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How to Distinguish Isodesmic from Cooperative Supramolecular Polymerisation

Maarten M. J. Smulders,[a] Marko M. L. Nieuwenhuizen,[a] Tom F. A. de Greef,[a] Paul van der Schoot,[b] Albertus P. H. J. Schenning,*[a] and E. W. Meijer*[a]

Abstract: To study the supramolecular polymerisation mechanisms of a self-assembling system, concentration- and temperature-dependent measurements can both be used to probe the transition from the molecular dissolved state to the aggregated state. In this report, both methods are evaluated to determine their effectiveness in identifying and quantifying the self-assembly mechanism for isodesmic and cooperative self-assembling systems. It was found that for a rapid and unambiguous determination of the self-assembly mechanism and its thermodynamic parameters, temperature-dependent measurements are more appropriate. These studies allow the acquisition of a large data set leading to an accurate determination of the self-assembly mechanism and quantification of the different thermodynamic parameters that describe the supramolecular polymerisation. For a comprehensive characterisation, additional concentration-dependent measurements can be performed.

Keywords: self-assembly · polymerization · reaction mechanisms · supramolecular chemistry · UV/Vis spectroscopy

Introduction

Self-assembly offers a powerful approach for the development of complex, functional supramolecular nanostructures starting from relatively small and simple molecules.[1] However, for the rational design of these supramolecular assemblies, an insight into the mechanisms of formation and the thermodynamic stability of the self-assembled supramolecular structures are of crucial importance.[2] The self-assembly model that is often used to describe the self-assembly of quasi-one-dimensional polymer-like chains is based on the isodesmic equilibrium in which every monomer addition to the growing chain is governed by a single equilibrium constant, K_e (equal-K model, Figure 1A).[3] To allow for cooperative processes in self-assembly, the isodesmic model can be augmented by assuming that an (unfavourable) activation step, governed by equilibrium constant K_a, precedes chain elongation or growth with equilibrium constant K_e (Figure 1B). If $K_a \ll 1$ the polymerisation becomes cooperative and is reminiscent of an actual phase transition, which implies a sharp polymerisation point below which assemblies do not form in appreciable numbers.[4,5]

For both the isodesmic and the activated model, appreciable degrees of polymerisation occur only when the dimensionless concentration exceeds unity: $c_T K_e > 1$, in which c_T is the total concentration (i.e., the critical concentration corresponds to K_e^{-1}). The elongation equilibrium constant is temperature-dependent, $K_e = K_e(T)$, and so the polymerisation may be promoted either by increasing the concentration beyond the critical concentration, K_e^{-1},[6–10] or by varying the temperature, T.[8,10–12] The isodesmic and cooperative nucleated self-assembly mechanisms show distinct features. For example, in isodesmic assembly, there is a gradual increase in the number and length of the aggregated species and it is only at high concentrations or for high association constants that long nanometre-sized objects are formed (Figure 1C). In the case of cooperative self-assembly, there is a bimodal distribution of monomers and elongated objects, which is present throughout the self-assembly process once the critical nucleus needed for chain elongation is

[a] M. M. J. Smulders, M. M. L. Nieuwenhuizen, Dr. T. F. A. de Greef, Dr. A. P. H. J. Schenning, Prof. Dr. E. W. Meijer
Laboratory of Macromolecular and Organic Chemistry
and Institute for Complex Molecular Systems
Eindhoven University of Technology
P.O. Box 513, 5600 MB Eindhoven (The Netherlands)
Fax: (+31) 40-245-1036
E-mail: A.P.H.J.Schenning@tue.nl
E.W.Meijer@tue.nl

[b] Prof. Dr. P. van der Schoot
Group Theory of Polymers and Soft Matter
Eindhoven University of Technology
P.O. Box 513, 5600 MB Eindhoven (The Netherlands)

