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How Large Can we Build a Cyclic Assembly? Impact of Ring Size on Chelate Cooperativity in Noncovalent Macrocyclizations

Carlos Montoro-García,[a] María J. Mayoral,[a] Raquel Chamorro,[a] and David González-Rodríguez[a,b]*

Abstract: Self-assembled systems rely on intramolecular cooperative effects to control their growth and regulate their shape, thus yielding discrete, well-defined structures. However, as the size of the system increases, cooperative effects tend to dissipate. We analyse here this situation by studying a set of oligomers of different lengths capped with guanosine and cytidine nucleosides, which associate in cyclic tetramers by complementary Watson-Crick H-bonding interactions. As the monomer length increases, and thus the number of σ-bonds in the π-conjugated skeleton, macrocycle stability decreases due to a notable reduction in effective molarity (*EM*), which has a clear entropic origin. We determined the relationship between *EM* or ΔS and the number of σ-bonds, which allowed us to predict the maximum monomer lengths up to which cyclic species would not be assembled quantitatively anymore, or would not able to compete at all with linear oligomers in the whole concentration range.

The formation of discrete molecular assemblies that constitute the functional elements of biological and synthetic systems relies on cooperative effects between multiple noncovalent interactions.[1] Self-assembly of a monodisperse (multi)cyclic object under thermodynamic conditions always competes with polymerization into open structures (Figure 1a).[2] The cyclic species may be formed quantitatively because it enjoys a thermodynamic stability that is substantially larger than the sum of the corresponding individual interactions. The effect that causes such increased stability is defined as *chelate cooperativity* and originates from the fact that intramolecular interactions are normally favored over intermolecular interactions due to the entropy loss stemming from bimolecular association.[3] Chemists have profited from these chelate effects to synthesize a wide variety of discrete assemblies, such as helicates, grids, macrocycles, prisms, capsules, etc, that often mimic those found in the natural world.[4]

Chelate cooperativity is quantified by the *effective molarity* (*EM*), that is defined as the ratio between intra- and intermolecular binding constants ($EM = K_{intra}/K_{inter}$).[5] Being a thermodynamic magnitude, *EM* has both an enthalpic and an entropic component:

$$EM = e^{-(\Delta H^0_{intra} - \Delta H^0_{inter}/RT)} \cdot e^{(\Delta S^0_{intra} - \Delta S^0_{inter}/R)}$$

The *enthalpic* component may depend on specific template effects with solvent or guest molecules or on electrostatic interactions that affect the cyclic and non-cyclic species differently. However, these effects are rare and difficult to predict, so in most cases this component is only associated with the strain generated upon ring closure. In the absence of strain, the enthalpic factor becomes negligible and the *EM* only depends on *entropic* effects, which depend on the symmetry and the number of components (*n*) of the cycle, since the reverse ring-opening reaction can occur statistically in *n* sites. The entropic contribution also decreases with the degrees of conformational freedom that are lost upon cyclization, particularly those related to torsional and rotational bond motions in the closed *vs* open *n*-mer, and hence *EM* tends to dissipate when shared among a large number of bonds.[6]

