$

where ΔG° is interpreted as the “free energy” of transferring S_i from water into the micelle. This interpretation is unsound, however, for the same reasons given in Appendix A.1 (see also Section 2.6). For our present

purposes, the fact that the CMC is not a singular point and the fact that the solute concentration does not remain strictly constant above the CMC are sufficient reasons to abandon the phase-separation model of micellar solutions.

The next, more realistic approach, is to assume a sequential series of association reactions of the form



where A_n is an aggregate consisting of n monomers M . Of course one could, in principle, make a finer distinction between aggregates with the same size n but having different shapes (or packing structures). However, since there are no experimental means to make such a distinction we can lump in A_n all aggregates containing n monomers.

A further assumption that is customarily made for these solutions is that they form an *associated ideal dilute* solution. This means that the solution, when viewed as a two-component system of water W and surfactant S , is *not* an ideal dilute solution. The deviation from the ideal behavior results from the solute-solute interactions. However, if these interactions are of short range, then any n -tuple of simultaneously interacting solutes may be identified as an aggregate and is assigned the symbol A_n . Thus, by definition, all the solute-solute interactions will be contained within the various aggregates A_n . Now, if we view the system as a multicomponent mixture, W, M, A_2, A_3, \dots , we can, to a good approximation, ignore the interactions between these species. This is the basic argument that leads to the idea of an associated ideal dilute solution. Within this model one may write for each solute species the chemical potential in the form

$$\mu_M = \mu_M^{\circ o} + kT \ln \varrho_M \quad (4.92)$$

$$\mu_{A_n} = \mu_{A_n}^{\circ o} + kT \ln \varrho_{A_n}, \quad n = 2, 3, \dots \quad (4.93)$$

where the standard chemical potential $\mu_i^{\circ o}$ of the i th solute species contains essentially the internal partition function of that species and the coupling work of the i th species to an essentially pure water environment (for more details see Appendix A.1). Now, from the condition of chemical equilibrium

$$n\mu_M = \mu_{A_n}, \quad n = 2, 3, \dots \quad (4.94)$$

we obtain the well-known result

$$K_n = \frac{\varrho_{A_n}}{\varrho_M^n} = \exp\left(-\frac{\mu_{A_n}^{\circ o} - n\mu_M^{\circ o}}{kT}\right) \quad (4.95)$$

where K_n is the equilibrium constant for the n th chemical reaction in (4.91). $\mu_{A_n}^{\circ} - n\mu_M^{\circ}$ is the standard free energy of formation of the aggregate A_n . This quantity is related to the free energy of transferring a monomer M from water into the micelle. However, in order to be more precise, one should specify under what conditions this process is carried out. This point is of crucial importance if we want to attempt to extract information relevant to HI from the quantity $\mu_{A_n}^{\circ} - n\mu_M^{\circ}$.

Before elaborating on this, however, it is appropriate at this stage to comment on the practice of using a relation of the form (4.95) with "mole fractions" as concentration units. This practice is quite commonplace and some authors claim that it has some advantages. We shall now show that the use of mole fractions is quite ambiguous, for the following reason: Writing an equation of the form

$$K_n' = x_{A_n}/x_M^n \quad (4.96)$$

and referring to x_M and x_{A_n} as the "mole fractions" of M and A_n leaves a certain ambiguity in the meaning of these "mole fractions." One can think of at least two possible definitions of the "mole fractions" in this system, namely,

$$x_M = \frac{N_M}{N_W + N_M + \sum_{i=2} N_{A_i}} \quad (4.97)$$

and

$$x_M' = \frac{N_M}{N_W + N_M + \sum_{i=2} iN_{A_i}} \quad (4.98)$$

In the first definition we count each aggregate as a different molecular species, whereas in the second we count only the total number of solvent and surfactant molecules in the system. To avoid this kind of ambiguity, one has to specify which definition of the "mole fraction" has been chosen. However, now we face another difficulty, since there is neither a theoretical nor a practical argument that may be used to guide us in making the "proper" choice of the mole fraction. Thus, the ambiguity already exists at the stage of making a choice of the "best" definition for the mole fractions in this system. These difficulties are avoided by using number or molar densities for all the species involved.