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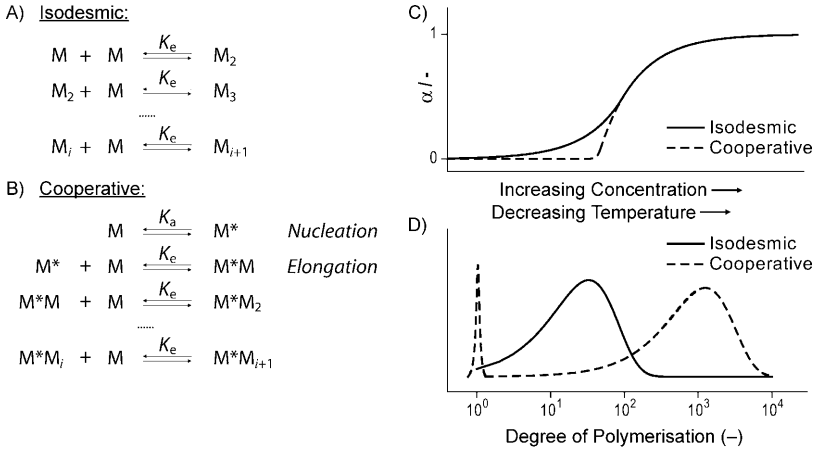


Figure 1. Schematic representation of A) the isodesmic and B) the cooperative self-assembly mechanism for monomers M. C) Schematic representation of the degree of aggregation, α, versus concentration and temperature. D) Schematic molecular weight distribution for an isodesmic and a cooperative self-assembly mechanism.

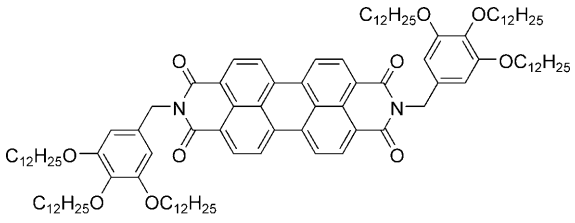
formed (Figure 1D).[4,5] Despite these fundamental differences in assembly behaviour, distinguishing between isodesmic and cooperative assembly is a delicate issue. This is because in an actual experiment the limited number of data points typically obtained from concentration-dependent (*C*-dependent) spectroscopic measurements makes it difficult to reliably establish the self-assembly mechanism and thus the use of additional techniques, such as vapour-pressure osmometry,[7,8,13] diffusion-ordered NMR spectroscopy,[8,14] isothermal titration calorimetry[15] or scattering techniques (light,[16] X-ray[17] or neutron scattering[18]), is required.

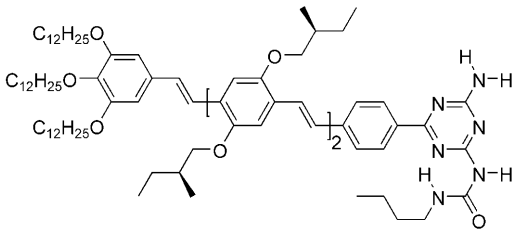
We show herein that it is more expedient to focus on temperature-dependent (*T*-dependent) measurements to obtain sufficient data points and unambiguously identify the mechanism of self-assembly. Indeed, the complete transition from the monomeric (at high *T*) to the polymeric state (at low *T*) can be probed by using high-resolution methods. Because the temperature can be varied continuously, the automated acquisition of a large number of data points from which all the relevant thermodynamic parameters can be deduced is possible. The models that we have applied to analyse the data are the standard isodesmic model[3] and a cooperative assembly model, which is a special case of a more elaborate helical assembly model[19] and resembles, but is not identical to, the Oosawa–Kasai model of actin polymerisation.[20] Although not immediately obvious, this model is similar to the widely used "K_2–K model".[5,21]

We have chosen perylene-bisimide derivative **1** and oligo(*p*-phenylenevinylene) derivative **2** as illustrative model compounds. We have already reported on the *C*-dependent isodesmic self-assembly of **1**[22] and the *T*-dependent cooperative self-assembly of chiral **2**.[12] Herein we extend and fully analyse the results in terms of the described models, which allows us to evaluate to what extent *T*- and *C*-dependent experiments are appropriate to assign and quantify each of the two self-assembly mechanisms. Although we will discuss only the supramolecular polymerisation of monomers into one-dimensional (linear) aggregates, the models presented herein are also applicable to the self-assembly of organogelators[23] as these systems often involve an (initial) one-dimensional polymerisation regime.

