

# Hydrogen-Bonding Cooperativity and Competing Inter- and Intramolecular Associations: A Unified Approach

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Cooperativity in hydrogen bonding has been repeatedly invoked in the literature. Very often a distinction is made between the association constant for the “dimer” formation and the corresponding constant for the formation of association complexes beyond dimer. This work examines this cooperativity hypothesis and proposes a straightforward manner of integrating it in the framework of the lattice-fluid hydrogen-bonding (LFHB) equation-of-state model. This integration is done without altering the basic rationale of the LFHB model for the enumeration of hydrogen bond configurations for the self-association and cross-association in the system. The model can accommodate hydrogen bond cooperativity in complex systems, even polymer mixtures forming three-dimensional networks of hydrogen bonds, and permits its study over an extended range of temperatures and pressures. As additional examples of the applicability of the method, the formation of cyclic associates and of intramolecular hydrogen bonds is also examined.

## Introduction

Hydrogen bonding is an important subject for both science and technology that has attracted over time the intensive interest of chemists, physicists, biologists, and engineers. Quantum and molecular mechanics on one hand and spectroscopy on the other have extensively been used for modeling and measuring hydrogen-bonding interaction forces.<sup>1–9</sup> Hydrogen-bonding interactions, being stronger and having a much longer lifetime than the ordinary van der Waals interactions, are often referred to as “chemical” interactions. The latter implies the formation of association complexes (dimers, trimers, etc.) or “associates”. Although the very existence of these associates as distinguishable molecular entities is a matter of controversy in the literature, it has been invoked often in the past and forms the backbone of the so called *association* approach.<sup>10</sup> We have followed this approach in the past for studying systems like alkanol–alkane mixtures,<sup>11</sup> alkanol–amine mixtures,<sup>12</sup> and polymer solutions in which the polymer can cross-associate with a self-associating solvent.<sup>13</sup>

For the description of the thermodynamic behavior of hydrogen-bonded networks, such as the aqueous systems or the mixtures of self-associated and cross-associated polymers, we realized that the above approach is confronted with a formidable combinatorial problem and another approach had to be followed. For aqueous systems, Levine and Perram<sup>14</sup> and Luck<sup>15</sup> have proposed an alternative approach where the focus was on the equilibrium of the formation and rupture of hydrogen bonds and not on the equilibrium of formation of the various associates. More recently and along these lines, in a lucid note,<sup>16</sup> Veytsman has proposed an approximate *combinatorial* expression for the number of ways of forming hydrogen bonds in systems of molecules with one type of proton-donor group and one type of proton-acceptor group that does not invoke the existence of associates but, instead, focuses on the donor–acceptor contacts.

Panayiotou and Sanchez<sup>17</sup> have properly generalized this latter *combinatorial* approach and incorporated it in an equation-of-state framework leading to an equation-of-state theory of fluids, known as lattice-fluid hydrogen-bonding (LFHB) model. For this generalization a clear rationale of the contact–counting process had to be followed. This model has been applied so far in diverse complex systems such as mixtures of poly(vinyl phenol) with poly(vinyl acetate),<sup>18</sup> polyoxalcohol/polyether systems,<sup>19</sup> hydrogels,<sup>20</sup> and recently in starch/water mixtures.<sup>21</sup> The above two approaches, namely, the *association* approach, and the *combinatorial* approach, are compared in a recent review.<sup>22</sup>

In the association approach, it is a common practice, especially in phase equilibrium and related thermodynamic calculations, to assign one value of the equilibrium constant for the association reaction



independent of the size  $n$  of the association complex. Thus, so far in both the association and the combinatorial approach, we have used one equilibrium constant for each type of donor–acceptor bond in the studied systems, regardless of the size of the associate, dimer or multimer.

Careful spectroscopic studies, however, over the last few decades have revealed that it is not always possible to explain the experimental data with only one equilibrium constant.<sup>1,3,6–9</sup> Very often spectroscopists use two, instead of one, equilibrium constants for the above association: one for the monomer/dimer association ( $K_d$ ) and one for the equilibria among the higher complexes ( $K_\infty$ ). Usually  $K_d$  is several times smaller than  $K_\infty$ , and the effect is called *hydrogen bond cooperativity*. The first theoretical justification for this came from the statistical treatment of associated solutions by Sarolea-Mathot,<sup>23</sup> who predicted that  $K_d$  should be smaller than  $K_\infty$  by a factor  $f$ , where

$f$  is the number of possible energetically equivalent orientations of the monomer. Thus, this difference is ascribed to an entropy factor: the entropy loss when two monomers form a dimer being greater than when only one monomer and a higher multimer unite. This association approach is discussed also by Coleman et al.<sup>24</sup>

Apart from the classical association approach, two complementary theoretical approaches for the hydrogen bond cooperativity have appeared recently in the literature.<sup>25,26</sup> Veytsman,<sup>25</sup> after describing the general case, focuses on the combinatorial problem in the simplest possible case: a fluid whose molecules have one donor group and one acceptor group with association constants  $K_d$  and  $K_\infty$  for the formation of dimers and higher multimers, respectively.

The hydrogen bond cooperativity is treated in the work of Sear and Jackson<sup>26</sup> by including in the association energy a three-body term which either increases or decreases the strength of the bonds in chains of three or more molecules. Their model (in essence, an association model) is able to account for the effect of density on the degree of association, and thus, it can describe vapor–liquid equilibria.

Two related aspects of hydrogen bonding of significant interest are the formation of cyclic associate structures and intramolecular hydrogen bonds, which are sometimes favored by forming stable cyclic structures.<sup>5</sup> Often intramolecular hydrogen bonding is an important contribution to the overall hydrogen bonding, especially, in systems of biological interest. Of interest to spectroscopists is the case of very dilute systems in inert solvents where intermolecular hydrogen bonding is absent and the only observed hydrogen bonds are the intramolecular ones.