Following Mukerjee (1974) we demonstrate in Figure 4.25 the variation of the monomer concentration as a function of the total concentration of the surfactant. In these calculations we have solved Equation (4.95) for different values of n as indicated next to each curve. (The equilibrium constant was arbitrarily chosen to be unity.)

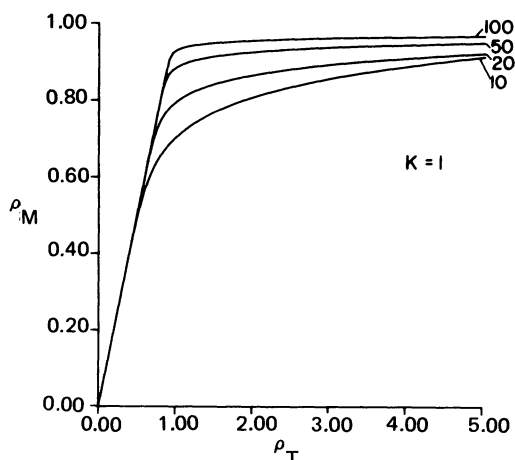


Figure 4.25. Variation of the monomer concentration ϱ_M with the total surfactant concentration ϱ_T for a single aggregation equilibrium with a fixed n . K_n was taken to be unity, and the different curves correspond to different aggregation numbers n .

The remarkable finding is that, with the use of a *single* equilibrium condition (4.95), one finds that a fairly sharp transition in the dependence of ϱ_M on ϱ_T is manifested, provided that n is large enough. We see that in this particular case for $n = 100$ the monomer concentration ϱ_M is almost (but not exactly) constant beyond $\varrho_T \geq 1.0$.

Of course, in a real system, there is no reason to exclude all the intermediate-size aggregates. If one takes a sequential series of aggregates and the corresponding equilibrium conditions (4.95), one can easily show that the change of ϱ_M as a function of the total concentration $\varrho_T = \varrho_M + \sum_{i=2}^n i\varrho_{A_i}$ will be much smoother. This is demonstrated in Figure 4.26. Clearly, one can proceed from the latter to the former case by taking K_n to be small for all n 's except for one, say $n = 50$, for which K_n is large. This is probably what really occurs in micellar solutions. Namely, some aggregation number n^* has a particularly large equilibrium constant, or equivalently, a particularly large (and negative) standard free energy of aggregation $\mu_{A_n}^{\circ} - n\mu_M^{\circ}$. The exact reason for singling out such a specific n , or a small range of n 's, is not known. However, we shall indicate below what might be its origin and how this origin is connected to the problem of HI.

We next turn to analyzing the content of the standard free energy of micellization $\Delta G^{\circ}(A_n)$. In most theoretical treatments of this problem one starts from the assumption that $\Delta G^{\circ}(A_n)$ may be split into two additive contributions. The particular notation and the meaning assigned to the two terms differs from one theory to another [see, for example, Mukerjee (1977), Tanford (1974), Birdi (1977)]; but the common idea is very similar. We write here a general form of such a split of $\Delta G^{\circ}(A_n)$ into two terms

$$\Delta G^{\circ}(A_n) = \Delta G_{RR}^{\circ} + \Delta G_{HH}^{\circ} \quad (4.99)$$

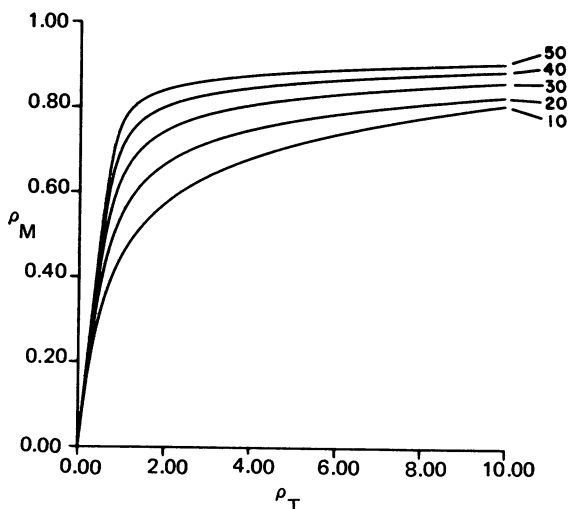


Figure 4.26. Variation of the monomer concentration ρ_M with the total concentration of the surfactant ρ_T for sequential aggregation processes. A series of equations (4.95) were solved for $n = 2, 3, 4, \dots, n_{\max}$. The equilibrium constants were chosen to increase with n as $K_n = \exp[(n - n_{\max})/10]$. This was repeated for $n_{\max} = 10, 20, 30, 40, 50$ as indicated next to each curve.