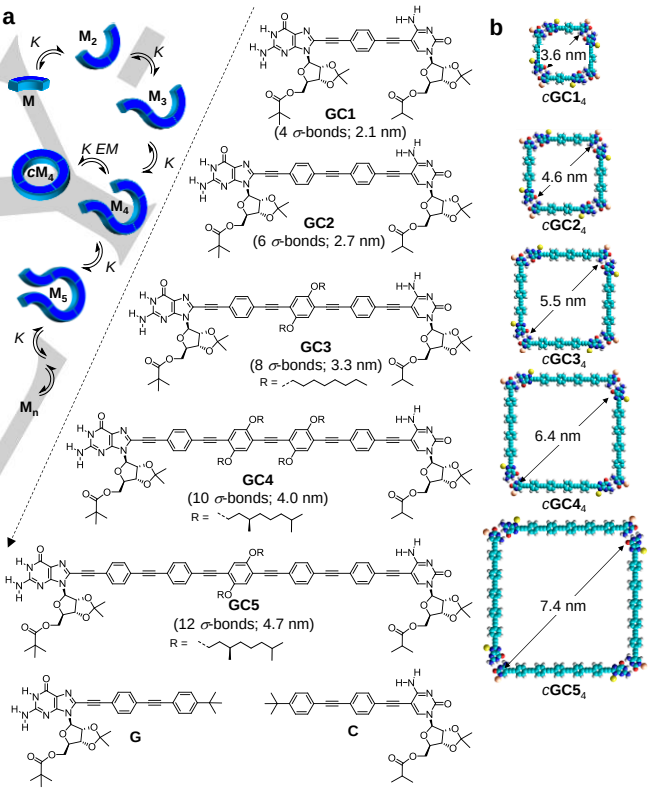

Figure 1. (**a**) Self-assembly of a ditopic molecule (**M**) into linear (**M**$_2$, **M**$_3$… **M**$_n$) or cyclic (*c***M**$_4$) structures. After reaching a certain size, a tetramer for example, binding may take place intramolecularly, to form a cycle, or intermolecularly, to yield a distribution of supramolecular polymers. The magnitude of the product *K*·*EM* will determine chelate cooperativity, and thus cyclization yields. (**b**) Chemical structure of dinucleoside monomers **GC1**-**GC5** and mononucleosides **G** and **C**. The number of σ-bonds in the linking π-conjugated blocks, the monomer length, and the cyclic tetramer diameter are also indicated.

We recently reported an example of a dinucleoside monomer (**GC1**; Figure 1b) based on a π-conjugated *p*-diethynylbenzene unit substituted with complementary nucleobases at the edges: guanine (G) and cytosine (C), which have bulky lipophilic ribose

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groups to afford solubility and prevent stacking interactions. This rigid and linear structure, together with the 90º angle provided by Watson–Crick pairing, resulted in the formation of unstrained squere-shaped H-bonded cyclic tetramers (*c***GC1**$_4$),[7a] that displayed remarkable thermodynamic and kinetic stabilities ascribed to the large *EM* values attained (10^2–10^3 M).[7b-c] Further investigations[7d] allowed us to conclude that such record chelate cooperativities stem from: (i) a rigid predisposed monomer geometry, and (ii) an unsymmetric (*i.e. ADD-DAA*), non-rotatable guanosine (G)–cytidine (C) Watson-Crick interaction,[8] which greatly aids in the preorganization of the system toward cyclotetramerization. Taking this monomer model structure, we analyse here the influence of the length of the central linker on chelate cooperativity, and thus on the thermodynamic stability of the cyclic assembly. While maintaining the same G:C binding interaction, we have synthesized a series of monomers (**GC1**–**GC5**; see S.I.) in which the terminal bases are separated by linear and rigid phenylene-ethynylene spacers of different lengths (2.1–4.7 nm; Figure 1), which results in self-assembled rings of diverse diameters (3.6–7.4 nm; Figure S1). We clearly prove that, as the length of the π-conjugated block increases, the macrocycles suffer a dramatic decrease in stability, which is exclusively due to entropic reasons. Moreover, by analysing the variation of *EM* as a function of the number of σ-bonds, which are the main responsible for rotational/torsional motions, we could extrapolate and predict the maximum cycle size up to which fidelity starts dropping from quantitative values, or reaches negligible values when compared to the competing linear oligomers.

Different methods, in which 1) solvent polarity and H-bond competing ability ($CHCl_3$/$CHCl_2CHCl_2$, THF, DMF), 2) monitoring technique (^{1}H NMR or CD), 3) concentration ($2{\cdot}10^{-2}$-10^{-4} M for NMR; $3{\cdot}10^{-4}$-$3{\cdot}10^{-6}$ M for CD), or 4) temperature range (213-403 K) are varied, were employed to evaluate qualitatively or quantitatively the thermodynamic stability of the *c***GC1**$_4$-*c***GC5**$_4$ assemblies. Their association behaviour was also contrasted to the one of a 1:1 mixture of mononucleosides **G** and **C**, in which a single Watson-Crick interaction is established. The results obtained in these experiments, which are displayed and detailed in the S. I., led to the conclusion that *the longer the central block connecting the bases, the lower the thermodynamic stability of the cyclic assembly*. Table 1 compiles the *EM* values that could be calculated for **GC1**-**GC5** in DMF, THF and $CHCl_3$ in the different dilution or competition experiments performed (see our previous work[7a-c] and the S.I. for further details). As the macrocycle becomes larger, the magnitude of *EM* experiences in THF and $CHCl_3$ a drastic decrease that encompasses 5 orders of magnitude, from over 10^2 M for **GC1** to 10^{-3} M for **GC5**. Since the G:C binding interaction that sustains the cyclic assemblies is the same in all cases, a weaker chelate cooperativity is identified here as the main cause for the notable reduction in stability observed.