In this series of papers we will study hydrogen bond cooperativity and intramolecular hydrogen bonding in rather complex systems such as polyoxalcohols, polyesters, and aqueous polymer solutions. This, however, requires the development of a generalized framework for easily handling hydrogen bonding in these complex cases. The objective of the present work is to show how the very same generalized rationale of the LFHB model,<sup>17</sup> which embodies the Veytsman statistics,<sup>16</sup> for the hydrogen bond enumeration process in self-associated and cross-associated systems can be applied to the cooperativity, cyclic associate formation, and intramolecular-hydrogen bonding problems. By adopting this rationale one can treat various aspects of hydrogen bonding in a straightforward manner, even in complex cases. This enumeration process will be exemplified by applying it to various cases of practical interest, especially in the case of cooperativity. The hydrogen-bonding term, in a more general case, will be incorporated into the lattice-fluid framework<sup>17</sup> leading to an equation-of-state theory of fluids with hydrogen bond cooperativity, which may easily be applied to vapor–liquid equilibria, as previously.<sup>11</sup>

## The Model

The systems of our interest here are systems containing molecules with groups of type 1 having one donor and one acceptor site (self-associating groups), such as the  $-\text{OH}$  groups. In the system there may be molecules with groups of type 2 with one acceptor site, such as  $-\text{C}=\text{O}$  or  $\text{R}_3\text{N}$ . If the same molecule has various groups 1 and 2, we assume for simplicity that they are sufficiently far apart so that they remain unaffected by the association of other groups of the molecule. Thus, in the frame of this work, we will have hydrogen bonds of types 1–1 and 1–2 for the self-association and cross-association, respectively.

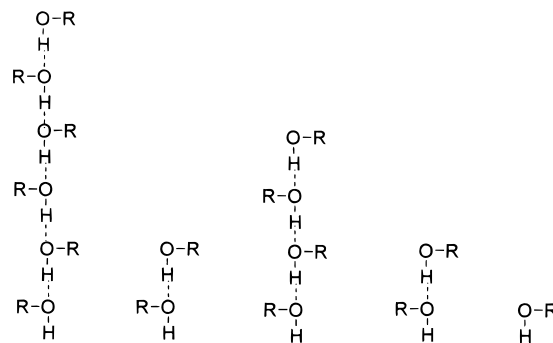


Figure 1. One configuration of a system with  $N = 15$  and  $N_{11} = 10$ .

The presentation in this paragraph will heavily be based on our previous work,<sup>17</sup> where the details of the original LFHB theory are presented.

As in the LFHB model, the partition function  $Q$  of our system is factored into a physical,  $Q_P$ , and a chemical or hydrogen-bonding,  $Q_H$ , term, or

$$Q = Q_P Q_H \quad (1)$$

We will focus attention first on the chemical factor. According to the LFHB model, this term may, in general, be written as

$$Q_H = \left( \frac{\tilde{p}}{rN} \right)^{N_H} \Omega \exp \left( - \frac{\sum N_{ij} G_{ij}^0}{kT} \right) \quad (2)$$

where  $N$  is the total number of molecules in the system,  $N_{ij}$  is the number of hydrogen bonds of type  $i-j$  characterized by a free energy change  $G_{ij}^0$ , and  $N_H = \sum N_{ij}$  is the total number of hydrogen bonds in the system. The term  $\tilde{p}/r$  will be explained later, but for the moment it may be considered a constant. The preexponential factor  $\Omega$  is the number of different ways of distributing the hydrogen bonds in the system without requiring that donor and acceptor groups be neighbors. This requirement of donor/acceptor proximity is taken into account by the first term in the rhs of the above equation.<sup>17</sup> The focus now is on the statistical derivation of  $\Omega$ . The method will be explained first by applying it to cases where we do not have bond cooperativity.

**The Enumeration of Configurations.** Let us recall first the rationale of the LFHB enumeration process and apply it to a simple case.

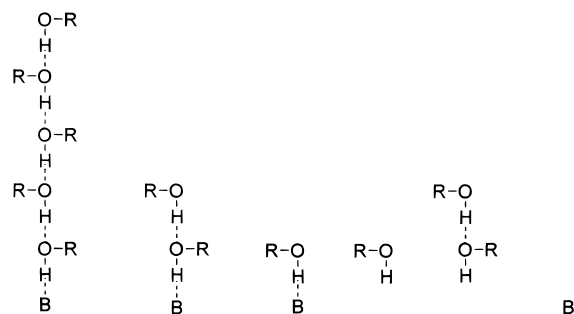
**Case 1:** Molecules with one proton donor and one acceptor group which self-associate but not cooperatively.

In order to find the different number of isoenergetic configurations of our system (number of the different ways of forming or distributing the hydrogen bonds in the system), we have to do the following:

- Find the number of different ways of selecting the associated donor sites from the donor population.
- Find the number of different ways of selecting the associated acceptor sites from the acceptor population.
- Find the number of different ways of making hydrogen bonds between the selected donor and acceptor sites.

The number of configurations of the system is the product of these three terms (a through c).

As a simple example, let us have a system with  $N$  molecules each having one donor and one acceptor site (1) with  $N_{11}$  hydrogen bonds among them. In Figure 1, the group 1 is  $-\text{O}-\text{H}$ . The number of ways of selecting the  $N_{11}$  associated donors from the donor population  $N$  is just the binomial coefficient  $N!/(N - N_{11})!N_{11}!$ . Similarly, the number of ways of selecting



