

Formation Thermodynamics of Cucurbit[6]uril Macrocyclic Molecules: A Theory Study

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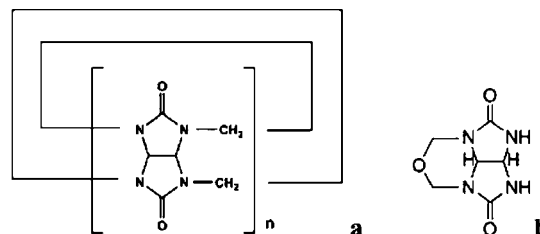
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Macrocyclic molecules are very important molecular cavitands for the supramolecular chemistry in view of host–guest complexation which is a basis for design of molecular devices. One striking example of macrocycles is the family of cucurbit[*n*]uril molecules (CB[*n*]). For effective application of the cavitands of this family it is needed to elucidate the stabilization mechanism of different homologues CB[*n*]. In this study we have carried out a thermodynamical analysis of macromolecule cyclization from a monomer to a pentamer and CB6. It was found that water molecules, which are formed as one of the products of the reaction of glycoluril with formaldehyde, construct dimer and oligomer CB(*m*) so that an angle between adjacent building units corresponds to the stable homologue CB[6]. In the framework of the density functional theory (DFT), the structures of hydrated oligomers were optimized. Calculated thermodynamical functions were used for a description of cyclization mechanism of oligomers up to formation of CB[6]. It is assumed that the proposed model can be extended to the formation of higher homologues in diluted water–acid solutions.

Introduction

Cucurbit[*n*]uril (CB[*n*]) is a family of homologues which are most favored cavitands for host–guest complexation.^{1–4} Effective chemical and physical properties of these complexes with organic molecules and cations^{5–7} as molecular switches and catalysts have been well demonstrated.^{8,9} At the present time, it is established that at various experimental conditions a number of homologues are formed in the process of synthesis. Considering CB[*n*] as a molecular container in supramolecular chemistry, we have to understand specific features of macrocycle formation and stabilization mechanism of each homologue. The homologues CB[*n*] are formed by an acid-catalyzed condensation reaction of glycoluril (GU) with formaldehyde.^{10,11} Many researchers believe that CB[6] is the most stable homologue of the CB[*n*] family. To explain the structural stability of CB[6], a very promising model¹⁰ was proposed in which the hydronium ion was considered as a template. Using the Hartree–Fock method (HF) and the density functional theory (DFT) in B3LYP version with the atomic 3-21G basis set, the structures and energies of CB[*n*] (*n* = 4–7) were calculated with full geometry optimization. Additional single-point B3LYP calculations were performed with a more extended 6-31G* basis set for fixed geometries obtained at the B3LYP/3-21G level. The difference between the total energy of CB[*n*] and the *n*-fold building unit energy, named *E*(extra), was directly related to the structural stability of CB[*n*]. Using a higher calculation level (PBE/TZ) it was shown¹² that the CB[6] formation is thermodynamically more favorable compared to other possible species, but this gain is not pronounced. The authors of studies^{10,12} concluded that the reason of preferable CB[6] formation may be explained by a hidden mechanism of the whole process.

To investigate template effects in the formation of CB[*n*], two H₃O⁺ ions were positioned at every portal of each molecule.¹⁰ The same levels of calculations as for the CB[*n*]

CHART 1: Building Units of CB[*n*] Macrocycles (a) and Its Precursor (b)

without H₃O⁺ ions were used. There exist several important questions concerning the applicability of this model. Can the model be extended on real acid solution systems where monomers, dimers of glycoluril groups (GU groups) appear to be a core of the solvates? What is the role of hydronium in dimer and oligomer formation before the macrocycle is closed. It is known that CB[6] product is polycrystalline one but if hydronium ions are situated in the carbonyl portals, the macrocycles have to undergo a repulsion due to the electrostatic charges of portals and therefore the crystal formation becomes impossible.

CB[*n*] molecular structures comprise [*n*] building units which are presented in the square brackets in Chart 1a.