where ΔG_{RR}° is the contribution due to the alkyl-alkyl free energy of interaction. This term is often described as the negative contribution to $\Delta G^\circ(A_n)$ and is related to the HI. The second, ΔG_{HH}° (often assumed to be positive) is associated with the free energy of interaction between the head groups. (There might be some variations in the meaning of this term according to whether the heads are ionic or nonionic.) The motivation for making the assumption (4.99) clearly stems from the desire to identify the contribution of the HI to $\Delta G^\circ(A_n)$. The argument of “additivity” used in (4.99) is similar to the one used for the dimerization of carboxylic acids, discussed in Section 3.7. The same criticism that we have raised there applies here also: namely, that there exist no theoretical grounds to support such a split, with the specific interpretation assigned to each of the terms ΔG_{RR}° and ΔG_{HH}° . It is at this point that a serious difficulty arises which precludes the extraction of information on HI from the study of micellar formation. We shall demonstrate now the origin of this difficulty and leave some further details to Appendix A.8.

To simplify the argument we consider a rigid monomer surfactant and a rigid spherical micelle built up of n molecules. With this assumption, both the monomers and the micelles have translational and rotational

degrees of freedom, but we ignore any specific reference to internal motions of each species (otherwise we should take proper averages over all possible internal conformations of each species—this complicates the presentation without adding to the argument). Using classical statistical mechanics, one can write $\Delta G^\circ(A_n)$ as

$$\Delta G^\circ(A_n) \equiv \mu_{A_n}^{\circ g} - n\mu_M^{\circ g} = [U(A_n) + kT \ln(q_M^n/q_{A_n})] + \delta G(A_n) \quad (4.100)$$

with

$$\delta G(A_n) = W(A_n | W) - nW(M | W) \quad (4.101)$$

Here $U(A_n)$ is the direct interaction energy of the n monomers at the configuration of A_n . The terms q_M and q_{A_n} include the translational and the rotational partition functions of the monomer and of the micelle, respectively. Thus the term in the square brackets is the standard free energy of formation of the micelle in the absence of the solvent. The contribution of the solvent is included in the term $\delta G(A_n)$. This is essentially the difference between the coupling work of one micelle and n monomers to the solvent, W .

In previous sections when we have dealt with nonpolar solutes we have used the notation δG^{HI} for the solvent contribution to $\Delta G^\circ(A_n)$, and referred to that term as the HI. Here we refrain from doing so since the monomers consist of at least two parts: head and tail. Hence the term $\delta G(A_n)$ may not be properly referred to as the HI term. We can still refer to this term as the solvent contribution to $\Delta G^\circ(A_n)$, whatever it may include.

We now focus on the direct interaction $U(A_n)$. This is the work required to bring n monomers from infinite separation to the final configuration of A_n in vacuum. If one assumes that the heads and tails interact in an additive manner, then we may write

$$U(A_n) = U(HH) + U(RR) + U(HR) \quad (4.102)$$

where $U(HH)$ is the total contribution to the energy of interaction due to the head-head interactions. A similar meaning applies to the other two terms. In particular, we note that we also have the cross term $U(HR)$.

Now, even if to a good approximation the direct interaction is additive (with respect to heads and tails), and even if we can ignore the cross term $U(HR)$, so that

$$U(A_n) \approx U(HH) + U(RR) \quad (4.103)$$

this cannot then lead to a similar split of $\Delta G^\circ(A_n)$ as proposed in (4.99). The reason is that in the first place the term that includes the translational and rotational partition functions in (4.100) may not be interpreted as “belonging” to either ΔG_{RR}° or to ΔG_{HH}° . Second, the quantity $\delta G(A_n)$ is a property of the interaction free energy of the aggregate A_n and the monomers M with the solvent. This again may not be viewed as composed of separate contributions due to head-head and tail-tail interaction as suggested in (4.99). We shall present some more detailed arguments on this point in Appendix A.8. Here, we can conclude that theory does not provide any sound argument to suggest a split of the form (4.99). This split, though admittedly appealing on intuitive grounds, probably stems from the desire to imitate the corresponding additive behavior of the interaction energy, such as in (4.103). The fact that “additivity” may not be transferred from the energy into the free energy of a process has already been demonstrated in Section 4.2.

