

ANALYSIS OF THE DEPENDENCE OF THE CONSTANT OF SELF-ASSOCIATION OF AROMATIC MOLECULES ON THE LENGTH OF AN AGGREGATE

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We have shown that the main factors affecting the equilibrium constant of self-association of aromatic molecules during the growth of an aggregate are the loss of translational and rotational degrees of freedom on the formation of a complex, the ordering of molecules (the entropy of mixing) into aggregates, and the electrostatic interaction (if molecules possess a charge). On the basis of these ideas, we have first obtained the formula for the equilibrium constant of self-association of aromatic compounds as a function of the number of molecules in the aggregate and drawn conclusion that, in the frame of the model in use, the profile of the constant is decaying.

usually characterized, is the equilibrium constant of self-association K_i which is determined in the reaction with the sequential addition of molecules X_1 in the monomeric state to the aggregate X_{i-1} including $i-1$ molecules (see Fig. 1):



At present, the determination of the equilibrium constant of self-association can be realized with high accuracy by various physical methods. In this case, the models of self-association, which establish the interrelation of the experimentally studied parameter and the constant of association given in the analytic form, are in use (see surveys [3, 4, 11]). The available literature indicates that the model of self-association, in which the equilibrium constants K_i are set independent of the number of molecules i in aggregates and complexes, is most widely used. At the same time, it was shown in works [12, 13] that, in the general case, K_i cannot but depend on the number of molecules i in the aggregate. This induced the development of a number of models, in which the dependence of the constant of self-association on i (further, we will use the term "the profile of the constant") was set empirically $K(i) = f(i)$ (see surveys [3, 14, 15]). The main advantage of these models is the possibility to obtain the final formulas in a simple analytic form convenient for the further application to the analysis of experimental data. The main drawback of empiric models is the actual absence of a physical substantiation for the records of profiles $K(i)$. Here, we will analyze the main factors, which can influence the constant of self-association K_i of aromatic molecules and obtain the profile of the dependence of $K(i) = f(i)$ on

1. Introduction

The phenomenon of the self-construction of low-molecular compounds in aqueous solutions is known long ago. However only at the recent time, it begins to attract the particular attention of researchers in connection with its possible application to various branches of nano- and biotechnologies (see surveys [1, 2]). One of the types of self-construction is the process of self-association (aggregation) which is most characteristic of the class of aromatic compounds [3, 4]. The base of aromatic molecules consists of a planar aromatic chromophore, whose peculiarity is the existence of the aromatic current behind its perimeter. During the approach of such compounds to one another in a solution, the stacks of molecules are formed. These stacks are stabilized by the van der Waals forces (mainly, by the dispersion interactions of aromatic currents) and hydrophobic interactions [4, 5] (Fig. 1). The self-association of aromatic compounds can significantly change the properties of various substances and materials and is widely used in solid-state physics for the fabrication of molecular magnets and a new class of conductors [6, 7], laser physics [8], chemistry of dye compounds [8], and a number of biological ingredients [5, 9, 10].

One of the basic quantitative parameters of self-association, by which the efficiency of complexation is

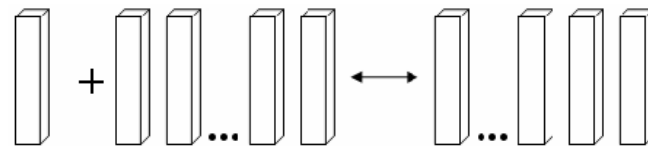


Fig. 1. Schematic image of the formation of a stack of aromatic molecules in a solution

the number of molecules i in the aggregate in the analytic form.

2. Results and Discussion of the Results

2.1. Analysis of the factors defining the profile of the constant of self-association

In most cases, the processes of self-association of aromatic molecules are considered under conditions of constant pressure and temperature. Therefore, we will use the Gibbs free energy as a basic thermodynamic potential in what follows.

In one of the first works analyzing the factors responsible for the self-association of aromatic molecules [13], it was shown that the main contribution to the Gibbs free energy of the reaction of self-association is given by four components:

$$\Delta G = \Delta G_{\text{disp}} + \Delta G_{\text{hyd}} + \Delta G_{\text{el}} + \Delta G_{\text{mix}}, \quad (2)$$

where ΔG_{disp} is the contribution of the dispersion interaction of aromatic currents of chromophores or, in the general case, van der Waals interactions of molecules in an aggregate. These interactions belong to the class of short-range forces and are manifested only at distances of the order of the van der Waals radius (0.3-0.4 nm for aromatic molecules [3-6,13]). Hence, this type of the molecular interaction cannot depend on the number of molecules in an aggregate and does not define the profile of the constant.