The linking of building units one after the other¹⁰ seems to be enough for a chemical description of dimer,..., oligomer,..., CB[*n*] formation. However, the building units do not exist in solution but appear as products of chemical reaction. If it is the case, we should first of all ascertain which molecule is a molecular precursor in solution. Such an approach was used in work¹³ for analysis of the mechanism of homologues sequence formation in CB[*n*] family. It was shown that formation of the sequence of CB[8] → CB[7] → CB[6] homologues is defined by thermodynamics of diluted water–acid solutions, the CB[6] being the most stable homologue. However, it was reported¹¹ that, as a rule, the yield of CB[6] homologue in water solutions

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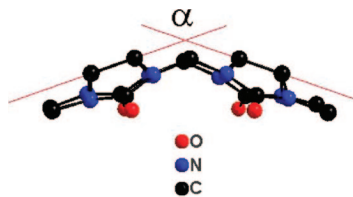
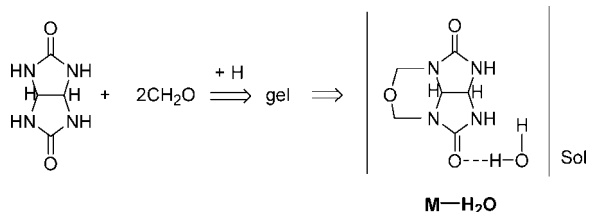


Figure 1. Angle α between adjacent building units. H atoms are not indicated.

SCHEME 1



reaches about of 50% and almost 90% yield takes place only in concentrated sulfuric acid. The mechanism of this effect is unknown.

A CB[n] formation begins with the formation of a dimer.^{10,11,14} It has been shown that the dimers and oligomers with single-sign curvature, C-shaped, are thermodynamically favored over reversal-curvature, S-shaped, molecules.^{14,15} The most incredible occasion is the line shape oligomer formation before CB[n] closing.⁴ Each homologue of the CB[n] family is characterized by a definite $\alpha(n)$ angle between adjacent GU groups as shown in Figure 1. It means that a connecting link of the adjacent GU groups by two methylene bridges is flexible enough and allows to change the $\alpha(n)$ angle in the range of 108–140 deg. The question arises whether the $\alpha(n)$ angle is created at the dimer (D–3H₂O) or trimer (CB(3)–5H₂O) formation step or as a result of the CB(n) oligomer closure. Because there are no clear scientific ideas of the closure of the CB(n) oligomer of an arbitrary shape, except a vague term “self-assembly”, it is needed to seek an answer to this question in kinetics and thermodynamics of the CB(m) oligomer formation (here $3 \leq m \leq n$).

The goal of this paper is to carry out a thermodynamic analysis of the formation and stabilization mechanism of the CB[6] homologue of cucurbit[n]uril family in H₂SO₄ concentrated acid as a real model of anhydrous solvent.

Methods. It is known that in the presence of acid catalysts such as H₂SO₄ the polyols are converted to ethers. In this case, one of the two species suggested earlier,¹¹ namely the ether presented in Chart 1b, might be considered as the probable precursor of building units forming CB[n].

The reaction of glycoluril with formaldehyde in acid solution may be presented as a route of the monomer M precursor formation according to Scheme 1.

At the beginning of reaction, a gel precipitates¹¹ and after prolonged time (many hours or even days), the hydrated monomers M–H₂O are realized in solution. The precursor differs from the one given earlier¹¹ in that the ether presented in Figure 1b is hydrated one. In support of the route of the hydrated monomer M–H₂O formation, one may note that the precipitated CB[6] is the crystalline product (~88%). Usually, CB[6] macrocycles are associated in solid by means of additional chemical species binding carbonyl portals of adjacent macrocycles.^{16,17} However, neither free water molecules or hydronium ions as well as other admissible binding species needed for association of macrocycles at their carbonyl portals in crystalline phase do not present in concentrated sulfuric acid.

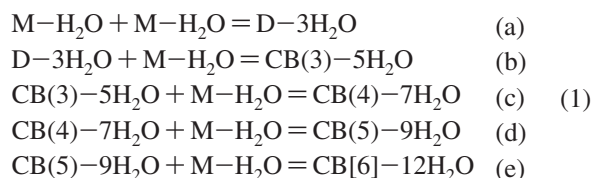
TABLE 1: Thermodynamic Function Changes of the Reactions of Monomer and Dimer Formation

reaction	Scheme 1 (M–H ₂ O)	reaction 3 (M + H ₂ O)	reaction 4 (D + 3H ₂ O)	reaction 1a (D–3H ₂ O)
ΔH_{298}^0 , kJ/mol	–146.7	–96.2	1.9	–66.4
ΔS_{298}^0 , J/mol·K	–352.8	–189.9	–65.5	–206.3
ΔG_{298}^0 , kJ/mol	–41.6	–39.6	21.4	–4.9

TABLE 2: α angles between HC–CH bonds of the adjacent GU Groups for different oligomers