Thus, although HI certainly plays an important role in the process of micellization, the above analysis shows that there exists no simple way of extracting information on HI from the study of $\Delta G^\circ(A_n)$, as might be suggested from a relation of the form (4.99).

The question of why micelles are formed and what molecular mechanism is responsible for singling out only a small range of aggregate sizes is still unanswered. As we have demonstrated above, one may simulate a sharp transition in the properties of the solution if one assumes a single equilibrium equation of the form (4.95) provided that n is large enough. Such an argument is valid for any phase in which the aggregation occurs, including even an ideal gas. However, we know that singular aggregates of one size do not occur even in water. The more realistic picture is that there exists a sequential series of equilibrium reactions, but one of these n 's, or a small range of them, has a particularly large equilibrium constant (or a particularly large negative standard free energy of aggregation). The question may then be asked, which term in (4.100) might be responsible for such a singular behavior of $\Delta G^\circ(A_n)$ as a function of n ? We know that micellization is a phenomenon that almost exclusively occurs in water. [There are claims that inverted micelles exist in organic liquids. These are usually much smaller aggregates and some doubts regarding their existence have been raised; see, e.g., Kertes (1977).] Therefore, we suspect that it is $\delta G(A_n)$ in (4.101) that is responsible for this phenomenon. In particular, it is probably the nonadditivity effect of the indirect part of the free energy change that causes the singular preference for some specific values of the aggregation numbers n . However, since we know nothing of the nonad-

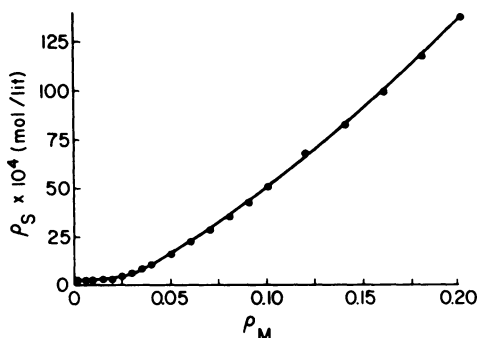


Figure 4.27. Solubility of naphthalene as a function of the concentration of sodium cholate in aqueous solution at 25°C. [Redrawn from Mukerjee and Cardinal (1976).]

ditivity of the HI, even for simpler systems (see Section 4.2), we cannot, at present, go beyond this speculation to find out how this nonadditivity arises from the peculiarities of aqueous systems.

We now briefly turn to an important aspect of micellar solutions which is also relevant to the problem of HI in the sense of Chapter 2. This is the phenomenon of solubilization. The experimental observation is the following. We take a nonpolar solute, such as naphthalene, which is sparingly soluble in water (about 2.55×10^{-4} mol/liter), and dissolve it in aqueous surfactant solution. One finds that in the premicellar region the solubility of the naphthalene changes very slowly with the concentration of the surfactant. At the CMC we find an abrupt change in the solubility of the solute as we add more surfactant. This behavior is illustrated in Figures 4.27 and 4.28. The common and well-justified interpretation of this phenomenon is quite simple. Once micelles are formed, they provide some “pockets” of nonpolar environments in which the nonpolar solute might enter. Since

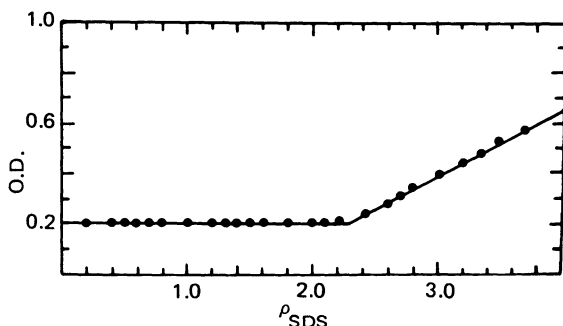


Figure 4.28. Dependence of the optical density (O.D.) of naphthalene in aqueous solutions of sodium dodecylsulfate (SDS) at 25°C. ρ_{SDS} is the total concentration, in grams per liter of SDS. These measurements were carried out in the presence of excess naphthalene. [Redrawn with changes from Birdi (1976).]