The quantity ΔG_{hyd} is the hydrophobic contribution caused by the destruction of a water structure on the formation of a complex of molecules. The energy of hydrophobic interactions is determined by a change of the solvent-accessible surface area of interacting molecules [16,17] and, in the approximation of reaction (1), cannot also depend on the number of molecules in the aggregate of i molecules.

The quantity ΔG_{el} is the contribution of electrostatic interactions which are long-range. Hence, this component of the Gibbs free energy can contribute, in principle, to the profile of the constant.

The quantity ΔG_{mix} is the energy of mixing, has the purely entropic nature, and is caused by the ordering of molecules on the formation of aggregates according to reaction (1). This component of the free energy can also affect the profile of the constant of self-association [12].

Relation (2) does not involve such a component of the Gibbs free energy as $\Delta G_{\text{tr}}^{\text{rot}}$. On the formation of a complex, molecules lose the freedom of motion relative to one another, which is a consequence of both the

loss of three translational (forward) and three rotational degrees of freedom of the molecular objects X_1 and X_{i-1} and the appearance of three new translational and rotational motions of the as-formed complex X_i according to reaction (1). Earlier, the consideration of the energy equivalent of the loss of the degrees of freedom on the self-association of aromatic molecules was not made generally; however, it is the practice to take this component of the free energy into account on the study of the binding of aromatic compounds with DNA [18]. In this connection, we will estimate the component of the Gibbs free energy $\Delta G_{\text{tr}}^{\text{rot}}$ under the self-association of aromatic molecules and consider its effect on the profile of the constant of self-association.

2.2. Effect of the loss of translational degrees of freedom on the profile of the constant of self-association

The formation of molecular complexes changes the number of possible microstates of the systems. Hence, the energy equivalent of the loss of translational degrees of freedom, ΔG_{tr} , has mainly the entropic nature,

$$\Delta G_{\text{tr}} = \Delta H_{\text{tr}} - T\Delta S_{\text{tr}}, \quad (3)$$

where ΔS_{tr} is a change of the translational entropy on the formation of a complex; $\Delta H_{\text{tr}} = -\frac{3}{2}RT$ is the enthalpic equivalent of the loss of translational degrees of freedom.

The quantity ΔS_{tr} can be determined from the Sackur-Tetrode equation [19]

$$S_{\text{tr}} = R \left(\ln \frac{V}{N} + \ln \left(\frac{2\pi mkT}{h^2} \right)^{\frac{3}{2}} + \frac{5}{2} \right) \quad (4)$$

which allows one to calculate the molar translational entropy of the ideal gas which contains $N = N_A = 6.02 \times 10^{23}$ mole⁻¹ of molecules with mass m and occupies the volume $V = 10^{-3}$ m³; k and h are, respectively, the Boltzmann and Planck constants; T is the Kelvin temperature. It is worth noting that formula (4) in its exact meaning cannot be used for the processes running in an aqueous medium. However, some authors think that the Sackur-Tetrode equation describes, with a sufficient degree of exactness, the entropy of a solution of low-molecular compounds [20].

Relation (4) yields the formula for the entropy of an aggregate which includes i molecules:

$$S_{\text{tr}}^i = R \left[\frac{5}{2} + \frac{3}{2} \ln \frac{2\pi imkT}{h^2} - \ln \frac{N}{V} \right]. \quad (5)$$

Then a change of the translational entropy in reaction (1) takes the form

$$S_{\text{tr}}^i = S_{\text{tr}}^i - S_{\text{tr}}^{i-1} - S_{\text{tr}}^1 =$$

$$= \frac{3}{2}R \ln \frac{i}{i-1} - R \left[\frac{5}{2} + \frac{3}{2} \ln \frac{2\pi mkT}{h^2} - \ln \frac{N}{V} \right]. \quad (6)$$

Equation (6) can be used to determine the translational component of the profile of the constant of self-association:

$$K_{\text{tr}}(i) = \exp \left(\frac{-\Delta H_{\text{tr}} + T\Delta S_{\text{tr}}^i}{RT} \right) = \left(\frac{i}{i-1} \right)^{3/2} \times$$

$$\times \exp \left[R \ln \left(\frac{5}{2} + \frac{3}{2} \ln \frac{2\pi mkT}{h^2} - \ln \frac{N}{V} \right) \right] \exp \left(-\frac{\Delta H_{\text{tr}}}{RT} \right).$$

With regard for the relation $\Delta H_{\text{tr}} = -\frac{3}{2}RT$ which is independent of i , the translational profile of the constant can be finally written in the form

$$K_{\text{tr}}(i) = \left(\frac{i}{i-1} \right)^{3/2} C_{\text{tr}}, \quad (7)$$

where C_{tr} is the constant which does not depend on the number of molecules in the aggregate. Equation (7) implies that the component of the equilibrium constant of self-association caused by a loss of translational degrees of freedom decreases with increase in the number i , i.e. the profile is decaying.