**Figure 2.** One configuration of a system with  $N_1 = 11$ ,  $N_2 = 4$ ,  $N_{11} = 6$ , and  $N_{12} = 3$ .

the  $N_{11}$  associated acceptors from the acceptor population  $N$  is again the binomial coefficient  $N!/(N - N_{11})!N_{11}!$ . The free donor groups in the system are  $N - N_{11} = N_{10}$ . This is also the number of free acceptor groups in this particular system. Now, a specific donor can hydrogen bond with any of the  $N_{11}$  acceptors, a second donor can hydrogen bond with any of the remaining  $N_{11} - 1$  acceptors, and so on. The number of ways that  $N_{11}$  bonds can be formed between  $N_{11}$  donors and  $N_{11}$  acceptors is just  $N_{11}!$ . Thus, the total number of ways that  $N_{11}$  bonds can form between  $N$  donors and  $N$  acceptors is the product of the above three terms, or

$$\Omega = \frac{N!}{(N - N_{11})!N_{11}!(N - N_{11})!N_{11}!}$$

$$N_{11}! = \frac{N!}{N_{10}!} \frac{N!}{N_{10}!N_{11}!} \quad (3)$$

**Case 2:**  $N_1$  molecules or groups 1 that self-associate and  $N_2$  molecules or groups 2 that cross-associate only with groups 1. In the system let there be  $N_{11}$  and  $N_{12}$  bonds of type 1–1 and 1–2, respectively (in Figure 2 the groups 1 and 2 are 1 = –O–H, 2 = B). Then, the free donors 1 are  $N_1 - N_{11} - N_{12} = N_{10}$  (the inner lower index is the donor) and the free acceptors 2 are  $N_2 - N_{12} = N_{02}$ . Following the above enumeration procedure, we must select first, out of the donor population  $N_1$ , the  $N_{11}$  and  $N_{12}$  donors participating in hydrogen bonds 1–1 and 1–2, respectively. This can be done in  $N_1!/[N_{10}!N_{11}!N_{12}!]$  ways. The  $N_{11}$  associated acceptors 1 can be selected in  $N_1!/[N_{11}!(N_1 - N_{11})!]$  ways, and the  $N_{12}$  associated acceptors 2 in  $N_2!/[N_{12}!(N_2 - N_{12})!]$  ways. Now, the bonds  $N_{11}$  between the  $N_{11}$  donors and the  $N_{11}$  acceptors can be done again in  $N_{11}!$  ways and, similarly, the  $N_{12}$  bonds can be done in  $N_{12}!$  ways. Thus,  $\Omega$  in this case is

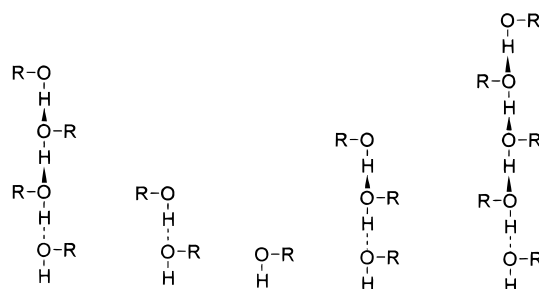
$$\Omega = \frac{N_1!}{N_{10}!N_{11}!N_{12}!} \frac{N_1!}{(N_1 - N_{11})!N_{11}!} \times$$

$$\frac{N_2!}{(N_2 - N_{12})!N_{12}!} N_{11}!N_{12}!$$

$$= \frac{(N_1!)^2 N_2!}{N_{10}!(N_1 - N_{11})!N_{11}!(N_2 - N_{12})!N_{12}!} \quad (4)$$

Let us now turn to hydrogen bond cooperativity.

**Case 3:** Molecules or groups whose self-association is cooperative. Let us consider a system similar to the system examined by Veytsman,<sup>25</sup> namely, a system of  $N$  molecules with one proton donor and one acceptor site (–O–H groups), which self-associate forming  $N_{11}$  bonds. However, the first dimer



**Figure 3.** One configuration of a system with  $N = 15$ ,  $N_{11} = 10$ . Out of the 10 bonds there are  $N_d = 4$  weak dimerlike bonds marked with dashed lines.

bond, now, is weaker than any subsequent bond in a multimer (trimer, tetramer, etc.) complex. In fact, it is not important for the enumeration of bonds whether the dimer bond is weaker or stronger than the others; it is sufficient that it be distinguishable.

The strength of a bond is assumed to depend on the state of the acceptor site. Thus, the acceptor sites of the molecules with the  $N - N_{11} = N_{10}$  free donors (elements of the lowest row in Figure 3) are interacting weakly. All other acceptor sites (acceptors above the first row in Figure 3) are assumed to be interacting with bonds of higher but the same strength.  $N_d$  of the  $N_{10}$  weak acceptors participate in the weak bonds of the system (initial dimerlike bonds).

Following the enumeration method of LFHB, we must choose first the donors that will be bonded in  $N_{11}$  bonds. It can be done in  $N!/(N_{10}!N_{11}!)$  ways. Having selected the  $N_{10}$  free donors, we have also selected the  $N_{10}$  “weak” acceptors 1 (the same OH group). Out of these  $N_{10}$  weak acceptors we must choose the  $N_d$  acceptors which participate in the (weak) hydrogen bonds. This can be done in  $N_{10}!/[N_d!(N_{10} - N_d)!]$  ways. Since we recognized that the acceptors in the groups with the free donors are weak, we must choose, out of the remaining  $N - N_{10} = N_{11}$  acceptors, the associated  $N_{11} - N_d$  ones that will participate in the strong bonds. This can be done in  $N_{11}!/[N_d!(N_{11} - N_d)!]$  ways. Since we have strong and weak acceptors, we must choose, out of the  $N_{11}$  associated donors, the  $N_d$  which will associate with the weak acceptors and the  $N_{11} - N_d$  which will interact with the strong acceptors. This can be done in  $N_{11}!/[N_d!(N_{11} - N_d)!]$  ways. Having selected the interacting donors and acceptors, the number of different ways that they can interact to form the  $N_d$  weak 1–1 bonds and the  $N_{11} - N_d$  strong 1–1 bonds is  $N_d!(N_{11} - N_d)!$ . Thus,  $\Omega$  is the product of the above terms, or