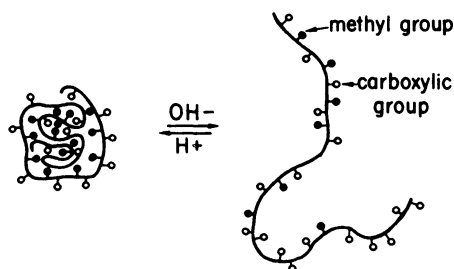
Thus the two polymers are essentially polyelectrolytes; in PMA we have an additional methyl group that is missing in PAA. Therefore, the difference in their behavior in aqueous solutions is largely attributed to the effect of the additional methyl group—hence the relevance to the problem of HI.

Experimental evidence indicates that the PMA in an acidified aqueous medium (i.e., when all the carboxylic groups are not charged) attains a compact structure. Upon increasing the pH of the solution, the compact structure breaks down and we get a random coil polyelectrolyte. The difference in the state of packing of the polymer may be followed, for example, through measurements of the intrinsic viscosity of the solution $[\eta]$. The interpretation of this phenomenon is quite simple. The intrinsic viscosity is related to the radius of gyration of the molecules, and hence gives a rough measure of the compactness of the polymer. At high pH values, the carboxylic groups are ionized and the charge-charge interaction between them tends to open up the conformation of the polymer. At low pH values, when the carboxylic groups are not ionized, the intramolecular hydrophobic interaction drives the conformational equilibrium towards the compact structure. The situation is schematically depicted in Figure 4.29. We have here a simple demonstration of the two competitive effects (the charge-charge vs. the hydrophobic interaction effects) on the conformational equilibrium of the polymer.

A similar effect is observed upon the addition of methanol, ethanol, or higher alcohols to aqueous solutions of PMA. Figure 4.30 shows the reduced intrinsic viscosity of aqueous solutions of PMA as a function of the mole fraction of alcohols. The overall effect of alcohol is to increase the intrinsic viscosity of the solution—a rough indication that the compact structure of the polymer breaks down at high concentration of the alcohol.

At very low alcohol concentration, however, one finds an opposite effect of the alcohol, namely, a decrease of the reduced intrinsic viscosity, indicating a stabilization of the compact form of the polymer. (All of

Figure 4.29. The two conformations of PMA. Increasing the pH shifts the equilibrium to the right, towards an open conformation. Decreasing the pH shifts the equilibrium to the left, towards a more compact conformation.



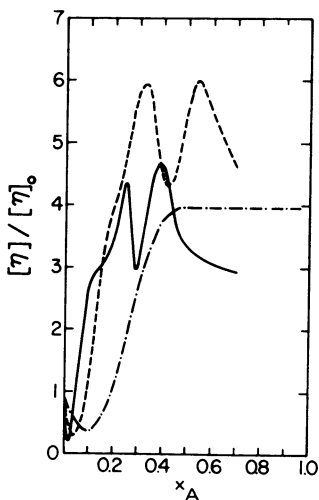


Figure 4.30. Reduced intrinsic viscosity of PMA in 0.002 *N* HCl, as a function of the mole fraction of methanol (— · —); ethanol (—); and *n*-propanol (— —). $[\eta]_0$ is the intrinsic viscosity in 0.002 *N* HCl. All measurements were carried out at 30°C. [Redrawn with changes from Priel and Silberberg (1970).]

these effects are observed in acidic solutions in which the charge-charge repulsion is not significant.)

The interpretation of the effect of the alcohol on the conformation of the PMA is based on the effect of alcohol on the HI. Thus, small amounts of alcohol ($x \lesssim 0.02$) seem to *increase* the strength of the HI, hence the conformational equilibrium is shifted towards the more compact form, as revealed by the lowered intrinsic viscosity. At high concentrations of alcohols the HI are weakened and the polymer opens up. This interpretation is consistent with what we have learned already on the effect of alcohol on the HI (except for the very small region of alcohol concentration where we have found, in Section 3.4, an initial weakening of the HI; this region is not revealed in these experiments, probably because of the presence of the HCl in the solution; thus the initial effect of the alcohol measured here is not relative to pure water, but relative to water and HCl).

