Поскольку при сворачивании белка вторичная структура формируется раньше третичной, следует полагать, что разрушение вторичной структуры приводит к дестабилизации третичных контактов и компактного глобулярного состояния. Однако процесс разворачивания сопровождается увеличением площади доступной растворителю неполярной поверхности, что невыгодно в случае растворов в чистой воде и может послужить причиной некоторой кинетической стабилизации компактного состояния. Молекулы ДМСО могут значительно ускорить этот процесс, сольватируя неполярные участки.

Яркое отличие компактных дезорганизованных структур, являющихся, по всей видимости, кинетически устойчивыми интермедиатами, в которые превращается белок в симуляциях с водой, от развернутых, близких к случайным клубкам конформаций, которые быстро образуются в бинарных смесях, требует экспериментальной проверки на основе детального исследования комплексом физических методов.

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## INTERRELATION OF ENTROPIC CONTRIBUTORS TO Π-STACKING IN SOLUTION

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**Abstract.** The recently published most complete set of thermodynamical data on self- and hetero-complexation of aromatic molecules measured under comparable conditions of experiment was analysed with an aim of getting insight into contribution of various entropic factors to π-stacking in aqueous solution. It was found that the experimental entropy change on π-stacking is determined by counterbalancing effect of two principal factors, *viz*. the hydrophobic interaction (positive contribution) and the loss of degrees of freedom (negative contribution), modulated by electrostatic contribution. The mixing entropy contribution originating from the overall ordering of system due to π-stacking complexation is zero.

**Key words:** self-assembly; hetero-complexation; mixing entropy; entropic contribution

**Introduction.**

Understanding the role of various physical factors in π-stacking of aromatic moieties in solution is of fundamental interest in physical chemistry, and is required for getting insight into a range of processes of chemical and biological interest [1-3]. Much theoretical and experimental work has been done towards understanding the nature of forces driving the complex formation stabilzed by stacking interactions, although the interrelation of enthalpic and entropic factors in the net Gibbs free energy of the π-stacking is still under discussion. The most vivid examples are the long-lasting problems of decomposition of π-stacking energy onto energetic contributions from various physical factors [4-6], the role of entropic factors [7-9] and hydration [10] in aggregation of aromatic moieties, the origin of enthalpy-entropy compensation [11], and the problem of overall meaning of π-stacking [12].

Aromatic molecules is the most representative example of the π-stacking forming domains used as model systems to get insight into the nature of π-stacking interactions [1-6]. Recently [13] the most complete set of thermodynamical data on aggregation of small aromatic molecules (experimental enthalpy and entropy changes, $\Delta H_{exp}$ and $\Delta S_{exp}$) was reported collecting more than 50 self- (*X*+*X*) and hetero-complexation (*X*+*Y*) systems measured under comparable conditions of experiment (*i.e.* aqueous solution, pH~7, *I*~0.1). The uniqueness of this dataset, as compared to analogous thermodynamic data collections published before, is determined by two main features: (*i*) solution conditions are close to

what is most often met in natural biological systems, and (*ii*) it mainly includes the heterogeneous complexations of different by structure molecules which allows more extended discussion of the role of various factors (e.g. electrostatic, charge-transfer, structural) in the stability of π-stacked complexes in aqueous solution.

In the present work the thermodynamic dataset [13] is anaysed in terms of a contribution of various entropic factors to π-stacking in aqueous solution.

**Results and discussion.**

*General patterns in thermodynamic parameters of π-stacking.*

Analysis of the thermodynamic data reported in [13] enables drawing the following set of conclusions:

(i) the π-stacking complexation follows standard linear enthalpy-entropy compensation, suggesting no apparent deviation of the complexation process from common thermodynamical behavior of small molecules in aqueous solutions,

(ii) the $\Delta H_{exp}$ quantity is always negative independent on the type of molecule *X* or *Y* involved in the aggregation process,

(iii) the $\Delta S_{exp}$ quantity also takes negative values (with few exceptions) independent on the type of molecule *X* or *Y*,

(iv) the thermodynamic patterns for the hetero-association *X*+*Y* and self-association of its components, *i.e. X* or *Y*, are generally similar suggesting that the overall thermodynamic properties of self- and hetero-association may be considered complementary to each other (the specific deviations of hetero-association from self-association are discussed in detail in [13]).