The calculated association constant between the complementary mononucleosides **G** and **C** (K_{ref}; Figure 1b)[7a] and *EM* values were then used to simulate speciation profiles (Figure 2) for each dinucleoside molecule in DMF, THF and $CHCl_3$. These curves relate the concentration of each supramolecular species with total concentration and are able to reproduce quite satisfactorily the dissociation behaviour observed for *c***GC1**$_4$-*c***GC5**$_4$ in dilution experiments within the NMR and/or CD concentration ranges (Figures S2 and S4). In the polar DMF solvent, the molar fraction of dinucleoside molecules assembled as cyclic tetramers (blue lines) is only relevant for **GC1** and, to a lower extent, **GC2** at relatively high concentrations. For all the other longer monomers with lower *EM*s, cyclic tetramer formation is insignificant and association into open oligomers (grey lines) start to dominate above 10^{-2} M. Due to the weak binding constant in this solvent (K_{ref} = 5.7 M^{-1}), the monomer (red line) is the only species present in solution at concentrations below 10^{-3} M. As G-C pairing becomes stronger in THF (K_{ref} = 1500 M^{-1}) the cyclic tetramer can now be formed quantitatively for the shorter monomers at concentrations above *ca.* 10^{-3} M. However, for **GC3**-**GC5**, the notable reduction in *EM* leads to a competition between linear and cyclic oligomers in the high concentration region. The same trend is observed in $CHCl_3$, but cycles are formed in higher yields and persist up to lower concentrations due to a higher G:C association constant (K_{ref} = 28000 M^{-1}). In fact, in this nonpolar solvent the cyclic tetramer can be formed quantitatively (**GC1**-**GC3**) or close to quantitatively (*i.e.* >90%; **GC4**-**GC5**) at intermediate NMR concentrations.

Table 1. Reference intermolecular association constants (K_{ref}), effective molarities (*EM*), and enthalpic (ΔH) and entropic (ΔS) changes associated to the cyclotetramerization process of **GC1**-**GC5** in different solvents.

Solvent	M	*EM* [b]	*ΔH*	*ΔS*
K_{ref} / M^{-1} [a]		M	kJmol^{-1}	Jmol^{-1}K^{-1}
DMF	**GC1**	$2.2{\cdot}10^2$ [c]	-155.2	-425.0
5.7	**GC2**		-166.3	-558.8
THF	**GC1**	$2.0{\cdot}10^2$ [c]	-98,7	-32,3
$1.5{\cdot}10^3$	**GC2**	$2.4{\cdot}10^0$	-91,9	-66,3
	GC3	$1.6{\cdot}10^{-1}$	-95,8	-87,6
	GC4			
	GC5	$1.2{\cdot}10^{-3}$	-101,6	-159,8
$CHCl_3$	**GC1**	$9.1{\cdot}10^2$ [c]		
$2.8{\cdot}10^4$	**GC2**	$1.1{\cdot}10^1$		
	GC3	$4.9{\cdot}10^{-1}$		
	GC4	$3.1{\cdot}10^{-2}$		
	GC5	$2.2{\cdot}10^{-3}$		

[a] K_{ref}: association constant between the complementary mononucleosides **G** and **C** (Figure 1b).[7a] [b] Determined as: $EM = K_T/K_{ref}^4$ using the data calculated from the NMR dilution in DMF-D_6 (Figure S2B), NMR dilution in THF-D_8 (Figure S2A), NMR competition experiments with **C** in $CDCl_3$ (Figure S3B), respectively. [c] *EM* values ranging between $2.2{\cdot}10^2$-$3.6{\cdot}10^2$ M (DMF), $1.8{\cdot}10^2$-$7.3{\cdot}10^2$ M (THF), or $8.1{\cdot}10^2$-$9.1{\cdot}10^2$ M ($CHCl_3$) were previously determined by us for **GC1**.[7a-c]

Temperature-dependent NMR experiments in THF (Figure S5B) and DMF (Figure S5C) were also performed and analysed to determine the enthalpic (ΔH) and entropic (ΔS) changes of the cyclotetramerization process, which are listed in Table 1.[7a] The corresponding van't Hoff plots are shown in Figure 3a,b. Parallel lines were obtained that manifest that the enthalpy of this cyclization process is very similar for all dinucleosides and that entropy is the actual responsible for differences in stability noted.