It should be noted that similar effects are not observed in PAA. This lends further support to the interpretation that the observed effect of alcohol is largely due to the presence of the methyl groups in PMA. Priel and Silberberg (1970) have studied, in great detail, the properties of these solutions. As we have noted before, the concept of HI was found very useful in the interpretation of the observed trends. Unfortunately, one cannot extract any quantitative information on the strength of the HI from such studies.

A closely related phenomenon, which is reminiscent of the solubilization phenomenon, is also observed in aqueous solutions of PMA. Barone

et al. (1966) have compared the solubility of low paraffins in aqueous solutions of PMA and PAA. The most striking difference between the two polymers is the following: An unneutralized solution of PMA causes a net solubilization effect on the alkenes. This effect increases with the molecular weight of the PMA. No similar effect has been observed for solutions of PAA.

We report in Table 4.7 some of their results for both alkenes and for large aromatic molecules. Note that the effect of addition of PMA is rather small for the low alkenes. It is quite pronounced for *n*-hexane, the solubility of which increases about fourfold compared with pure water. The solubilization effect is far more dramatic for the aromatic molecules, where an increase in solubility of more than an order of magnitude is observed. (Of course, that depends on the concentration and the molecular weight of the polymer.)

The interpretation of this effect is similar to the solubilization effect of micellar solutions. There, we encountered a solution of surfactant molecules which above some concentration form nonpolar regions that can absorb nonpolar solutes. Here, on the other hand, we have a polymer, which under certain conditions (say low pH) attains a compact form, in

Table 4.7

Solubility of Alkenes (mol/liter at 25°C) in Water and in Unneutralized Solution of 0.4 *N* PMA (mol wt = 1.4×10^4)^a and the Solubilities of Aromatic Hydrocarbons in Water and in Unneutralized Solution of 0.1 *N* PMA (mol wt = 85×10^4)^b

| Solute | Solubility in water | Solubility in PMA solution |
|-------------------|------------------------|----------------------------|
| Cyclopropane | 11.10×10^{-3} | 11.24×10^{-3} |
| Propane | 1.50×10^{-3} | 1.83×10^{-3} |
| <i>n</i> -Butane | 1.09×10^{-3} | 1.37×10^{-3} |
| <i>n</i> -Pentane | 1.03×10^{-3} | 2.27×10^{-3} |
| <i>n</i> -Hexane | 0.96×10^{-3} | 3.77×10^{-3} |
| Phenanthrene | 9.0×10^{-6} | 2.7×10^{-4} |
| Anthracene | 4.47×10^{-7} | 0.31×10^{-4} |
| Pyrene | 7.7×10^{-6} | 2.08×10^{-4} |
| 1,2-Benzpyrene | 2.9×10^{-8} | 0.67×10^{-4} |
| 3,4-Benzpyrene | 1.6×10^{-8} | 1.25×10^{-4} |

^a From Barone *et al.* (1966).

^b From Barone *et al.* (1967).

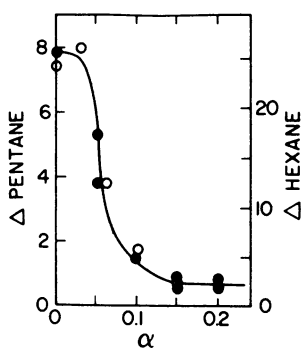


Figure 4.31. Dependence of the enhancement of the solubility Δ of *n*-pentane and of *n*-hexane as a function of the degree of neutralization of PMA at 25°C; open circles are for *n*-pentane, filled circles for *n*-hexane. [Redrawn with changes from Barone *et al.* (1966).]

the interior of which nonpolar molecules may be accommodated. The capability to form such a compact conformation is largely ascribed to the HI among the methyl groups of the PMA. No such effect has been observed in PAA solutions.

It is interesting to follow the extent of the solubilization effect upon changing the pH of the solution.