Let us further try to understand how this data can extend our knowledge of thermodynamic nature of π-stacking.

The negative values of $\Delta H_{exp}$ is quite expected and can be explained by predominant contribution to the enthalpy of van der Waals and electrostatic interactions. In contrast to $\Delta H_{exp}$, the negative magnitudes of $\Delta S_{exp}$ does not have an apparent interpretation. The common view, currently dominating in literature states that classical hydrophobic interactions give the largest contribution to π-stacking in solution, or the hydrophobic and van der Waals/electrostatic factor commensurate at the best [2,13]. It suggests that $\Delta S_{exp}$ should take large positive values or small values close to zero (negative or positive). However, the experimental values of $\Delta S_{exp}$ do not support this expectation. To the best of our knowledge, this fact has not been explained so far, and reveals a gap in current understanding of such fundamental phenomenon as π-stacking in solution.

*The composition of the net experimental entropy of the π-stacking.*

Let us consider the principal contributors to the experimentally measured entropy change on aggregation of aromatic molecules.

The entropic part of the Gibbs free energy change on aggregation in solution is made of the following principal components, *viz.*

$$\Delta S_{exp} = \Delta S_{hyd} + \Delta S_{el} + \Delta S_{df} + \Delta S_{mix} \quad (1)$$

(i) hydrophobic contribution, $\Delta S_{hyd}$, originating from disordering of water shell on formation of stacked complexes,

(ii) electrostatic contribution, $\Delta S_{el}$, originating from changes in ionic environment and dielectric properties of nearest hydration shell on complexation,

(iii) changes in the overall number of degrees of freedom (translational, rotational and vibrational), $\Delta S_{df}$. This factor has recently been recognised as being responsible for the dependence of equilibrium aggregation constant on the number of molecules in an aggregate [7,9] and is used to explore the experimental aggregate distributions [7,14,15],

(iv) contribution due to overall ordering of the interacting molecules into the distribution of various by length π-stacked oligomers (dimers, trimers etc), $\Delta S_{mix}$. This factor is often called 'the mixing entropy contribution' [8] and is sometimes included into analysis of thermodynamic quantities [7,14].

The hydrophobic contribution always results in positive values of $\Delta S_{hyd}$ and cannot be responsible for the observed negative values of $\Delta S_{exp}$. The sign of the electrostatic contribution, $\Delta S_{el}$, may either take negative or positive values depending on the sign of interacting molecules. Although it is currently difficult to unambigously quantify the entropic part of electrostatic contribution to π-stacking, however, analysis of literature (see [13] for review) allows drawing the following qualitative conclusions:

- reactions of the formation of π-stacked complexes in aqueous solution are commonly characterized by small net electostatic contribution to the energetics of complexation due to counterbalancing effect of interaction with solvent and intermolecular interaction,
- the interacting molecules collected in Supplementary feature different charges changing from repulsive (++ or – –) to attractive (+–) contribution of the electrostatics to the net energetics of complexation. However, it does not affect the sign of $\Delta S_{exp}$,
- attempts to quantify the electrostatic contribution to the heat capacity change for ligand-DNA binding reactions (typically following the attractive +– pattern of electrostatic interaction) [16] have generally concluded that the hydrophobic contribution dominates over the electrostatic.

From these statements it follows that the electrostatic contribution (ii) is most likely not the dominant factor in the magnitude of $\Delta S_{exp}$. It acts as a fine tuning of the magnitudes of thermodynamical parameters, as evidenced by the recognized concept of 'electrostatic complementarity' in aromatic π-stacking [17].