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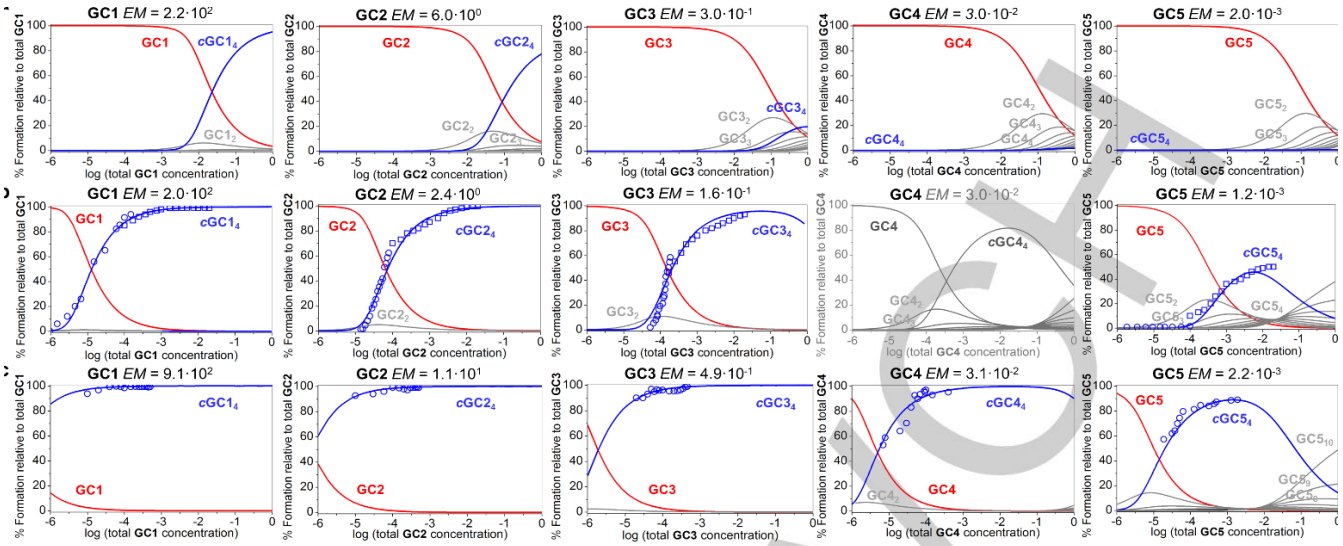

Figure 2. Simulated speciation curves (lines) and experimental dilution data (squares (NMR) and circles (CD)) indicating the molar fraction of each species (cyclic tetramer: blue; monomer: red; open oligomers: grey) as a function of the total **GC1**-**GC5** concentration in (**a**) DMF, (**b**) THF and (**c**) $CHCl_3$. K_{ref} values were set to 5.7 (DMF), $1.5{\cdot}10^3$ (THF) and $2.8{\cdot}10^4$ ($CHCl_3$), whereas the *EM* value used is displayed on top of each diagram (see also Table 1). The *EM* values for *c***GC2**$_4$-*c***GC5**$_4$ in DMF and for *c***GC4**$_4$ in THF, which could not be determined experimentally (see the S.I.), were taken close from those found in the other solvents, since *EM*s are typically not much impacted by the solvent nature. **GC4** in THF, shown in grey, was the only sample that did not follow the simulated behavior (see below).

In order to rationalize this entropic origin in the reduction of *EM*, let us focus on the cyclization event and compare open and cyclic tetramer species (Figure 3c). The gain in stabilization when going from an open to a cyclic system, the magnitude of the chelate effect, is represented by the product $K{\cdot}EM$, where K is the reference G:C association constant, since there is an additional binding event to form the cycle and it is the same for all cycles independently of their size, while *EM* is the factor that takes into account that this last binding event is intramolecular and different from the rest. In our case, all **GC1-GC5** monomers share a rigid structure that is designed to produce square-shaped assemblies devoid of strain. This is demonstrated by the fact that cyclization is not associated with large enthalpic differences between the different monomers. However, we should take into account other issues that affect the entropic term in *EM* and that are related with the *degrees of freedom that are lost upon cyclization*.