Results and Discussion

Isodesmic self-assembly of perylene-bisimide 1: The self-assembly of **1** in methylcyclohexane (MCH) solutions was studied by UV/Vis spectroscopy as a function of temperature (Figure 2A). Upon cooling, a hypochromic effect was observed as





well as a broadening of the spectrum with a loss of the fine structure in a similar fashion to that observed previously.[22] Also, a shoulder at 556 nm appeared upon cooling. To follow the self-assembly of **1** in detail we recorded the UV/Vis absorption at 556 nm at 0.1 K intervals while slowly cooling the sample from 363 to 273 K at a rate of 1 K min^{-1}. This low cooling rate was applied to ensure that the supramolecular polymerisation occurred under thermodynamic control.[12]

The UV/Vis absorption at 556 nm displays a clear sigmoidal shape as a function of temperature, indicative of an isodesmic self-assembly mechanism, in agreement with the results of the *C*-dependent data published for **1** previously[22] and related perylene-bisimides described by others.[6,8] Furthermore, by selecting an interval of 0.1 K it was possible to obtain a practically continuous curve which allows for a reliable fit of the data (Figure 2B). To fit the *T*-dependent absorption data, we normalised the data[24] to obtain the degree of aggregation, α, and fitted the data to the predic-

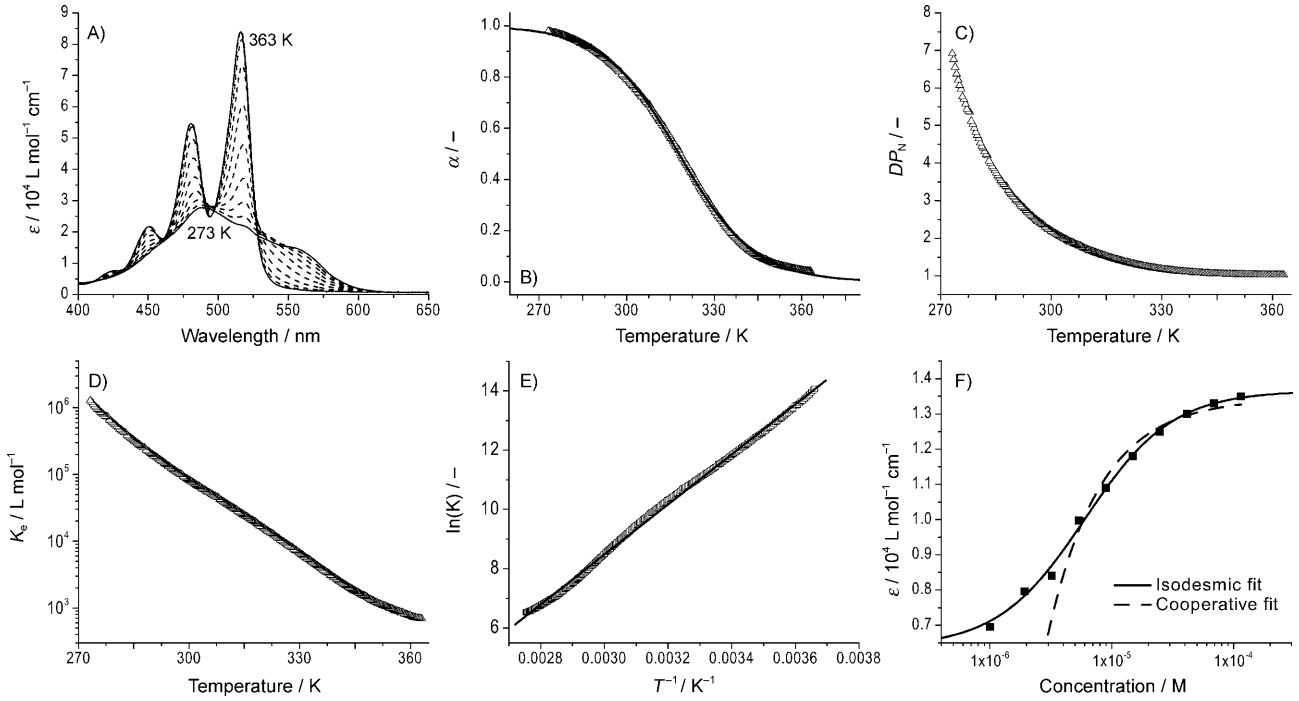


Figure 2. A) UV/Vis spectra of **1** in MCH recorded at 363–273 K at 10 K intervals. B) Temperature-dependent degree of aggregation, α, calculated from the UV/Vis absorption at 556 nm and the corresponding isodesmic fit. C) Number-averaged degree of polymerisation, DP_N, as a function of temperature. D) Elongation equilibrium constant, K_e, as a function of temperature. E) Van't Hoff plot for **1** in MCH. The equilibrium constant was rendered dimensionless by dividing it by the molar volume of MCH (0.128 L mol^{-1}). F) Molar absorptivity, ε, at 556 nm as a function of concentration of **1** in MCH fitted with the isodesmic model (solid line), yielding a K_e value of 2×10^5 M^{-1}. For comparison, the cooperative model (dashed line) was also used to fit the data. Concentration of **1** (in graphs A–E): 3.2×10^{-5} M in MCH.