The factor (iii) of the changes in the number of degrees of freedom has been quantified in [6] and takes deep negative values of the entropy change, $\Delta S_{df}$, commensurable with $\Delta S_{hyd}$. Hence, the factor (iii) may potentially be responsible for $\Delta S_{exp}<0$.

The factor (iv) of the overall ordering of the system should also give negative entropic contribution, $\Delta S_{mix}$, however, it has not been quantified so far. This is the hole in current understanding of the entropic composition of π-stacking which will be considered in detail below.

*Grand partition function of the self-assembling system.*

It is known that the overwhelming majority of aromatic molecules exert pronounced tendency to aggregate in aqueous solution (also referred to as self-association or self-assembly) resulting in formation of π-stacked dimers, trimers etc. [13,18]. The aggregation is most often considered to be non-cooperative and isoenergetic allowing to take the equilibrium aggregation constant, *K*, equal on each stage of aggregation. This model although being simplified, nevertheless, remains the most extensively-used approach enabling to describe wide variety of aggregations and extract the thermodynamical parameters from experiment. Hence, as a partial case, this model also includes the π-stacking complexation, discussed here. Let us find the exact form of the grand partition function, *Z*, of non-cooperatively self-assembling system.

The most appropriate for the context of the present paper investigation of the grand partition function of the non-cooperatively self-assembling system was accomplished in [19]. Detailed derivation of *Z* with further anaysis of equilibrium state is given in Supplement. Below we shall discuss the key points and conclusions of this analysis.

If the system, containing $N_0$ idential molecular units which are able to interact with each other and form complexes with unrestricted number of molecules in them, is at isobaric-isothermal equilibrium, hence, the equilibrium distribution of oligomers with different number of molecules, *i*, in them is being formed, viz. $N_1$, $N_2$, … $N_i$, … Further construction of the grand partition function of such system yields the expression

$$Z = \frac{N_0!}{N_1!N_2!\cdot\ldots}\exp\left(-\sum_{i=1}^{\infty}(i-1)N_i\frac{\Delta G_1}{kT}\right) \qquad (2)$$

where $\Delta G_1 = -kT\ln K$ is the Gibbs free energy change and the aggregation constant, *K*, related to the formation of each interface between the molecules in any oligomer; *k* is the Bolzmann constant.

(2) can be further used to get the Gibbs free energy of the system (taking monomer molecule as a reference state $G_1$) as

$$G = G_1N_0 - kT\ln Z = G_1N_0 + \sum_{i=1}^{\infty}(i-1)N_i\Delta G_1 - kT\ln\frac{N_0!}{N_1!N_2!\cdot\ldots} \qquad (3)$$

The principal feature of (3) is decomposition of the net energy, *G*, onto the sum of the terms containing $G_1$ and $\Delta G_1$ representing the thermodynamics of formation of immediate interface between neighboring molecules in complex, and the third term containing factorials. The latter term accounts for the overall ordering of the system due to formation of different-by-length aggregates, and, thereby, may be related to the mixing entropy contribution to the Gibbs free energy.

Evaluation of (3) under equilibrium state (i.e. searching for the condition of *G* minimum) results in expression

$$N_i = K^{i-1}N_1^i \qquad (4)$$

By transforming *K* and $N_i$ to standard molar units, eq.4 will thus represent the fundamental law of mass action, used arcross different fields of physical chemistry which deal with the aggregation or complexation phenomena. Let us think over the importance of the result obtained.