α	α_1	α_2	α_3	α_4	α_{av}
D–3H ₂ O	119				119
CB[3]–5H ₂ O	115	113			114
CB[4]–7H ₂ O	116	116	98		110
CB[5]–9H ₂ O	117	135	122	122	124

The CB(m) oligomer and CB[6] macrocycle formation may be presented as a sequence of the following reactions



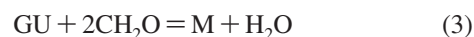
where D–3H₂O, CB(3)–5H₂O, CB(4)–7H₂O and CB(5)–9H₂O are the dimer, trimer, tetramer, and pentamer, respectively. The reactions 1a–e occur when the chemical affinities A of each chemical stage have positive values:

$$A = -\Delta G = \Delta\mu(\text{reactants}) - \Delta\mu(\text{products}) > 0 \quad (2)$$

where ΔG is the change of Gibbs free energy, and $\mu(\text{reactants})$ and $\mu(\text{products})$ are the chemical potentials of reactants and products.

Our quantum-chemical calculations were carried out using the PRIRODA program package¹⁸ and employing the density functional theory (DFT). The latter used the PBE exchange-correlation functional.¹⁹ For all the atoms, a full double- ζ (DZ) basis set (an analogue to the well-known cc-pVDZ basis set) with the Gaussian exponents specially optimized for DFT calculations was applied.²⁰ The total geometry optimization of the structures under study was performed without any symmetry constrains. No imaginary frequencies were found in the calculated vibration spectra of these systems. It means that the optimized structures correspond to minima on the total potential energy surfaces. We can take into account that solvate structure in concentrated sulfuric acid is invariable over each joining monomer and thus we can take a suggestion that solvent effect is invariable over each building unit (M–H₂O). Thus, solvent effect does not change too much right up to a macrocycle CB[n] closure.

Using a special thermodynamical analysis procedure implemented into the PRIRODA program package, the total standard enthalpies, entropies and Gibbs free energies of the model systems at 298.15 K were obtained. These values were used for subsequent calculations of the enthalpy, entropy and Gibbs free energy changes for model reactions. Table 1 lists the thermodynamical function changes for reactions of Scheme 1 in comparison with condensation reaction



Found negative meanings of ΔG_{298}^0 for Scheme 1 and reaction 3 correspond to a reality because a formation of the M–H₂O monomers has really place. Hence, an existing

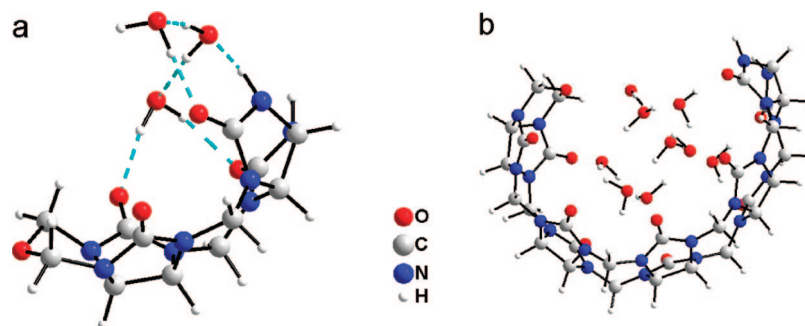


Figure 2. Optimized structures of hydrated dimer D-3H₂O (a) and pentamer CB(5)-9H₂O (b). H bonds are marked by blue dot lines.

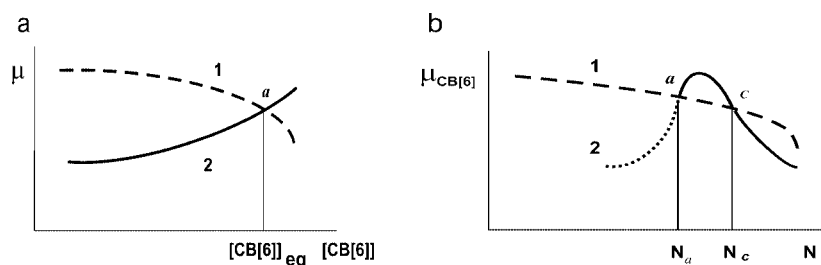


Figure 3. Dependences of the chemical potential μ_M of monomer M-H₂O in solution (1) and $\Delta\mu = \mu_{CB(m)} - \mu_{CB(m-1)}$ (2) on a macrocycle concentration (a). Change of chemical potentials of macrocycles CB[6] in solution (1) and in nucleus (2) (b). Points *a* and *c* correspond to equilibrium.