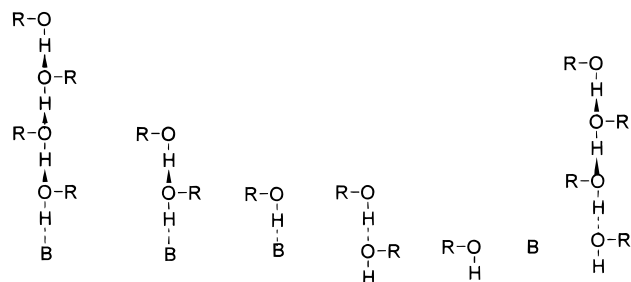
$$\Omega = \frac{N!}{N_{10}!N_{11}!} \frac{N_{10}!}{N_d!(N_{10} - N_d)!} \frac{N_{11}!}{(N_{11} - N_d)!N_d!} \times$$

$$\frac{N_{11}!}{(N_{11} - N_d)!N_d!} N_d!(N_{11} - N_d)!$$

$$= \frac{N!N_{11}!}{(N_{10} - N_d)!(N_{11} - N_d)!(N_d!)^2} \quad (5)$$

which is identical to Veytsman’s result.<sup>25</sup>

**Case 4:** Same as case 2 but, now, there is cooperativity in self-association 1–1. Let us have again  $N_1$  and  $N_2$  molecules (groups) between which there are  $N_{11}$  self-association and  $N_{12}$  cross-association bonds (1 = –O–H, 2 = B). However, now, the bond for dimer formation is weaker than any subsequent bond of the multimer complex.



**Figure 4.** One configuration of a system with  $N_1 = 14$ ,  $N_2 = 4$ ,  $N_{11} = 8$ , and  $N_{12} = 3$ . Out of the 8 1–1 bonds  $N_{d1} = 2$  are weak dimerlike bonds marked with dashed lines.

For simplicity we will consider that in a complex 1–1–1...–1–1–2, the bond 1–1 next to the 1–2 bond is as strong as any other 1–1 bond beyond the first dimer bond in a 1–1–1...–1–1 multimer (bond cooperativity), as shown in Figure 4. In the system there are  $N_{10} = N_1 - N_{11} - N_{12}$  free donors of type 1 and  $N_{11} + N_{12}$  “strong” acceptor groups of type 1. These acceptors are shown in Figure 4 located above the lowest row of acceptors. The strength of the 1–2 bonds is not important; it is sufficient that it be the same for all 1–2 bonds.

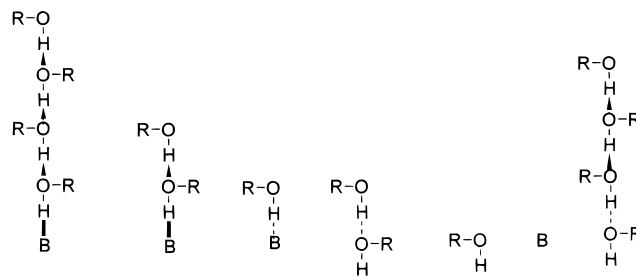
In this case,  $\Omega$  can be obtained as follows: The  $N_{11}$  and  $N_{12}$  interacting donors 1 can be selected in  $N_1!/[N_{10}!N_{11}!N_{12}!]$  ways. As in the previous case, with the selection of the  $N_{10}$  free donors we have also selected the  $N_{10}$  weak acceptors 1. Out of these, the associated  $N_{d1}$  acceptors can be selected in  $N_{10}!/[N_{d1}!(N_{10} - N_{d1})!]$  different ways. Since the  $N_{10}$  acceptors 1 (at the groups of the free donors) have been recognized to be weak, we are left to choose, out of the remaining  $N_1 - N_{10}$  acceptors 1, the acceptors that will participate in the  $N_{11} - N_{d1}$  strong bonds. It can be done in  $(N_1 - N_{10})!/[(N_1 - N_{10} - (N_{11} - N_{d1}))!(N_{11} - N_{d1})!]$  ways. Out of the  $N_{11}$  interacting donors 1 we must select the  $N_{d1}$  and  $N_{11} - N_{d1}$ , which associate with the weak and the strong acceptors, respectively. This can be done in  $N_{11}!/[N_{d1}!(N_{11} - N_{d1})!]$  different ways. The  $N_{12}$  interacting acceptors 2 can be chosen in  $N_2!/[N_2!N_{12}!]$  ways. The  $N_{11}$  and  $N_{12}$  interacting donors can be combined with the  $N_{d1}$  weak acceptors 1, the  $N_{11} - N_{d1}$  strong acceptors 1, and the  $N_{12}$  acceptors 2, in  $N_{d1}!(N_{11} - N_{d1})!N_{12}!$  ways. Thus,  $\Omega$  is given by

$$\Omega = \frac{N_1!}{N_{10}!N_{11}!N_{12}!} \frac{N_{10}!}{N_{d1}!(N_{10} - N_{d1})!} \frac{(N_{11} + N_{12})!}{(N_{11} - N_{d1})!(N_{12} + N_{d1})!} \times \frac{N_{11}!}{N_{d1}!(N_{11} - N_{d1})!} \frac{N_2!}{N_{12}!(N_2 - N_{12})!} N_{d1}!(N_{11} - N_{d1})!N_{12}!$$

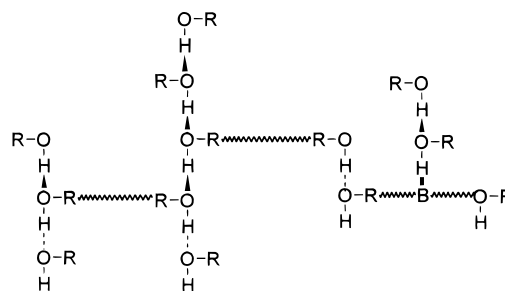
$$= \frac{N_1!N_2!(N_{11} + N_{12})!}{N_{d1}!N_{12}!(N_{10} - N_{d1})!(N_{12} + N_{d1})!(N_{11} - N_{d1})!(N_2 - N_{12})!} \quad (6)$$

This equation reduces to eq 5 by setting  $N_2 = N_{12} = 0$ .