Let's first consider *rotational motions* around C*sp*-C*sp*^{2} σ-bonds in the oligo(phenylene-ethynylene) spacer. These rotations are usually fast[9] and not restricted upon cyclization: all σ-bonds should still rotate freely in the cyclic species. However, as shown in Figure 3c, rotation around these bonds in the open oligomers can produce multiple conformations in which the Watson-Crick edges alternate between *syn* and *anti* relative arrangements, but cyclization demands these edges to arrange exclusively in a *syn* relative conformation (Figure 3c). If we now consider *torsional motions*, which can be accessed by stretching and bending of (mainly) the σ-bonds in the phenylene-ethynylene skeleton, it is clear that these collective motions should be considerably more restricted in the rigid cyclic structure, which presents an additional binding site, than in the flexible linear oligomers, which possess free end-groups. In short, when going from an open to a closed species the number of degrees of freedom associated with rotational and torsional motions of (mainly) σ-bonds is decreased, which contributes to an entropic reduction in the maximum attainable *EM* of the cyclic system. As a matter of fact, we noticed that both Ln *EM* and ΔS follow a linear relationship with the number of C*sp*-C*sp*^{2} σ-bonds in the spacer, as shown respectively in Figures 4a and 4b,[10] whereas ΔH is not strongly affected and remains virtually constant for all assemblies.

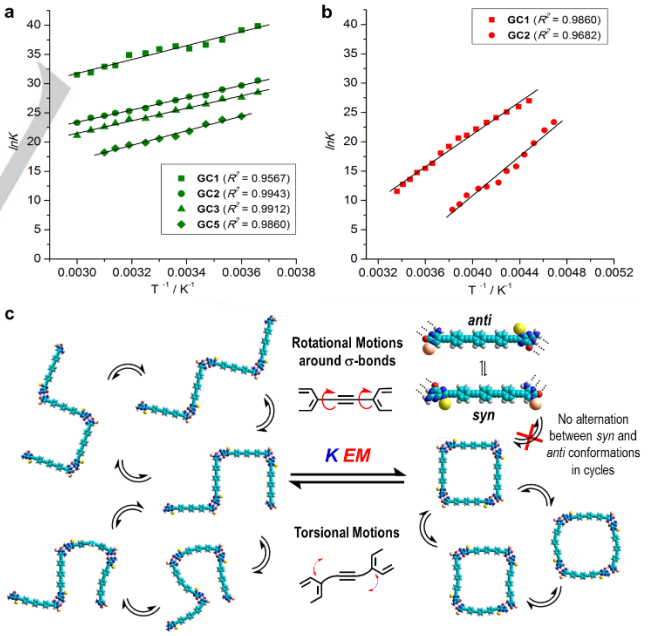

Figure 3. (**a**-**b**) Van't Hoff analysis of the temperature dependent NMR data of (**a**) **GC1-GC3**, **GC5** in THF-D_8 at $5.0{\times}10^{-4}$ M (Figure S5B) and (**b**) **GC1-GC2** in DMF-*D7* at $1.0{\times}10^{-2}$ M (Figure S5C). (**c**) Comparison of the degrees of freedom related with rotational and torsional motions between open and cyclic tetramers.

The question posed at the title, "*How large can we build a cyclic assembly?*", can at this point be addressed in different ways.

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Ercolani defined the expression: K_{ref}·*EM* ≥ 185·*n*, (*n* being the number of monomers in the cycle; *n* = 4), as the condition for *quantitative* cycle assembly at a given concentration.[5a,c] We are showing as horizontal dashed lines in Figure 4a the threshold above which this condition is met for the three main solvents studied herein: DMF, THF and $CHCl_3$. As can also be deduced from Figure 2, this condition is (hardly) met by **GC1** (4 σ-bonds) in DMF, **GC3** (8 σ-bonds) in THF and **GC4** (10 σ-bonds) in $CHCl_3$. Monomer **GC5** (12 σ-bonds), on the contrary, is not able to cyclize quantitatively in any of these solvents. Obviously, strengthening G:C association in apolar solvents (in toluene K_{ref} > 10^5 M^{-1})[11] would allow **GC5** and longer monomers to form quantitatively.

Another way of answering this question would be to estimate for which monomer length the macrocyclization process becomes *endergonic*, that is, the length at which cyclic species would not be able to compete at all with linear oligomers, independently of the concentration. Figure 4b displays the $\Delta G°$ values of the cyclotetramerization process, calculated in THF either *via* $\Delta G = \Delta H$-TΔS (from the variable temperature NMR experiments; Figure S5B) or *via* ΔG = -RT ln K_T (from the NMR dilution experiments; Figure S2A), which show a satisfactory match. The extrapolation to $\Delta G° = 0$ indicates that the cyclotetramerization process becomes energetically unfavourable in THF when the number of σ-bonds in the spacer reaches *ca.* 26, which would correspond to 12 phenylene-ethynylene units. Again, this analysis strongly depends on K_{ref}, which can be tuned by the solvent employed. Reinforcing H-bonding strength in $CHCl_3$ would make this number higher, while decreasing it in DMF would make it lower. In fact, Figure 2 shows that **GC5**, with 12 σ-bonds, would be unable to cyclize in DMF independently of the concentration, and only linear oligomers are formed in the high concentration regime.