*The role of various entropic factors.*

The general form of the grand partition function (2) either accounts for the mixing entropy, $\Delta S_{mix}$ (as the factorial coefficient before the exponent), and defines *K* as a function of the energy, $\Delta G_1$, of immediate interface between neighboring molecules which does not contain any contribution from the ordering, $\Delta S_{mix}$. So, if the aggregation/complexation process is investigated using the mass action law, eq.4, hence the experimental entropy change, $\Delta S_{exp}$ (no matter how it is measured, *viz.* using direct heat effect determination in calorimetry, or using temperature dependence of *K* within the framework of van't Hoff approach), does not contain the contribution from $\Delta S_{mix}$. The overwhelming majority of known thermodynamic studies of the π-stacking in solution (including the dataset [13] discussed here) uses the law of mass action, hence, $\Delta S_{mix}$ should be excluded from analysis of the composition of $\Delta S_{exp}$. It immediately allows answering the main question of this work concerning the origin of the negative sign of $\Delta S_{exp}$ and interrelation of various contributors to the net entropy change on π-stacking, *viz.*

- the major reason for $\Delta S_{exp}<0$ appears to be the loss of degrees of freedom on complexation ($\Delta S_{df}$),
- the overall ordering of system due to aggregation does not contribute to $\Delta S_{exp}$ (i.e. $\Delta S_{mix}=0$),
- electrostatic contribution, $\Delta S_{el}$, is not predominant, acting as a fine tuning of the net entropy of stacking in solution,
- summary: the experimental entropy change on π-stacking is determined by counterbalancing effect of two principal factors, *viz*. the hydrophobic interaction (positive contribution) and the loss of degrees of freedom (negative contribution), modulated by electrostatic contribution, i.e. $\Delta S_{exp} \approx \Delta S_{df} + \Delta S_{hyd} + \Delta S_{el}$.

It is important to note that the set of conclusions formulated is valid for aqueous solutions only. π-stacking in non-aqueous systems may feature different interrelation of electrostatic / hydrophobic factors, whereas the mixing entropy contribution, $\Delta S_{mix}=0$, is independent of the type of solution.

*Concluding remark regarding the zero contribution from $\Delta S_{mix}$.*

The above-discussed result, $\Delta S_{mix}=0$, is not apparent from the very beginning and may be questionable. For example one may argue on the validity of the argument regarding the distinguishability of the monomers consituting each oligomer (raised by anonymous referee), which was used for derivation of the grand partition function in (2). In fact the zero value of $\Delta S_{mix}$ directly originates from this assumption and therefore is of principal importance for the main conclusion of this work. An opposite viewpoint assumes the dynamic exchange of the molecules inside an aggregate, which requires modification of (2) and will eventually yield $\Delta S_{mix}\neq 0$ (see [8] for more discussion). If that would be true the aggregate of molecules would be equivalent to ideal gas (in terms of statistical thermodynamics) constrained within a container in which all molecules are freely exchangeable by their positions, and thereby are really indistinguishable. We consider that such view is incorrect at least for the π-stacked oligomers of aromatic molecules discussed in the present work. First, the direct proton-proton intermolecular nOes in nuclear magnetic resonance spectra do not average down to zero (as would be the case for freely tumbling molecules), thus evidencing the formation of stable complexes of aromatic molecules (see [13] for review). Second, the translational diffusion coefficient of aromatic molecules features well pronounced concentration dependence which is well predictable using concept of formation of linear aggregates with fixed positions of molecules forming them (see [21] and references therein). Third, it has long been experimentally shown that the loss of translational entropy on covalent and non-covalent complexation of protein units results in similar values well predicted from statistical-thermodynamic grounds [22], which suggests that the positions of the molecules within a complex are not exchangeable. Fourth, recent attempts to decompose experimental Gibbs free energy on separate contribution from various physical factors based on the concept of fixed molecules forming π-stacked dimers, have been characterized as successful (see [6] and references therein). In summary we consider that once the complexation of molecules has occurred (resulting in formation of an aggregate), each of the molecule in the aggregate looses three translational and rotational degrees of freedom (part of the lost freedom may actually be restored due to formation of intermolecular vibrational degree of freedom or other residual motions inside the complex [6]). It means that the positions of molecules within an aggregate are getting labeled, and, hence, they are becoming distinguishable, which supports the result $\Delta S_{mix}=0$ obtained in the present work.