**Case 5:** Same as case 4 but, now, there is cooperativity in both self-association and cross-association. Let us have again  $N_1$  and  $N_2$  molecules (groups) 1 and 2, between which there are  $N_{11}$  self-association and  $N_{12}$  cross-association bonds. However, now, the 1–1 bond for dimer formation is weaker than any subsequent bond of the multimer complex. In addition, the 1–2 bond is becoming stronger (bond fortification) when it is associated with a multimer complex of molecules of type 1. In order to simplify the situation, we will consider that in a complex 1–1–1...–1–1–2, the bond 1–1 next to the 1–2



**Figure 5.** One configuration of a system with  $N_1 = 14$ ,  $N_2 = 4$ ,  $N_{11} = 8$ , and  $N_{12} = 3$ . Out of the 8 1–1 bonds  $N_{d1} = 2$  are weak dimerlike bonds marked with dashed lines. Out of the 3 1–2 bonds  $N_{d2} = 2$  are fortified 1–2 bonds marked with a heavy solid line.



**Figure 6.** One complex associate of a system with  $N_1 = 13$ ,  $N_2 = 1$ ,  $N_{11} = 8$ , and  $N_{12} = N_{d2} = 1$ . Out of the 8 1–1 bonds  $N_{d1} = 3$  are weak dimerlike bonds marked with dashed lines. The 1–2 bond is fortified (heavy solid line). The springs connect different hydrogen-bonding groups of the same molecule.

bond is equally strong as any other 1–1 bond beyond the first dimer bond in a 1–1–1...–1–1 multimer (see Figure 5). Thus, in the system we have  $N_{11}$  1–1 bonds distributed in  $N_{d1}$  multimers of the 1–1–1...–1–1 type and  $N_{d2}$  multimers of the 1–1–1...–1–1–2 type. In addition, we have  $N_{12}$  1–2 bonds,  $N_{12} - N_{d2}$  of which are dimers 1–2 (with no bond fortification). In the system there are  $N_{10} = N_1 - N_{11} - N_{12}$  molecules (groups) 1 with the  $N_{10}$  free donor sites 1 and the  $N_{10}$  weak acceptor sites 1.

In order to calculate  $\Omega$ , we must first select, out of the donor population  $N_1$ , the  $N_{11}$  and  $N_{12}$  donors 1, which will participate in hydrogen bonds. This can be done in  $N_1!/[N_{10}!N_{11}!N_{12}!]$  different ways. In each such selection we select not only the  $N_{10} = N_1 - N_{11} - N_{12}$  free donors but, also, the  $N_{10}$  “weak” acceptors 1, which belong to the groups with the free donors. Out of these “weak” acceptors we must select the  $N_{d1}$  participating in hydrogen bonds. It can be done in  $N_{10}!/[N_{d1}!(N_{10} - N_{d1})!]$  ways. Out of the remaining  $N_1 - N_{10} = N_{11} + N_{12} = N_H$  “strong” acceptors 1, we must select the  $N_{11} - N_{d1}$  which participate in hydrogen bonds. It can be done in  $(N_1 - N_{10})!/[(N_{11} - N_{d1})!(N_{12} + N_{d1})!]$  ways. The  $N_{12}$  acceptors 2, which participate in hydrogen bonds, can be selected out of the population  $N_2$  in  $N_2!/[N_2!N_{12}!]$  ways. However, now, the  $N_{12}$  bound acceptors 2 are differentiated in  $N_{d2}$  acceptors participating in “fortified” 1–2 bonds and in  $N_{12} - N_{d2}$  acceptors participating in the “weak” 1–2 bonds. Their selection can be done in  $N_{12}!/[N_{d2}!(N_{12} - N_{d2})!]$  different ways. Out of the  $N_{11}$  donors 1 we must select the  $N_{d1}$  and  $N_{11} - N_{d1}$  donors, which associate with the weak and the strong acceptors 1, respectively, and out of the  $N_{12}$  donors 1, we must select the  $N_{d2}$  and  $N_{12} - N_{d2}$  which participate in fortified and weak 1–2 bonds, respectively. This can be done in  $N_{11}!N_{12}!/[N_{d1}!(N_{11} - N_{d1})!N_{d2}!(N_{12} - N_{d2})!]$  ways. Again, all the above  $N_{d1}$ ,  $N_{11} - N_{d1}$ ,  $N_{d2}$ , and  $N_{12} - N_{d2}$  different types of bonds can be done in  $N_{d1}!(N_{11} - N_{d1})!N_{d2}!(N_{12} - N_{d2})!$  ways. Thus,  $\Omega$  in this case is

$$\Omega = \frac{N_1!}{N_{10}!N_{11}!N_{12}!} \frac{N_{10}!}{N_{d1}!(N_{10} - N_{d1})!} \frac{N_H!}{(N_{11} - N_{d1})!(N_{12} + N_{d1})!} \frac{N_2!}{N_{12}!(N_2 - N_{12})!} \frac{N_{12}!}{N_{d2}!(N_{12} - N_{d2})!} \times$$

$$\frac{N_{11}!N_{12}!}{N_{d1}!(N_{11} - N_{d1})!N_{d2}!(N_{12} - N_{d2})!} N_{d1}!(N_{11} - N_{d1})!N_{d2}!(N_{12} - N_{d2})!$$

$$= \frac{N_1!N_2!(N_{11} + N_{12})!}{N_{d1}!N_{d2}!(N_{10} - N_{d1})!(N_{11} - N_{d1})!(N_{12} + N_{d1})!(N_2 - N_{12})!(N_{12} - N_{d2})!} \quad (7)$$

which reduces to eq 6 by setting  $N_{d2} = 0$ .

**A More General Case.** The above enumeration method can be extended easily to the more general case of a system of  $N_1, N_2, \dots, N_t$  molecules of type 1, 2, ...,  $t$ , respectively, which may have both donor/acceptor groups of type 1 and acceptor groups of type 2. Let each molecule of type  $i$  have  $d_1^i$  donors 1,  $a_1^i$  acceptors 1, and  $a_2^i$  acceptors 2. The total number of donors 1 in the system are

$$N_d^1 = \sum_{i=1}^t N_i d_1^i \quad (8)$$

Similarly, the total number of acceptors 1 in the system are

$$N_a^1 = \sum_{i=1}^t N_i a_1^i = N_d^1 \quad (9)$$

and the acceptors of type 2

$$N_a^2 = \sum_{i=1}^t N_i a_2^i \quad (10)$$

In this system let there be  $N_{11}$  and  $N_{12}$  hydrogen bonds of type 1–1 and 1–2, respectively. The free donors 1 are