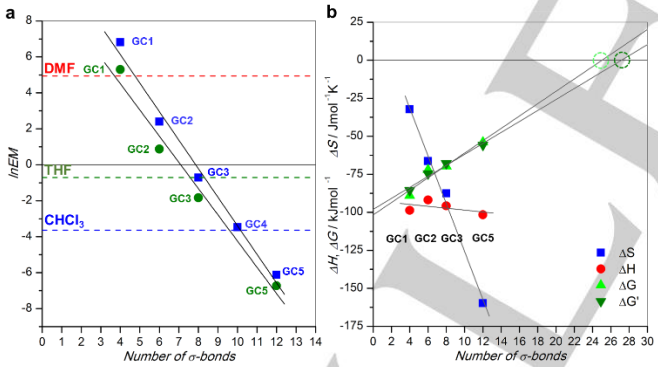

Figure 4. Plots of (**a**) Ln *EM vs* number of σ-bonds for **GC1-GC5** in THF (green circles) and $CHCl_3$ (blue squares). Dashed lines show the threshold above which the K_{ref}·*EM* ≥ 185·*n* condition is met for DMF, THF and $CHCl_3$. (**b**) ΔH, ΔG and ΔS values *vs* number of σ-bonds for **GC1-GC3** and **GC5** in THF.

The analysis made herein is of course only applicable to our particular monomer structure and binding interaction. Any change to the repeating unit in the central spacer may lead to important deviations. We are also ignoring the influence of the lateral alkyl chains in the spacers, which had to be installed due to synthetic and solubility reasons. The length and relative position of these chains can influence the moments of inertia around σ-bonds and introduce diverse local solvation, conformational and steric effects that make that not all σ-bonds in the spacer rotate and bend equally. For instance, we believe the reason why **GC4** exhibited a slightly anomalous behaviour in some of the experiments is because of the presence of two consecutive aryl groups equipped with alkoxy chains. This spacer was designed in this way in order to keep the same symmetry as in the others, but rotation (for instance) around the σ-bonds connecting these two units should be considerably affected by the presence of the 4 neighbouring alkyl chains. As a matter of fact, **GC4** is the only compound that did not assemble as cyclic tetramers at room temperature in THF (see ^{1}H NMR in Figures S2A and S5B and CD spectra in Figure S6A), thus deviating from the simulated trends displayed in Figure 2. Only lower temperatures (10 °C; see Figure S5B) or more apolar environments ($CHCl_3$) promoted *c***GC4**$_4$ macrocyclization.

In short, we have analyzed the effect of monomer lenght on a supramolecular ring-chain equilibrium. The extrapolation of our trends afforded an estimation on how large we can build a cyclic assembly in competition with linear oligomers. The quantitative results obtained in this work only apply to our particular monomer structure, but the analysis performed and our general conclusions could in principle be extended to many supramolecular cycles or cages in which size is tuned.[12] Thus, a careful design of the respective building blocks, linking motifs, and the substituents that confer solubility must be carried out to limit the number of degrees of freedom that are lost upon cyclization, so that the desired supramolecular structure can be assembled with high fidelity.

Acknowledgements

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Keywords: Supramolecular Chemistry • Noncovalent Synthesis • Chelate Effect • Nucleoside Self-assembly • Effective Molarity

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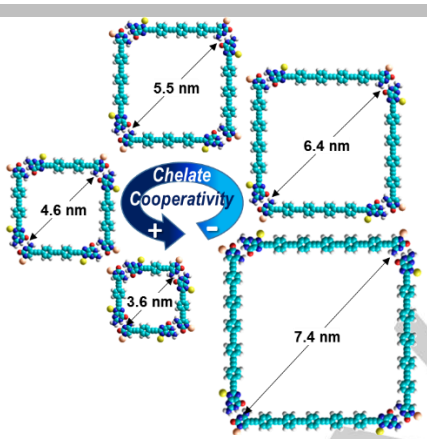
Decoding the relationship between monomer length and chelate cooperativity allowed us to predict the monomer length up to which cyclic species are not be able to compete anymore with linear oligomers in ring-chain self-assembly processes.



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