tion of the isodesmic model, derived for constant concentration,[4,21] in which α is approximated by Equation (1) in which T_m is the melting temperature defined as the temperature for which $\alpha=0.5$, ΔH is the molar enthalpy release related to the formation of non-covalent intermolecular interactions and R is the gas constant.

$$\alpha \cong \frac{1}{1+\exp\left[-0.908\Delta H\frac{T-T_m}{RT_m^2}\right]} \quad (1)$$

By using Equation (1), T_m and ΔH were determined for all concentrations tested (the results are tabulated in Table 1). Inserting the degree of aggregation into Equation (2) yields the average stack length, DP_N, as well as the equilibrium constant, K_e, from which we could also calculate the change in entropy, ΔS.

$$DP_N = \frac{1}{\sqrt{1-\alpha(T)}} = \frac{1}{2}+\frac{1}{2}\sqrt{4K_e(T)c_T+1} \quad (2)$$

Table 1. Thermodynamic parameters describing the self-assembly of **1** in MCH at different concentrations.

C [μM]	ΔH [kJ mol^{-1}]	T_m [K]	K_e[a] [10^5 M^{-1}]	ΔS [J mol^{-1} K^{-1}]	DP_N[a]
15.5	−79.4	308.3	1.7	−154	2.2
25.7	−75.6	313.6	1.5	−142	2.5
32.0	−72.1	320.1	1.5	−118	2.7
37.9	−68.4	318.0	1.4	−130	2.8
98.0	−75.3	337.0	2.0	−138	5.0

[a] Values determined at 293 K.

The average enthalpy value of -74 kJ mol^{-1} that was found by applying the model is somewhat higher than the value of -58 kJ mol^{-1} found when plotting the logarithm of the concentration versus the reciprocal melting temperature.[21] The gradual stack growth with decreasing temperature or increasing concentration, characteristic of isodesmic assembly (Table 1), implies that for all measured concentrations low DP_N values are obtained at 293 K (Figure 2C).

An important consequence of using temperature to regulate the degree of self-assembly is that it directly affects the value of the equilibrium constant. If we assume that the enthalpy release, ΔH, upon bonding is independent of temperature, this means that K_e depends exponentially on temperature and so should be quite sensitive to it (Figure 2D). The average K_e value at 293 K of 1.6×10^5 M^{-1}, as determined by T-dependent spectroscopy, corresponds well with the value of 2×10^5 M^{-1} obtained from C-dependent measurements at 293 K (Figure 2F). Also, by plotting the logarithm of K_e versus the reciprocal temperature (Van't Hoff plot, Fig-

ure 2E), we find a ΔH value of $-70\,\mathrm{kJ\,mol^{-1}}$ and a ΔS value of $123\,\mathrm{J\,mol^{-1}\,K^{-1}}$, in good agreement with the values in Table 1.[25] Thus, our results are internally consistent.

