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Alix Arnaud, Laurent Bouteiller. Isothermal Titration Calorimetry of Supramolecular Polymers. Langmuir, 2004, 20 (16), pp.6858–6863. 10.1021/la049365d . hal-01696748

HAL Id: hal-01696748

<https://hal.science/hal-01696748>

Submitted on 29 Aug 2020

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Isothermal titration calorimetry of supramolecular polymers

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ABSTRACT. A method to characterize the self-association of supramolecular polymers by isothermal titration calorimetry (ITC) has been designed. Association constants in the range 10^4 to $10^6 \text{ dm}^3 \text{ mol}^{-1}$ have been successfully determined from the heat exchange occurring when a supramolecular polymer solution is injected into a calorimetric cell containing pure solvent. Very good agreement with literature values has been obtained. Compared to other techniques (such as NMR or FTIR spectroscopy), the use of ITC presents several advantages: (i) the enthalpy of association is obtained together with the association constant from the same experiment, (ii) the measurements can be performed in almost any solvent, and (iii) systems with higher association constants can be characterized.

1. Introduction

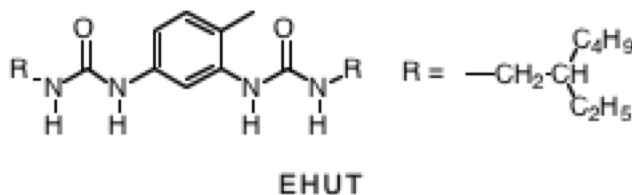
Supramolecular polymers are chains of small molecules held together through reversible non-covalent interactions.¹⁻⁴ This reversibility is responsible for the appearance of new properties, as compared to those of usual covalent polymers. For instance, the molar mass of supramolecular polymers depends on concentration, solvent polarity and temperature. Thus, the best way to characterize the length of a supramolecular polymer is to measure the association constant (K_a) of the interaction involved. Of course, potentially useful properties in dilute solutions are obtained only if the interaction is strong enough,

typically $K_a > 10^6 \text{ dm}^3 \text{ mol}^{-1}$.^{5,7} In the case of supramolecular polymers, such large association constants have mostly been determined indirectly by fluorescence techniques, with the help of model compounds.^{8,9} It is thus desirable to adapt other techniques for this purpose. The aim of the present paper is to show that isothermal titration calorimetry (ITC) is perfectly suited to this problem.

ITC is widely used by biochemists and supramolecular chemists to characterize interacting systems.¹⁰⁻¹⁶ The usual procedure is to titrate a solution of compound A placed in the calorimetric cell, by aliquots of a solution of compound B placed in an automated syringe. The exchanged heat is measured and reveals quantitative information about the interaction between A and B. Self-assembling mono-component systems can also be studied by ITC, but with a different procedure: a concentrated solution of the self-associated compound is placed in the syringe and injected into the cell containing pure solvent. If the final concentration is low enough, the supramolecular assemblies are dissociated and the exchanged heat is characteristic of the dissociation event. This procedure has been used to measure the CMC of low molecular weight surfactants,^{17,18} to study amphiphilic polyelectrolytes,¹⁹ to derive the partition coefficient of solutes in lipid vesicles,²⁰ and to measure the heat of dilution of non-ideal solutions.²¹ In principle, this procedure can also be used in the case of supramolecular polymers, but no experimental demonstration has been reported yet.

The experimental system chosen to test the present procedure is a bis-urea based supramolecular polymer **EHUT** (Chart 1). This compound has been shown to reversibly self-assemble by hydrogen bonding in low polarity solvents, where it forms long wire-like structures.^{7,22} In chloroform, the association is moderate, so that the association constants have been previously measured by infrared spectroscopy.²³ This system (**EHUT** in chloroform) thus allows a quantitative assessment of the characterization of supramolecular polymers by ITC. In toluene, the association of **EHUT** is much stronger, which makes it possible to test the limits of this characterization technique.

Chart 1. Structure of **EHUT**.



2. Experimental Section

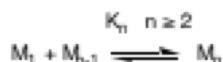
The solutions of **EHUT** (Chart 1) in chloroform (resp. toluene) were prepared at room temperature, under stirring for at least one day (resp. one week). The solvents (analytical grade) were used as received, except CDCl_3 , which was dried on molecular sieves.

Heats of dissociation were measured using a MicroCal VP-ITC titration microcalorimeter. The sample cell (1.435 cm^3) was filled with pure solvent. A relatively concentrated **EHUT** solution in the same solvent was placed in a 0.295 cm^3 continuously stirred (310rpm) syringe. A first $2 \mu\text{L}$ aliquot was injected, without taking into account the observed heat, to remove the effect of solute diffusion across the syringe tip during the equilibration period. Subsequent aliquots of the solution (2 to $10 \mu\text{L}$) were automatically injected into the sample cell every 200s, until the syringe was empty.

The uncertainty of the parameters reported in Table 1 was evaluated by fitting each experimental curve separately instead of all curves simultaneously (see part 3).