$$N_{10} = N_d^1 - N_{11} - N_{12} = N_d^1 - N_H \quad (11)$$

the free acceptors 1 are

$$N_{01} = N_a^1 - N_{11} \quad (12)$$

and the free acceptors 2 are

$$N_{02} = N_a^2 - N_{12} \quad (13)$$

Let the (weak) dimerlike bonds 1–1 be  $N_{d1}$ , and the fortified 1–2 bonds be  $N_{d2}$ . By following the above enumeration method, we obtain for O the following expression:

$$\Omega = \frac{N_d^1!N_a^2!(N_{11} + N_{12})!}{N_{d1}!N_{d2}!(N_{10} - N_{d1})!N_{02}!(N_{12} - N_{d2})!(N_{d1} + N_{12})!(N_{11} - N_{d1})!} \quad (14)$$

which is the generalization of eq 7. This equation can cope with more complex associates, such as the one shown in Figure 6. It can be applied, for example, to hydrogen-bonding networks of polyoxalcohols or to mixtures of polyalcohols and polyethers or polyesters.

**The Gibbs Free Energy Equation.** Let us now return to eq 2 and find the expression for the free energy  $G_H$  for the above general case of a hydrogen-bonded system with bond cooperativity. In this case, there are four types of hydrogen bonds:  $N_{d1}$  (weak) 1–1 bonds with free energy of bond formation  $G_{d1}^0$ ,  $N_{11} - N_{d1}$  (strong) 1–1 bonds with free energy of bond formation  $G_{11}^0$ ,  $N_{d2}$  (strong) 1–2 bonds with free energy of bond formation  $G_{d2}^0$ , and  $N_{12} - N_{d2}$  (weak) 1–2 bonds with free energy of bond formation  $G_{12}^0$ . The free energy of the  $i$ – $j$  bond formation can be resolved as follows:

$$G_{ij}^0 = E_{ij}^0 + PV_{ij}^0 - TS_{ij}^0 \quad (15)$$

$E_{ij}^0$ ,  $V_{ij}^0$ , and  $S_{ij}^0$  being the energy, volume, and entropy change of  $i$ – $j$  bond formation, respectively. The hydrogen-bonding term  $Q_H$  of the partition function in eq 2 can then be written as follows:

$$Q_H = \left( \frac{\tilde{p}}{rN} \right)^{N_H} \frac{N_d^1!N_a^2!N_H!}{N_{d1}!N_{d2}!(N_{10} - N_{d1})!N_{02}!(N_{12} - N_{d2})!(N_{d1} + N_{12})!(N_{11} - N_{d1})!} \times$$

$$\exp \left( - \frac{N_{d1}G_{d1}^0 + (N_{11} - N_{d1})G_{11}^0 + N_{d2}G_{d2}^0 + (N_{12} - N_{d2})G_{12}^0}{kT} \right) \quad (16)$$

where  $N = \sum N_i$  is the total number of molecules in the system.

The hydrogen-bonding part of the free energy of the system is obtained from the equation

$$G_H = -kT \ln Q_H \quad (17)$$

By minimizing this equation with respect to the unknowns  $N_{11}$ ,  $N_{12}$ ,  $N_{d1}$ , and  $N_{d2}$ , we obtain the following coupled equations:

$$\frac{N_{11} - N_{d1}}{(N_{11} + N_{12})(N_{10} - N_{d1})} = K_{11} \quad (18)$$

$$\frac{(N_{12} - N_{d2})(N_{d1} + N_{12})}{N_{02}(N_{11} + N_{12})(N_{10} - N_{d1})} = K_{12} \quad (19)$$

$$\frac{N_{d1}(N_{d1} + N_{12})}{(N_{10} - N_{d1})(N_{11} - N_{d1})} = \frac{K_{d1}}{K_{11}} \quad (20)$$

$$\frac{N_{d2}}{N_{12} - N_{d2}} = \frac{K_{d2}}{K_{12}} \quad (21)$$

where the equilibrium constant  $K_{ij}$  for the formation of the bond  $i-j$  is given by the equation

$$K_{ij} = \frac{\tilde{p}}{rN} \exp\left(-\frac{G_{ij}^0}{kT}\right) \quad (22)$$

The coupled eqs 18 through 21 must be solved simultaneously by an appropriate iteration scheme. This solution can be facilitated by replacing equation 19 with the ratio of eqs 18 and 19, leading to the new equation

$$\frac{N_{02}(N_{11} - N_{d1})}{(N_{12} - N_{d2})(N_{d1} + N_{12})} = \frac{K_{11}}{K_{12}} \quad (19a)$$

By using these minimization conditions—eqs 18–21—in eq 17, we obtain for  $G_H$

$$\frac{G_H}{kT} = N_H + N_d \ln\left(1 - \frac{N_H + N_{d1}}{N_d}\right) + N_a \ln\left(1 - \frac{N_{12}}{N_a}\right) \quad (23)$$

**The Equation of State.** Equation 23 can be integrated to any equation-of-state framework leading to an equation-of-state theory of hydrogen-bonded systems. The procedure used in the LFHB model<sup>17</sup> can be applied directly here. In this work we will give directly the equations, but the interested reader may refer to the original reference for the details. In the LFHB framework, the total free energy of the system is given by

$$G = G_P + G_H \quad (24)$$

where

$$\frac{G_P}{kT} = rN \left\{ -\frac{\tilde{p}}{\tilde{T}} + \frac{\tilde{p}\tilde{v}}{\tilde{T}} + (\tilde{v} - 1) \ln(1 - \tilde{p}) + \frac{1}{r} \ln \tilde{p} + \sum_{i=1}^t \frac{\phi_i}{r_i} \ln \frac{\phi_i}{\omega_i} \right\} \quad (25)$$

$rN$  in this equation is the total number of segments in the system ( $rN = \sum r_i N_i$ ),  $\phi_i = r_i N_i / rN$  is the segment fraction of component  $i$ , and  $\omega_i$  is a constant characteristic of component  $i$ .  $\tilde{v}$  ( $= 1/\tilde{p}$