2.3. Effect of the loss of rotational degrees of freedom on the profile of the constant of self-association

The formula for the calculation of the rotational entropy follows from the general principles of statistical

Table 1. Calculated values of the inertia moments of aromatic compounds relative to the principal inertia axes

Molecule	I_x , amu·Å ²	I_y , amu·Å ²	I_z , amu·Å ²
Actinomycin D	20260	28486	31333
Acridine orange	469	3329	3668
Caffeine	424	657	1082
Daunomycin	3500	8145	10536
Doxorubicine	3668	8673	11181
Ethidium bromine	1607	2849	4210
Flavin-monomonucleotide	2825	5492	7289
Nogalamycin	6748	21507	24115
Novatron	4811	7039	11821
Proflavin	284	1779	2063

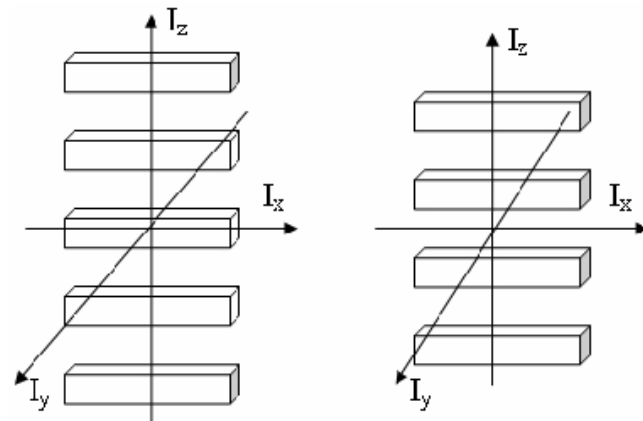


Fig. 2. Principal inertia axes for odd and even numbers of molecules in the aggregate

thermodynamics [19, 20]:

$$S_{\text{rot}} = R \left(\frac{3}{2} + \frac{1}{2} \ln \pi I_x I_y I_z + \frac{3}{2} \ln \frac{8\pi^2 kT}{h^2} - \ln \sigma \right). \quad (8)$$

Here, I_x , I_y , and I_z are the inertia moments relative to the principal axes of the object under consideration, σ is the symmetry parameter which is set to unity here, which is true for asymmetric objects. In Table 1, we give values of the inertia moments for various aromatic compounds studied in the present work. The calculation of the inertia moments was performed with the software of molecular simulation X-PLOR [21] on the basis of the crystallographic structures of the molecules under study taken from the Protein Data Bank [22].

For any aggregate containing i molecules, the rotational entropy is as follows:

$$S_{\text{rot}}^i = R \left(\frac{3}{2} + \frac{1}{2} \ln \pi I_x^i I_y^i I_z^i + \frac{3}{2} \ln \frac{8\pi^2 kT}{h^2} \right). \quad (9)$$

The inertia moments of the aggregate I_x^i , I_y^i , and I_z^i can be determined with the use of the Steiner theorem on the basis of the known values of the inertia moments of a single molecule I_x^i , I_y^i , and I_z^i . In this case, the analysis of the inertia moments must be performed separately for even and odd i , which is explained in Fig. 2:

– i is odd

$$I_x^i = I_x + 2(I_x + md^2) + 2(I_x + m(2d)^2) + 2(I_x +$$

$$+ m(3d)^2) + \dots = iI_x + md^2 \sum_{k=1}^{\frac{i-1}{2}} \frac{(2k)^2}{4} \quad (10)$$

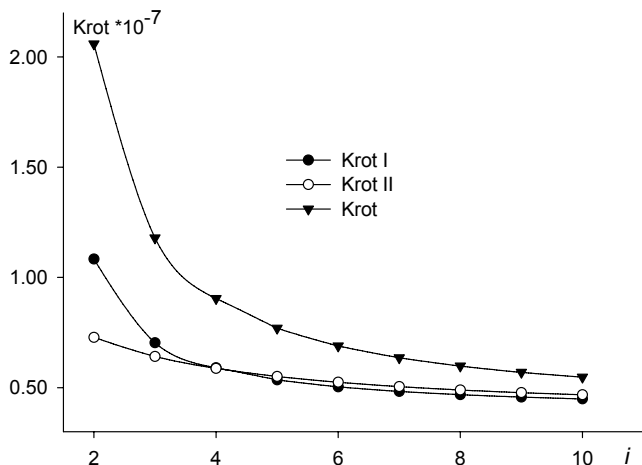


Fig. 3. Dependence of various components of the rotational profile of the constant on the number of molecules in the aggregate