We define the relative enhancement of the solubility of a nonpolar solute *S* per unit concentration of the polymer by

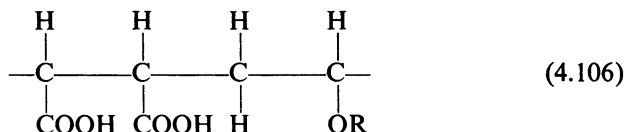
$$\Delta = \frac{\varrho_S(\text{in PMA solution}) - \varrho_S(\text{in water})}{\varrho_S(\text{in water})\varrho_{\text{PMA}}} \quad (4.105)$$

where ϱ_S is the solubility (in mol/liter) of the solute *S*, and ϱ_{PMS} is the polymer concentration.

Figure 4.31 shows the values of Δ for *n*-pentane and *n*-hexane as a function of the degree of neutralization α . The case $\alpha = 0$ corresponds to the unneutralized PMA, i.e., the case when the polymer has a compact structure and hence is capable of absorbing nonpolar solutes. As we increase the value of α , which corresponds to increasing the pH of the solution, the relative enhancement of the solubility, Δ , drops sharply to almost zero value. This is clearly a manifestation of the conformational change that takes place—from the globular to the random coil structure. Similar behavior has also been reported for aromatic solutes (Barone *et al.*, 1967). Again, it was reported by the same authors that no such effects were observed in the case of PAA.

Similar effects of solubilization of simple solutes, such as butane and pentane, by proteins have been observed [see for example Wishnia (1962), Wishnia and Pinder (1964, 1966)]. We have chosen to illustrate the effect of solubilization in a relatively simple polymer where many of the complexities of real biopolymers are eliminated.

We now turn to a slightly more complicated system. Dubin and Strauss (1970) have studied the properties of alternating copolymers of maleic and *n*-alkylvinyl ethers in aqueous solutions. The monomer unit is



The alkyl groups were chosen to be methyl, ethyl, butyl, and hexyl. Clearly one would expect that for the small alkyl groups, the behavior of the polymer would resemble that of a typical polyelectrolyte. For the larger alkyl groups, the intramolecular HI are expected to favor (at least at low pH values) the formation of the compact structures. For this reason, these molecules provide good models for the systematic study of the effect of HI on the conformation of the polymers.

In Figure 4.32 we present some potentiometric titration data on aqueous solutions of these polymers. Here we follow the pH of the solution as a function of the degree of neutralization α of the polymer. The case $\alpha = 0$ corresponds to the unneutralized polymer where the charge-charge

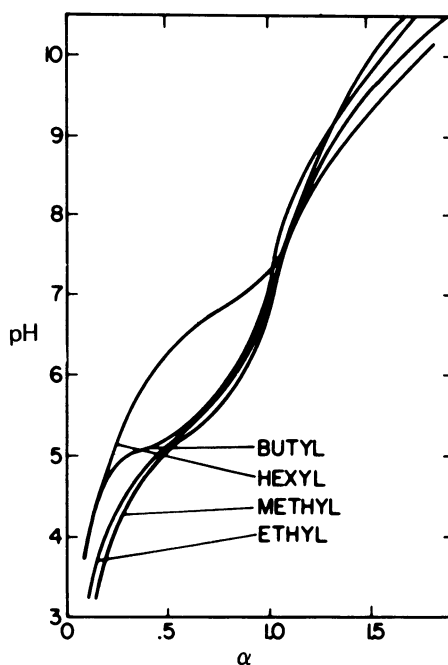


Figure 4.32. Potentiometric titration of aqueous solutions of copolymers of maleic acid and *n*-alkyl vinyl ethers, at 30°C. The alkyl groups are methyl, ethyl, butyl, and hexyl, as indicated. [Reproduced with changes from Dubin and Strauss (1970).]

interactions are relatively minor. The case $\alpha = 2$ corresponds to complete neutralization of the polymer (note that there are two carboxylic groups per monomer), hence the predominance of the charge-charge repulsive forces.

For the methyl and ethyl radicals, we find an almost linear dependence of the pH on α —this is considered to be the “regular” behavior of the polyelectrolyte. For the butyl and the hexyl radicals, a considerable deviation from the regular behavior is observed. We see that for the larger alkyl groups a considerable change in the pH, say from pH = 3 to pH = 5, has almost no effect on α . This clearly indicates a retention of the compact form of the polymer. The larger the alkyl group, the stronger the intramolecular HI, and the stronger is the resistance of the polymer to opening up its compact structure upon increasing the pH.