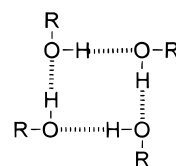
$= \rho^*/\rho$ ), is the reduced volume of the system ( $\rho$  is the density), while  $\tilde{T} = T/T^*$  and  $\tilde{P} = P/P^*$  are the reduced temperature and pressure of the system.  $\rho^*$ ,  $T^*$ , and  $P^*$  are the characteristic lattice-fluid<sup>27</sup> scaling constants of the system (see ref 17 for the details). Minimizing, now, eq 24 with respect to the reduced volume (or density), we obtain the following equation of state of our hydrogen-bonded system:

$$\tilde{p}^2 + \tilde{P} + \tilde{T} \left[ \ln(1 - \tilde{p}) + \tilde{p} \left( 1 - \frac{1}{\tilde{r}} \right) \right] = 0 \quad (26)$$

where

$$\frac{1}{\tilde{r}} = \frac{1}{r} - \frac{N_H}{rN} \quad (27)$$

**The Case of Cyclic Associates.** Cyclic associates can be handled in a straightforward manner in the LFHB frame. Let us consider a simple case with one type of cyclic associates: cyclic tetramers. In the above case 3, in addition to linear associates, let there also be  $N_q$  cyclic tetramers. There are  $N_{11}$  bonds in the system,  $4N_q$  of which belong to the cyclic tetramers and  $N_d$  to weak dimerlike bonds. In the system there are  $N_{10}$



$= N - N_{11}$  free donor groups. The strength of a hydrogen bond in the tetramer may or may not be the same as in the strong bonds of the linear associates.

In the enumeration process we have first to find the number of ways of selecting out of the  $N$  donor population the  $4N_q$  donors which participate in the cyclic tetramer bonds and the  $N_{11} - 4N_q$  which participate in the hydrogen bonds of the linear associates. This can be done in  $N! / [(4N_q)! N_{10}! (N_{11} - 4N_q)!]$  ways. Having selected the  $4N_q$  donors of the cyclic associates we have also selected the  $4N_q$  acceptors which participate in the hydrogen bonds of the cyclic associates (the same OH group). As previously, having selected the  $N_{10}$  free donors, we have also selected the  $N_{10}$  “weak” acceptors (the same OH group). Out of these  $N_{10}$  weak acceptors we must choose the  $N_d$  acceptors which participate in the (weak) hydrogen bonds. This can be done in  $N_{10}! / [N_d! (N_{10} - N_d)!]$  ways. Since we recognized that the acceptors in the groups with the free donors are weak, we must choose, out of the remaining  $N - N_{10} - 4N_q = N_{11} - 4N_q$  acceptors, the associated  $N_{11} - 4N_q - N_d$  ones which will participate in the strong bonds of the linear associates. This can be done in  $(N_{11} - 4N_q)! / [N_d! (N_{11} - 4N_q - N_d)!]$  ways. Since we have strong and weak acceptors in the linear associates, we must choose, out of the  $N_{11} - 4N_q$  associated donors, the  $N_d$  which will associate with the weak acceptors and the  $N_{11} - 4N_q - N_d$  which will interact with the strong acceptors. This can be done in  $(N_{11} - 4N_q)! / [N_d! (N_{11} - 4N_q - N_d)!]$  ways. Having selected the interacting donors and acceptors, the number of different ways that they can interact to form the  $N_d$  weak 1–1 bonds, the  $4N_q$  bonds in the cyclic associates, and the  $N_{11} - 4N_q - N_d$  strong 1–1 bonds in the linear associates is  $N_d! (4N_q)! (N_{11} - 4N_q - N_d)!$ . Thus,  $\Omega$  is the product of the above terms, or

$$\Omega = \frac{N!}{N_{10}!(4N_q)!(N_{11} - 4N_q)!} \frac{N_{10}!}{N_d!(N_{10} - N_d)!} \times \frac{(N_{11} - 4N_q)!}{(N_{11} - 4N_q - N_d)!N_d!} \frac{(N_{11} - 4N_q)!}{(N_{11} - 4N_q - N_d)!N_d!} \times \frac{N!(N_{11} - 4N_q)!}{(N_{10} - N_d)!(N_{11} - 4N_q - N_d)!(N_d!)^2} \quad (28)$$

The exponential term in the partition function (see eq 16) becomes now

$$\exp\left(-\frac{N_d G_d^0 + (N_{11} - 4N_q - N_d)G_{11}^0 + 4N_q G_q^0}{kT}\right)$$

As previously, from the minimization conditions one may obtain the values of  $N_{11}$ ,  $N_d$ , and  $N_q$  at equilibrium.

**The Case of Intramolecular Hydrogen Bonding.** We now turn to the interesting case of molecules that possess complementary groups permitting the formation of intramolecular hydrogen bonds in addition to or in competition with intermolecular hydrogen bonds. Typical examples are polyether molecules or polyesters or polyketones with hydroxyl groups at their ends. Let us apply the above rationale to the case of a mixture of  $N_1$  molecules having one hydroxyl group and  $x$  proton acceptor sites (carbonyl, ether oxygen, etc.) at positions favoring the formation of intramolecular hydrogen bonds with  $N_2$  molecules of an inert solvent ( $N = N_1 + N_2$ ). In order to simplify the presentation, we will consider that all  $x$  acceptor sites are equivalent.