– i is even

$$I_x^i = 2 \left(I_x + m \left(\frac{d}{2} \right)^2 \right) + 2 \left(I_x + m \left(\frac{3d}{2} \right)^2 \right) + 2 \left(I_x + m \left(\frac{5d}{2} \right)^2 \right) + \dots = iI_x + md^2 \sum_{k=1}^{\frac{i}{2}} \frac{(2k-1)^2}{4}, \quad (11)$$

where d is the distance between molecules in the aggregate. Both sums in Eqs. (10) and (11) are reduced to the same expression $\frac{i(i-1)(i+1)}{24}$ irrespective of the parity of i . Then the inertia moments of the aggregate with i molecules can be written finally in the form

$$I_x^i = iI_x + md^2 \frac{i(i-1)(i+1)}{24},$$

$$I_y^i = iI_y + md^2 \frac{i(i-1)(i+1)}{24}, \quad I_z^i = iI_z. \quad (12)$$

A change of the entropy on the formation of an aggregate with i molecules is determined analogously to (6) as

$$\Delta S_{\text{rot}}^i = S_{\text{rot}}^i - S_{\text{rot}}^{i-1} - S_{\text{rot}}^1. \quad (13)$$

Substituting (9) and (12) in (13), we can obtain the final formula for a change of the rotational entropy,

$$\Delta S_{\text{rot}}^i = - \left(\frac{3}{2} + \frac{3}{2} \ln \frac{8\pi^2 kT}{h^2} \right) R - \frac{1}{2} R \ln(\pi I_x I_y I_z) + \frac{3}{2} R \ln \left(\frac{i}{i-1} \right) + \frac{1}{2} R \ln \left[\left(1 + \frac{md^2(2i-1)}{12I_x + i(i-2)md^2} \right) \times \right.$$

$$\left. \times \left(1 + \frac{md^2(2i-1)}{12I_y + i(i-2)md^2} \right) \right], \quad (14)$$

and the rotational component of the profile of the constant at $\Delta H_{\text{rot}} = \frac{3}{2}RT$,

$$K_{\text{rot}}(i) = \exp \left(\frac{-\Delta H_{\text{rot}} + T\Delta S_{\text{rot}}^i}{RT} \right) = \exp \left(\frac{\Delta S_{\text{rot}}^i}{R} \right) \times \exp \left(-\frac{3}{2} \right). \quad (15)$$

Formula (14) is rather awkward and inconvenient for the subsequent analysis. In Fig. 3, we give the plot of $K_{\text{rot}}(i)$ calculated as an example for the aromatic acridine orange dye. This plot presents the general profile of the constant according to formulas (14) and (15), by neglecting the last term, K_{rot}^I , and the penultimate one, K_{rot}^{II} , in (14) which depend on i .

It follows from Fig. 3, that the dependence K_{rot}^{II} on i is pronounced significantly weaker than that for K_{rot}^I . An analogous regularity is observed for all aromatic compounds, which are presented in Table 1, without exception. This means that the main contribution to the general dependence $K_{\text{rot}}(i)$ is given by the penultimate term in (14). Hence, the approximate expression for the rotational profile of the constant of self-association can be written in the simplified form as

$$K_{\text{rot}}(i) \approx \left(\frac{i}{i-1} \right)^{\frac{3}{2}} C_{\text{rot}}, \quad (16)$$

where C_{rot} is a constant independent of the number of molecules in the aggregate. On the whole, relation (16) implies that the rotational profile turns out to be similar to the translational one [compare with (7)] and is also decaying.

2.4. Effect of the entropy of mixing on the profile of the constant of self-association

A change of the entropy of mixing in the reaction of the formation of a complex containing i molecules can be represented as [12]:

$$\Delta S_{\text{mix}}^i = R \Delta \ln \Omega_i + \text{const}, \quad (17)$$

where Ω_i is the number of means which allow one to realize the sampling of an aggregate with i molecules.