The cooperative self-assembly of oligo(*p*-phenylenevinylene) derivative 2: Next, we investigated the helical self-assembly of **2** in MCH solutions as a function of concentration.[26] Previous *T*-dependent spectroscopic studies have already revealed that upon cooling below a critical temperature, the self-assembly of **2** in solution is highly cooperative.[12] Because temperature and concentration should be exchangeable in driving the assembly, we recorded the CD spectrum of **2** in MCH at a constant temperature of 313 K while varying the concentration. At 10^{-6} M no Cotton effect was observed, which indicates that **2** is molecularly dissolved under these conditions (Figure 3A). With increasing concentration, a bisignated Cotton effect appears, indicative of the formation of one-handed helical stacks.

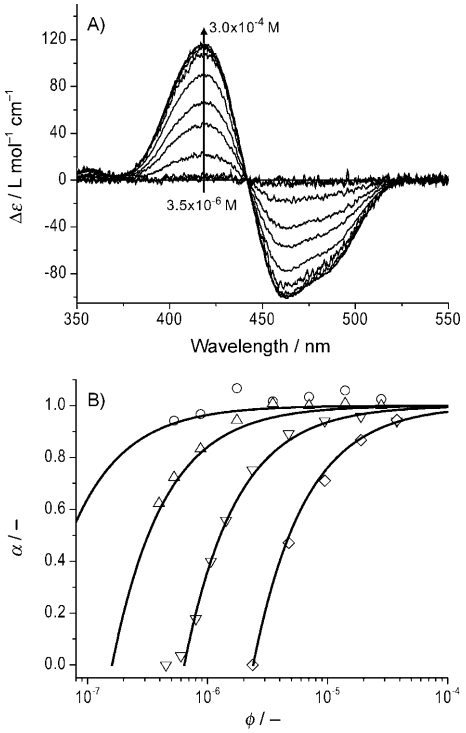


Figure 3. A) CD spectra of **2** in MCH at 313 K for different concentrations between 3.5×10^{-6} and 3.0×10^{-4} M.[21] The arrow indicates the increase in concentration. B) Degree of aggregation, α, calculated from absorption data and the corresponding fits at four temperatures (○ = 293 K, △ = 303 K, ▽ = 313 K, ◇ = 323 K).

We related the maximum Cotton effect at 419 nm to the degree of aggregation, α, which was plotted as a function of the volume fraction, ϕ, of **2** in MCH for four different temperatures (Figure 3B).[27]

From Figure 3B it is clear that for the lowest temperature, 293 K, the molecules are aggregated over the whole concentration range. Measurements at lower concentrations were not possible due to the high optical path length required. With increasing temperature, however, it is possible to observe the transition from the monomeric to the fully aggregated state. This transition appears to be non-sigmoidal, indicative of a cooperative mechanism.

To describe the *C*-dependent spectroscopic data, we applied the two-constant nucleated assembly model, which, at constant temperature, is only a function of concentration.[4,21,28] This model is based upon the same statistical mechanical considerations as the *T*-dependent model that was previously applied to **2**.[4] In this model, at each temperature, α can, to a good approximation, be described by Equation (3) for $\phi > \phi_{p,i}$ and by $\alpha \cong 0$ for $\phi < \phi_{p,i}$. Here, ϕ is the volume fraction of the molecule in MCH, $\phi_{p,i}$ is the critical volume fraction at which the degree of aggregation becomes zero at a temperature T_i, $\Delta\varepsilon$ is the molar circular dichroism and $\Delta\varepsilon_{MAX}$ is the maximum molar circular dichroism.