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## СТАТИСТИЧЕСКИЙ АНАЛИЗ ЭКСПЕРИМЕНТАЛЬНЫХ ЗНАЧЕНИЙ ХИМИЧЕСКИХ СДВИГОВ ПРОТОНОВ ДЕЗОКСИОЛИГОНУКЛЕОТИДОВ РАЗЛИЧНОГО СОСТАВА И ПОСЛЕДОВАТЕЛЬНОСТИ ОСНОВАНИЙ В ЦЕПИ

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**Аннотация**. Методом главных компонент проведен анализ экспериментальных значений химических сдвигов необменивающихся протонов само- и несамокомплементарных дезоксиолигонуклеотидов различного состава и последовательности оснований в цепи. Выявлены признаки, наиболее существенно влияющие на магнитное экранирование протонов оснований рассмотренных коротких фрагментов ДНК.

**Ключевые слова**: дезоксиолигонуклеотид, химический сдвиг, триплет, главные компоненты**.**

## STATISTICAL ANALYSIS OF EXPERIMENTAL VALUES OF PROTONS CHEMICAL SHIFTS OLIGONUCLEOTIDES OF VARIOUS CONTENT AND BASE SEQUENCE IN THE NUCLEOTIDE CHAIN

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**Abstract**. The analysis of experimental values of chemical shifts of non-exchanging protons of deoxyoligonucleotides of various content and base sequence in the nucleotide chain has been made using the method of Principal Components Analysis. Most important factors influencing the shielding of protons of the considered short fragments of DNA are revealed.

**Keywords**: deoxyoligonucleotide, chemical shift, triplet, the principal components**.**

В настоящей работе проведен статистический анализ экспериментальных значений химических сдвигов необменивающихся протонов само- и несамокомплементарных дезоксиолигонуклеотидов. В качестве статистического метода обработки данных использовался метод главных компонент (МГК). МГК является классическим методом снижения размерности данных путем определения незначительного числа линейных комбинаций исходных признаков, объясняющих большую часть изменчивости данных в целом.

Целью данной работы являлось проведение сравнительного анализа резонансных сигналов (химических сдвигов) протонов дезоксиолигонуклеотидов, отличающихся длиной и последовательностью оснований в цепи. Химический сдвиг, являющийся одним из экспериментальных параметров ЯМР, непосредственно связан с электронным и магнитным окружением молекул и позволяет изучить конформационные особенности соединений непосредственно в растворе. Тетрануклеотиды, рассмотренные в работе, представлены пятью самокомплементарными последовательностями: 5'-d(GCGC), 5'-d(CGCG), 5'-d(ACGT), 5'-d(AGCT), 5'-d(TGCA), гексануклеотидами - 5'-d(CGTACG), 5'-d(CGCGCG), 5'-d(TACGTA) и октамером - 5'-(GACATGTC) [1,2]. К несамокомплементарным последовательростям, изученным в работе, относятся тетрамеры 5'-d(AAGC), 5'-d(CTGA), 5'-d(CGAA), 5'-d(GAAG) и гептамер - 5'-d(GCGAAGC) [3]. Каждый из дезоксиолигонуклеотидов был разбит на триплеты, отличающиеся составом и локализацией оснований, что позволило проанализировать особенности магнитного экранирования протонов центрального в триплете основания [4].

В зависимости от длины последовательности триплеты одного состава могут быть как терминальными, так и внутренними; терминальные триплеты, в свою очередь, могут принадлежать как к 5'- , так и к 3'- концу цепи; центральное основание может быть окружено двумя пуринами, пиримидинами или какой-либо чередующейся комбинацией оснований. Все эти «признаки» могут быть использованы для выявления особенностей экранирования протонов азотистых оснований методом главных компонент.

В таблице 1, в качестве примера, приведены химические сдвиги протонов центрального аденина и сахарных остатков, входящих в триплеты, содержащие только пуриновые основания. Триплеты взяты как из само-, так и несамокомплементарных дезоксиолигонуклеотидов. Вероятность образования молекулярных дуплексов для