In our system, the number of proton donors of type 1 ( $-\text{OH}$ ) is  $N_1$ , of proton acceptors of type 1 ( $-\text{OH}$ ) is  $N_1$ , and of proton acceptors of type 2 ( $\text{A} = -\text{O}-$  or  $\text{C}=\text{O}$ ) is  $xN_1$ . Let there be in the system  $N_{11}$  hydrogen bonds  $\text{OH} \cdots \text{OH}$ ,  $N_{12}$  intermolecular bonds  $\text{OH} \cdots \text{A}$ , and  $B$  intramolecular bonds  $\text{OH} \cdots \text{A}$ . The number of free proton donors are

$$N_{10} = N_1 - N_{11} - N_{12} - B \quad (29)$$

Let us now find the number of different ways of distributing the above hydrogen bonds in the system. We must, first, select the  $N_{11}$ ,  $N_{12}$ ,  $B$ , and  $N_{10}$  donors out of the  $N_1$  donor population. From simple combinatorics, this can be done in  $N_1!/[B!N_{11}!N_{12}!N_{10}!]$  ways. In a second step we have to select the  $N_{11}$  acceptors 1 out of the  $N_1$  acceptor population. This can be done in  $N_1!/[N_{11}!(N_1 - N_{11})!]$  ways. In a third step we have to select the  $B$  acceptors 2 out of the  $xN_1$  acceptor population. However, once we have selected the  $B$  proton donors that participate in intramolecular bonds, we have also selected the molecules with the acceptor 2 sites that participate in the  $B$  intramolecular bonds. In each of these  $B$  molecules we must now select the acceptor 2 site for the intramolecular bond out of the  $x$  acceptor 2 population. For each molecule this can be done in  $x!/[(x-1)!]$  ways. Thus, for the  $B$  molecules it can be done in  $\{x!/[(x-1)!]\}^B = x^B$  ways. Having selected the  $B$  acceptor 2 sites we must now select, out of the remaining  $xN_1 - B$  acceptor 2 population, the  $N_{12}$  which will participate in the intermolecular bonds. This can be done in  $(xN_1 - B)!/[(xN_1 - B - N_{12})!N_{12}!]$  ways. The  $N_{11}$  and  $N_{12}$  bonds can be done in  $N_{11}!N_{12}!$  ways, while the  $B$  bonds in only one way after we have selected both the donor and the acceptor site in each molecule. Thus, the number of configurations in the hydrogen bonded system is

$$\Omega = \frac{N_1!}{B!N_{11}!N_{12}!N_{10}!} \frac{N_1!}{N_{11}!(N_1 - N_{11})!} \left(\frac{x!}{(x-1)!}\right)^B \times \frac{(xN_1 - B)!}{(xN_1 - B - N_{12})!N_{12}!} N_{11}!N_{12}! = \frac{x^B(N_1!)^2(xN_1 - B)!}{B!N_{11}!N_{12}!N_{10}!(N_1 - N_{11})!(xN_1 - B - N_{12})!} \quad (30)$$

For the expression for  $Q_H$  we have to find the probability factor for the close proximity of each pair of donor and acceptor sites that hydrogen bond. As far as the intermolecular bonds are concerned, this factor is, as before,<sup>17</sup> equal to  $(\bar{p}/rN)^{N_{11}+N_{12}}$ . The corresponding probability for the proximity of the pair of intramolecular hydrogen bonds is primarily a characteristic property of the molecule, and it will be considered here as being a constant  $c$ . Thus, the total probability factor becomes equal to  $(\bar{p}/rN)^{N_{11}+N_{12}} c^B$ .

In our case, there are  $N_{11}$ ,  $N_{12}$ , and  $B$  hydrogen bonds with free energy of bond formation  $G_{11}^0$ ,  $G_{12}^0$ , and  $G_B^0$ , respectively. Thus, the exponential factor in the partition function (see eq 16) becomes now

$$\exp\left(-\frac{N_{11}G_{11}^0 + N_{12}G_{12}^0 + BG_B^0}{kT}\right)$$

As before, from the minimization conditions one may obtain the values of  $N_{11}$ ,  $N_{12}$ , and  $B$  at equilibrium. By consistently following the above procedure, one may easily combine eqs 16 and 30 in the case of mixtures where hydrogen bonding cooperativity is also important.

## Discussion and Conclusions

In the previous section it has been shown that the original LFHB enumeration procedure, which adopts and generalizes the Veytsman statistics,<sup>16</sup> can be used to describe in a uniform manner self-association, cross-association, cyclic associate formation, intramolecular hydrogen bonding, and hydrogen bond cooperativity, assuming the bonds of different strength be treated as different types of hydrogen bonds. By consistently following this procedure, one can handle various aspects of hydrogen bonding in rather complex systems, including hydrogen-bonded polymer networks.

The focus in the above analysis of cooperativity was on systems with bifunctional interacting groups, such as the hydroxyls or the hydrogen fluoride. In this analysis we have indirectly invoked the existence of association complexes; otherwise we could not distinguish between dimers and multimers. The number of free donors, for example, in the above case 1 is equal to the number of the association complexes in the system. It is important to point out that the interest in the counting process is on the complexes of interacting groups and not on the complexes of the molecules. The single molecular complex in Figure 6, for example, has many association complexes of interacting groups. In the present work, the focus in the enumeration procedure was on the formation of the different hydrogen bonds and not on the size of the association complexes. In this respect, what matters is the number of interacting groups and not the number of molecules in the system.

Since the (instantaneous) existence of complexes has been invoked, one could use alternative enumeration schemes for the distribution of hydrogen bonds in the system. In the above case 1, for example, one such scheme could focus on the selection

of the  $N_{10}$  free groups and on the number of different ways of distributing the  $N$  groups in  $N_{10}$  complexes. The latter is equivalent to the classical combinatorial problem of distributing  $N$  objects in  $N_{10}$  nonempty pools, or to the number of positive integer solutions in the equation

$$\sum_{i=1}^{N_{10}} n_i = N \quad (31)$$

where  $n_i$  is the number of groups that have been associated for the formation of the complex  $i$  (an  $n_i$ -mer) in the system. In our case of large  $N$  and  $N_{10}$ , this number is equal to  $N!/(N_{10}!N_{10}!)$ . By following consistently this approach, one may recover the corresponding equations of the present work.

It is expected<sup>22</sup> that the two approaches to hydrogen bond cooperativity, the *association* and the *combinatorial*, will be equivalent in the cases where both apply. In a forthcoming paper we will present the corresponding formalism with the *association* approach and will compare the two approaches with experimental data. Application of the association approach to complex cases of hydrogen bond networks remains a challenging task. These cases, however, can be handled easily with the *combinatorial* approach, as it has been shown in the present work.

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