$$\alpha = \frac{\Delta\varepsilon}{\Delta\varepsilon_{MAX}} \cong 1 - \frac{\phi_{p,i}}{\phi} \tag{3}$$

By selecting an arbitrary reference temperature T_0, the critical volume fraction, $\phi_{p,i}$, can be expressed for any temperature, T_i, by Equation (4) in which ΔH is the enthalpy release due to the formation of a non-covalent bond in an assembly, assumed to be independent of temperature. By taking 313 K as the reference temperature T_0, we modelled the data for each temperature (Table 2), which yielded a ΔH of $-110\,\mathrm{kJ\,mol^{-1}}$ and a ΔS of $-280\,\mathrm{J\,mol^{-1}\,K^{-1}}$, in good agreement with the values of $-100\,\mathrm{kJ\,mol^{-1}}$ and $-215\,\mathrm{J\,mol^{-1}\,K^{-1}}$, respectively, found previously by *T*-dependent optical measurements in dodecane.[12]

Table 2. Parameters determined from modelling the *C*-dependent self-assembly of **2** in MCH at different temperatures.

T [K]	$\phi_{p,i}$ (–)	ΔG [kJ mol^{-1}]
293	3.6×10^{-8}	−39
303	1.6×10^{-7}	−36
313	6.4×10^{-7}	−32
323	2.4×10^{-6}	−29

$$\phi_{p,i} = \exp\left[\frac{\Delta G_i}{RT_i}\right] = \phi_{p,0}\exp\left[\frac{\Delta H}{RT_0}\left(\frac{T_0}{T_i} - 1\right)\right] \tag{4}$$

Although from the data in Figure 3B a cooperative mechanism can be deduced, no meaningful quantification of the degree of cooperativity is possible due to the lack of sufficient data points at concentrations in the vicinity of $\phi_{p,i}$.

Evaluation: For the two molecules discussed above, their self-assembly mechanisms have already been determined from previous spectroscopic measurements. Hence, it was known in advance which assembly model was needed to describe the (*C*- or *T*-dependent) data reported in this article.

However, for a new self-assembling system the supramolecular polymerisation mechanism is often not known a priori and as a result the mechanism needs to be determined from the experimental data. In this case, the limited number of data points typically obtained in a *C*-dependent measurement hampers the exact determination of the self-assembly mechanism. For example, due to the limited number of data points in Figure 3B, a sigmoidal relation, indicative of isodesmic self-assembly, could in fact also be used to model the degree of aggregation of **2** as a function of concentration. The relatively few data points in particular around the a priori unknown value of the critical concentration $\phi_{p,i}$ is a general drawback of *C*-dependent measurements, which makes it difficult to unambiguously determine the mechanism of self-assembly. To circumvent this problem, more (time-consuming) experiments are required or additional techniques need to be used to determine the self-assembly mechanism. We argue that it is more straightforward to use *T*-dependent measurements because in one experiment the complete transition from the monomeric (at high temperatures) to the polymeric state (at low temperatures) can be probed, directly revealing the mechanism of self-assembly.[29]

This can be seen in Figure 4 in which the *T*-dependent degree of aggregation of **2** in MCH is shown, clearly revealing a non-sigmoidal transition, which unambiguously indicates a cooperative self-assembly mechanism. Furthermore, the temperature can be varied continuously, enabling the acquisition of a large number of data points from which all the relevant thermodynamic parameters characterising the self-assembly can be derived. This includes the degree of cooperativity, expressed by activation constant K_a, which is found by modelling the onset of the degree of aggregation at the elongation temperature (inset in Figure 4B) and was found to be 1×10^{-4} for **2** in MCH. Obtaining the same information from *C*-dependent measurements is impractical as it requires many dilution experiments to acquire sufficient data points around the starting point of the self-assembly process (i.e., the critical temperature). However, it should be noted that when performing such *T*-dependent measurements, care should be taken to ensure that a cooling rate is selected such that the self-assembly is under thermodynamic control (i.e., equilibrium conditions). That is, no hysteresis should be observed upon heating the sample again, nor should a lower cooling rate lead to a different transition.