For the process of self-association described by reaction (1) for relatively small i ($i \ll N$), relation (17) takes the form

$$\Delta S_{\text{mix}}^i = R \left[\ln \frac{1}{i!} - \ln \frac{1}{(i-1)!} - \ln 1 \right] + \text{const} =$$

$$= -R \ln i + \text{const}.$$

Whence the equilibrium constant of the reaction of association takes the form

$$K_{\text{mix}}(i) = \exp \left(\frac{\Delta S_{\text{mix}}^i}{R} \right) \text{const},$$

$$K_{\text{mix}}(i) = \frac{C_{\text{mix}}}{i}. \quad (18)$$

Relation (18) sets the profile of a change of the equilibrium constant with regard for the entropy of mixing which is also decaying.

2.5. General profile of the constant of self-association

In view of the above-considered contributions of the translational (7) and rotational (16) entropies and the entropy of mixing (18) to the total entropy of the reaction of aggregation, we can write the general profile of the equilibrium constant of self-association as

$$K(i) = K_{\text{tr}}(i)K_{\text{rot}}(i)K_{\text{mix}}(i) = C_0 \frac{i^2}{(i-1)^3}, \quad (19)$$

where C_0 is some constant. We now clarify the physical sense of the constant C_0 . The NMR data for all aromatic compounds under study allow us to determine the

Table 2. Calculated values of the equilibrium constants of self-association versus the length of the aggregate ($T = 298 \text{ K}$)

Molecules	Equilibrium constant of self-association, l/mole						
	K_D	K_3	K_4	K_5	K_6	K_7	K_8
Novatron	15000 [23]	4219	2222	1465	1080	851	700
Nogalamycin	3700 [23]	1041	548	361	266	210	173
Acridine	2300 [4]	647	341	225	166	130	107
Orange							
Doxorubicine	832 [23]	234	123	81	60	47	39
Actinomycin D	710 [4]	200	105	69	51	40	33
Daunomycin	360 [23]	101	53	35	26	20	17
Proflavin	350 [4]	98	52	34	25	20	16
Ethidium	153 [4]	43	23	15	11	9	7
bromine							
Flavin- mononucleotide	133 [23]	37	20	13	10	8	6
Caffeine	6 [23]	1.7	0.9	0.6	0.4	0.34	0.28

equilibrium constants of dimerization $K_D = K_2$ with high accuracy (Table 2). At $i = 2$, relation (19) yields

$$C_0 = \frac{K_D}{4}.$$

Hence, the equilibrium constant of self-association in reaction (1) with regard for the profile of its dependence on the number of molecules in the aggregate takes the form

$$K_i = \frac{K_D}{4} \frac{i^2}{(i-1)^3}. \quad (20)$$

Relation (20) is our main result which allows us to evaluate the constant of self-association during the growth of the aggregate. Relation (20) implies that the constant decreases with increase in i (in Table 2, we give the results of calculations of K_i for various i). In this case, we note that the derivation of relation (20) is valid for $i \ll N$.

If the aggregating compound has the electric charge, then, according to the results of work [13], the profile of the constant caused by the electrostatic interaction takes the form

$$K_{\text{el}}(i) = \frac{C_{\text{el}}}{i}.$$

In this case, the general profile of constant (19) is proportional to $\frac{i}{(i-1)^3}$, and the absolute value of the constant is

$$K_i = \frac{K_D}{2} \frac{i}{(i-1)^3}. \quad (21)$$

Thus, the action of electrostatic forces on the association of charged molecules induces the sharper decrease of the constant of self-association, than that for neutral molecules.

3. Conclusion

Here, we have shown that the main factors affecting the equilibrium constant of self-association of aromatic molecules during the growth of the aggregate are the loss of translational and rotational degrees of freedom on the formation of a complex, the ordering of molecules (the entropy of mixing) in aggregates, and the electrostatic interaction (if molecules have a charge). On the basis of these ideas, we have first obtain the formula for the equilibrium constant of self-association of aromatic compounds depending on the number of molecules in the aggregate and made conclusion that, in the frame of the model in use, the profile of the constant is decaying.

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АНАЛІЗ ЗАЛЕЖНОСТІ КОНСТАНТИ САМОАСОЦІАЦІЇ АРОМАТИЧНИХ МОЛЕКУЛ ВІД ДОВЖИНИ АГРЕГАТУ

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Резюме

В даній роботі показано, що основними факторами, які впливають на величину рівноважної константи самоасоціації ароматичних молекул по мірі нарощування агрегату, є втрата трансляційних та ротаційних ступенів свободи при утворенні комплексу, упорядкування молекул (ентропія змішування) в агрегатах і електростатичні взаємодії (у випадку, якщо молекули несуть заряд). На основі цих уявлень вперше було отримано вираз для розрахунку рівноважної константи самоасоціації ароматичних сполук в залежності від числа молекул в агрегаті і зроблено висновок про те, що в межах моделі, яка використовується, профіль константи є затухаючим.