TABLE 3: Thermodynamic Function Changes of the Reactions of Trimer and Tetramer formation

reaction	trimer			tetramer		
	reaction 1b	reaction 5	reaction 6	reaction 1c	reaction 7a	reaction 7b
ΔH_{298}^0 , kJ/mol	-102.1	187.6	-168.4	-446.4	246.1	-150.9
ΔS_{298}^0 , J/mol·K	-218.6	578.1	-424.9	-203.1	898.9	-205.8
ΔG_{298}^0 , kJ/mol	-36.9	15.3	-41.8	-57.6	-21.9	-89.6

TABLE 4: Thermodynamic Function Changes of the Reactions of Pentamer and Macrocycle Formation

reaction	reaction 1d (pentamer)	reaction 8 (pentamer)	reaction 9 (macrocycle)
ΔH_{298}^0 , kJ/mol	-96.2	-145.1	-116.3
ΔS_{298}^0 , J/mol·K	-228.6	-215.8	-282.8
ΔG_{298}^0 , kJ/mol	-28.1	-80.8	-32.0

solvent effect does not disturb this correlation. In view of weak change of solvent effect mentioned above, the presented below data for other reactions will be close to a reality, too. The results show that the reaction of monomer formation (Scheme 1) is slightly preferable in accord with ΔG_{298}^0 values. However, if we consider the next step of the process, namely, the dimer formation, the reaction 1a is evidently more preferable compared to the condensation reaction

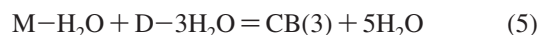


in accord with ΔG_{298}^0 values. The value $\Delta G_{298}^0 = -4.9$ kJ/mol corresponds to optimal configuration of D-3H₂O complex presented in Figure 2a that gives an angle α of 119 deg between adjacent GU groups which is close to the angle $\alpha = 120$ deg in the CB[6]. The lengths of H bonds marked by blue dot lines in Figure 2a are not larger than 0.19 nm.

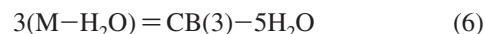
Hence, the D-3H₂O complex configuration determines the formation of stable CB[6] homologue beginning from the second stage of CB(6) oligomer formation. Angles α between HC-CH bonds of adjacent GU groups calculated for different optimized oligomers are listed in Table 2. It can be seen that the angles vary with increase of the oligomerization number but before the macrocycle closing an average α_{av} is equal to 124 deg. This value is close to the angle α of 120 deg in the CB[6]. α

angles are equal to 108, 129, and 135 deg for CB[5], CB[7] and CB[8], respectively.

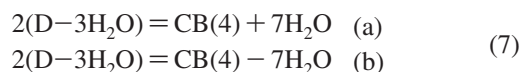
Table 3 lists the thermodynamical function changes for reactions of trimer and tetramer formation. The results show that reaction 1b is more preferable compared to the condensation reaction



According to the data in Table 3, the trimolecular reaction

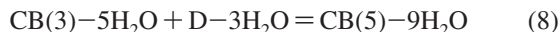


is thermodynamically more preferable compared to the reaction 1b but it is well-known that from the viewpoint of kinetics the probability of trimolecular reaction is less than that of bimolecular one. This is valid also for formation of other higher oligomers up to CB(5) as well as for CB[6] macrocycle. The reaction 1c of CB(4)-7H₂O complex formation is preferred to the condensation reaction because the last reaction has the positive value of $\Delta G_{298}^0 = 10.4$ kJ/mol. According to Table 3 the reaction 7b is preferred to the reaction 7a



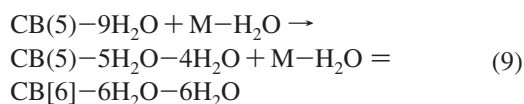
However, reaction 1c is preferred to the reaction 7b because a rate constant of the reaction of small weight M-H₂O molecule joining is higher than that of D-3H₂O, in accord with known kinetics of the second order reaction.²¹ In other words, the assembling rate of the oligomer is higher with small building units.

In accord with the calculated thermodynamical functions (Table 4), the pentamer CB(5) formation can be presented as both the reaction 1d and reaction



but the reaction 8 is discriminated by the slower kinetics, as it mentioned above. Figure 2b represents the optimal $\text{CB}(5)-5\text{H}_2\text{O}-4\text{H}_2\text{O}$ oligomer structure where five H_2O molecules are located on concave side and four H_2O molecules in carbonyl portals of the pentamer. The $\text{CB}(5)$ oligomer is distorted circle but a distance between opposite pentamer ends is about 0,63 nm which is close to the $\text{M}-\text{H}_2\text{O}$ complex size of 0,56–0,77 nm. The shapes of monomer, dimer and all oligomers can be looked over in detail in Supporting Information.