To underline our point, it is instrumental to compare the *C*-dependent data for **1** (Figure 2F) and **2** (Figure 3B) with the corresponding *T*-dependent data (Figure 2A and Figure 4, respectively). Only in the latter case (i.e., for the *T*-dependent data) is the transition from high to low *T* immediately identified as isodesmic or cooperative (for **1** and **2**, respectively).

Still, it should be noted that for a full characterisation and internal consistency, *C*-dependent measurements are also required to obtain all the thermodynamic parameters, but these parameters can only be determined once the self-assembly mechanism has been established, which requires *T*-dependent measurements.[30]

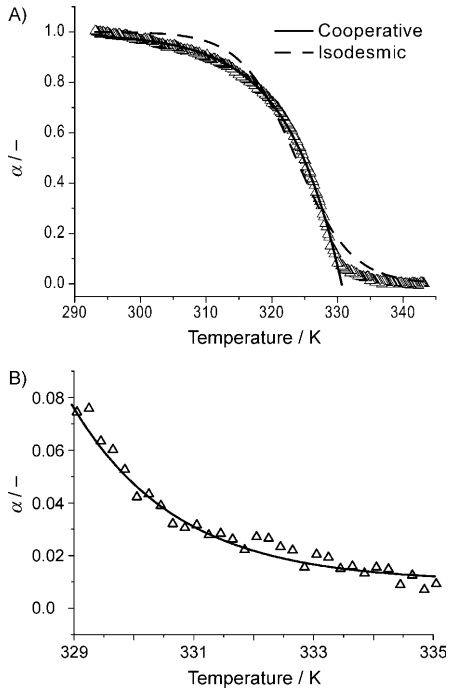


Figure 4. A) Degree of aggregation, α, for **2** in MCH determined from *T*-dependent CD absorption data ($C=1.14\times10^{-4}$ M), fitted with the isodesmic (dashed line) and cooperative models (solid line). B) Transition around the elongation temperature, fitted with the cooperative model from which the degree of cooperativity is determined.

Conclusions

Compared with concentration-dependent (optical) measurements, temperature-dependent measurements are the more convenient and preferred method for rapidly and unambiguously determining the self-assembly mechanism of a particular supramolecular system. In contrast to *C*-dependent measurements, the acquisition of a large set of data points is straightforward and the transition from monomeric to the (fully) self-assembled state is possible in a single measurement. This allows for an accurate determination of different thermodynamic parameters describing the supramolecular polymerisation.

Our results will help researchers to reliably study and quantify self-assembly, a topic of great interest.[31] They will also help gain an insight into why some molecules follow the isodesmic pathway and others the cooperative mechanism, allowing for a better design of routes towards well-defined nano-sized objects.

Acknowledgements

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[24] To normalise the data we fitted it with a standard sigmoid equation to arrive at the asymptotic values of the UV/Vis absorption at high and low temperatures. See the Supporting Information for more details.

[25] The spread in ΔH and ΔS values is most likely the result of experimental errors.

[26] Note that during the self-assembly of **2** the hydrogen-bonded dimer is the actual monomer that self-assembles into helical, one-dimensional stacks.

[27] The concentration was expressed as the (dimensionless) volume fraction to be able to use Equation (4).

[28] The simplest model that can describe a cooperative self-assembly process requires two equilibrium constants.

[29] By using differential scanning calorimetry (DSC) it is also possible to distinguish between an isodesmic and a cooperative mechanism. For the former a broad peak in C_p around the transition temperature can be observed, whereas for the latter a rather sharp peak in C_p is observed. However, to actually measure this effect, rather high concentrations are required (millimolar range) or the use of ultrasensitive DSC is necessary.

[30] Note that in the case in which K_a becomes close to unity, that is, weakly cooperative self-assembly, it will become difficult to distinguish an isodesmic from a cooperative supramolecular polymerisation mechanism.

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