Next we turn to real biopolymers. Here HI might enter on various levels, from conformational changes of a single biopolymer, to a combination of a substrate to an enzyme, to association of subunits to form multi-subunit enzymes, etc. One of the central problems in molecular biology is the way in which a polypeptide that has just been synthesized folds itself into the “native” structure of the protein. It is known that such a process occurs spontaneously. What is less understood is the mechanism of this process. Does the polymer proceed by way of trial and error to search for its most stable conformation, or is there a well-defined path, which is dictated by the sequence of the amino acids, along which the folding process takes place? Estimates indicate that a random search for the “native” conformation would take too long a time. It seems likely, therefore, that the sequence of amino acids contains the information required to find an efficient path for folding up. In this process hydrogen bonds and hydrophobic interaction might play crucial roles.

Regarding the final (secondary and tertiary) structure of the protein, it has been established recently that in some proteins the so-called hydrophobic amino acids occupy the interior, and the polar amino acids the exterior of the protein. This arrangement is beautifully illustrated by the structure of cytochrome *c* (Dickerson, 1972). Clearly, this particular product is a result of the tendency of the “hydrophobic” amino acids to gather together, so as to minimize their exposure to the aqueous environment.

The next level in which we find the involvement of HI is in the so-called quaternary structure, i.e., the way subunits associate to form multisubunit proteins, such as hemoglobin, regulatory enzymes, ribosomes, etc. An interesting example, in which the concept of HI has also led to a practical application, is the case of sickle cell anemia.

It is well known that the normal hemoglobin molecule (Hb A) consists of four chains of amino acids. Two are identical α -chains (with 141 amino acid residues each) and two are β -chains (with 146 amino acid residues each). The association of these four subunits to form the Hb A molecule probably also involves HI, but this is not the point we would like to stress here.

Sickle cell anemia is a hereditary disease caused by an abnormal form of hemoglobin, referred to as Hb S. It is found that when the oxygen content of the blood is high, most of the blood cells have the normal round shape. However, at low oxygen content, a variety of forms of cells are observed, and some of them have the crescent shape—hence the name “sickle cells.”

It is now known that the abnormal hemoglobin is almost identical to the normal Hb A except for *one* amino acid: a valine substitutes for glutamic acid at position 6 of the β -chain. It should be noted that the location of this amino acid is on the exterior of the molecule (Cerami and Peterson, 1975), hence one may expect that this substitution will cause an overall increase of the “hydrophobicity” of the hemoglobin molecules. This fact led to the contention that the abnormal form of hemoglobin tends to aggregate in an abnormal fashion, and that this process is the primary molecular reason for the sickle cell disease. The involvement of HI in the aggregation process has suggested also a method of treatment. The basic idea is that administration of solutes that weaken the HI might help to reverse, or perhaps prevent, the abnormal aggregation of Hb S. Indeed, some solutes such as urea and cyamate have been used as anti-sickling agents [for a review, see Murayama (1973)]. Of course, the process is more complex than merely association involving purely HI. However, this is an interesting example that demonstrates the use of the concept of HI both in the understanding of a biological phenomenon and in providing a guide for a possible molecular therapy.

There are many other more complicated processes of self-assembly of subunits to form large functional proteins. Examples are the recombination of the 21 proteins and the RNA to form the small subunit of ribosome (the 30S component), and the spontaneous reassembly of subunits and RNA to form the tobacco mosaic virus (TMV), which consists of a large number of identical subunits.

It is often claimed that the spontaneous association process indicates that the information for this process is already contained in the primary structure of the proteins. This might be true; however, it could also be the result of the structural dependence of the nonadditivity effect of the HI (see Section 4.2). In other words, if the subunits “know” how to associate

because of some sort of genetic information that is carried within the sequence of the amino acids, then they should “know” to do the same thing in any medium—not necessarily aqueous solutions—and the whole question of the involvement of HI becomes irrelevant to such processes. On the other hand, if spontaneous association processes take place exclusively in aqueous solutions, then we may suspect that HI are indeed involved. This is likely to originate from the nonadditivity part of HI, an aspect about which we still know nothing.