It was shown that the inclusion of more than five H_2O molecules on concave side of the pentamer leads to its disclosing. A closure of $\text{CB}(5)-5\text{H}_2\text{O}-4\text{H}_2\text{O}$ with macrocycle $\text{CB}[6]$ formation takes place in accord with the following reaction



Reaction 1e is not correct because only six H_2O molecules inside the $\text{CB}[6]$ cavity could be realized in accord with the calculated ΔG_{298}^0 value for optimized hydrated $\text{CB}[6]$ macrocycle. Table 4 lists corresponding thermodynamical function changes of the reactions of pentamer and macrocycle formation.

The formation of the $\text{CB}[6]$ macrocycle population might be described in terms of the chemical affinity (inequality 2). In accord with this the homogeneous reactions 1 take place when

$$\begin{aligned} \Delta\mu = \mu_{\text{CB}(m)} - \mu_{\text{CB}(m-1)} < \mu_{\text{M}}, \quad m < 6 \quad (a) \\ \Delta\mu = \mu_{\text{CB}(6)} - \mu_{\text{CB}(5)} < \mu_{\text{M}} \quad (b) \end{aligned} \quad (10)$$

where m is the number of building units in $\text{CB}(m)$ oligomer. Here the water molecules are not noticed. In this process the concentration of the $\text{CB}(m)$ molecules increases and $\mu_{\text{CB}(m)}$ increases, respectively. In accord with that the differences $\mu_{\text{CB}(m)} - \mu_{\text{CB}(m-1)}$ tend to μ_{M} . As a result, the $\text{CB}[6]$ macrocycle population increases up to equilibrium concentration at condition

$$\Delta\mu = \mu_{\text{CB}[6]} - \mu_{\text{CB}(5)} = \mu_{\text{M}} \quad (11)$$

Figure 3a represents a dependence of $\Delta\mu$ on the $\text{CB}[6]$ macrocycle concentration in the system closed with respect to the initial reactants (glycoluril and formaldehyde).

If the $\text{CB}[6]$ concentration in solution reaches a saturated value, critical-size nuclei can be formed and a $\text{CB}[6]$ solid precipitates. In accord with the nucleation theory, the change of Gibbs free energy required to form a nucleus (Figure 3b) is defined by an equation

$$\Delta G_{\text{Solid}} = \int_a^c (\mu_{\text{CB}[6]*} - \mu_{\text{CB}[6]}) dN \quad (12)$$

where $\mu_{\text{CB}[6]*}$ and $\mu_{\text{CB}[6]}$ are the chemical potentials of $\text{CB}[6]$ macrocycles in the nucleus and the solution, respectively, and N is a number of aggregation of macrocycles. Six H_2O molecules located in macrocycle carbonyl portals lead to a template binding of macrocycles in the solid due to H bonds.

Conclusions

In conclusion, the thermodynamical analysis of $\text{CB}[n]$ nanocavities formation showed a significant role of water molecules

in the stabilization of $\text{CB}[6]$ homologue. Cyclization of macromolecule is defined by the optimal fixed angle between adjacent GU groups; its value is close to 120 deg. This angle is specified by templating action of H_2O molecules. The angle values vary somewhat with increasing of the oligomerization number up to 5. In this last stage the average angle is equal to 124 deg so that a distance between oligomer ends is close to the size of the hydrated monomer $\text{M}-\text{H}_2\text{O}$ and the cyclization becomes preferable. Even in anhydrous solution, like concentrated sulfuric acid, formation of $\text{M}-\text{H}_2\text{O}$ monomers is thermodynamically preferable by the chemical reaction of glycoluril with formaldehyde. Thermodynamical function calculations showed that macromolecule assembling from $\text{M}-\text{H}_2\text{O}$ up to $\text{CB}[6]$ can be described by sequence of monomer joining reactions. In accord with the model considered above we can suggest that the formation of higher homologues $\text{CB}[n]$ in water diluted solutions are defined by a participation of much more H_2O molecules in construction of macrocycles.

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Supporting Information Available: Cif files containing optimal calculated structures of hydrated monomer, dimer and all oligomers of $\text{CB}(n)$, which are precursors of macrocycle $\text{CB}[6]$. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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