3. Theory

Scheme 1. Association equilibria involved in the formation of a supramolecular polymer (M_1 =monomer, M_n =oligomer of degree of polymerization n).



Self-association model. The self-association of supramolecular polymers can be described by the infinite set of equilibria mentioned on Scheme 1. Most systems studied so far have been shown to follow an isodesmic model, such that $K_n = K$ for $n \geq 2$.²⁴ However, cooperative^{23,25,26} ($K_2 < K = K_n$, $n > 2$) or anti-

cooperative²⁷ ($K_2 > K = K_n$, $n > 2$) systems have also been reported. We will thus consider the more general model with 2 constants: a dimerization constant (K_2) and an oligomerization constant ($K = K_n$, $n > 2$). Within this model, the concentration of all supramolecular chains of degree of polymerization n ($C_n = [M_n]$) can be expressed by applying the mass action law.

$$C_n = K_2 K^{n-2} (C_1)^n \quad (1)$$

If the formation of cyclics is neglected, conservation of mass yields a third degree equation

$$K(K - K_2)C_1^3 + (2K_2 - 2K - K^2 C_0)C_1^2 + (1 + 2KC_0)C_1 - C_0 = 0 \quad (2)$$

from which the free monomer concentration (C_1) can be determined, if K_2 , K and the overall concentration (C_0) are known.²⁵ Through eq (1), the whole molecular weight distribution can then be determined.

Exchanged heat. At the beginning of an experiment, pure solvent is placed in the calorimetric cell of volume V_0 , and a solution of supramolecular polymer of total solute concentration C_0^s is placed in the syringe. Let C_n^s be the concentration of supramolecular chains of $DP_n = n$ in the syringe:

$$C_0^s = \sum_{n=1}^{\infty} n C_n^s \quad (3)$$

When i injections of volume ΔV_i have occurred, the total volume injected is

$$V_i = \sum_{j=1}^i \Delta V_j \quad (4)$$

and the total solute concentration in the cell is $C_0^c(i)$. Let $C_n^c(i)$ be the concentration of supramolecular chains of $DP_n = n$ in the cell, after the i^{th} injection:

$$C_0^c(i) = \sum_{n=1}^{\infty} n C_n^c(i) \quad (5)$$

Because of the total-fill nature of the cell, each injection acts to drive liquid out of the cell. Consequently, the concentration in the cell is given by eq (6).²⁸

$$C_0^c(i) = C_0^s \frac{V_i}{V_0} \left(1 - \frac{V_i}{2V_0} \right) \quad (6)$$

The heat exchanged during the i^{th} injection of the supramolecular polymer solution into the cell ($Q_{\text{obs}}(i)$) is the sum of two terms:

$$Q_{\text{obs}}(i) = \Delta Q(i) + Q_{\text{dil}} \quad (7)$$

$\Delta Q(i)$ results from the dissociation of supramolecular chains into shorter chains (according to Scheme 1). Q_{dil} takes into account both the mechanical heat related to the flow of the solution (which is independent of i), and the heat of dilution of solutes. This heat of dilution does not involve dissociation, and can be considered to be independent of i , if the concentration in the syringe is so low that non-ideality effects are negligible.²¹ $\Delta Q(i)$, which corresponds to the injection of volume $\Delta V_i = V_i - V_{i-1}$, can be expressed as

$$\Delta Q(i) = Q(i) - Q(i-1) + \frac{\Delta V_i}{V_0} \left[\frac{Q(i) + Q(i-1)}{2} \right] \quad (8)$$

where $Q(i)$ is the heat exchanged when a supramolecular polymer solution of volume V_i and concentration C_0^s is injected into the cell containing pure solvent. The last term in eq (8) takes into account the displaced volume which overflows the cell, but contributes partially to the heat measured.²⁸ The heat $Q(i)$ corresponds to the dissociation of supramolecular chains when the concentration of a solution is reduced from C_0^s (in the syringe) to $C_0^c(i)$ (in the cell). It can be conveniently evaluated by considering the fictitious process of first diluting the solution from concentration C_0^s to infinite dilution, where only monomers are present, and then concentrating back to $C_0^c(i)$:

$$Q(i) = Q(i)_{C_0^s \rightarrow 0} + Q(i)_{0 \rightarrow C_0^c(i)} \quad (9)$$

These hypothetical heats are related to the molar enthalpies of association corresponding to dimerization (ΔH_2) and oligomerization (ΔH) (Scheme 1, with $n=2$ or $n>2$ respectively):

$$Q(i)_{C_0^s \rightarrow 0} = -\Delta H \left(\sum_{n=3}^{\infty} (n-2) C_n^s V_i \right) - \Delta H_2 \left(\sum_{n=2}^{\infty} C_n^s V_i \right) \quad (10)$$

$$Q(i)_{Q \rightarrow C_0^c(i)} = \Delta H \left(\sum_{n=3}^{\infty} (n-2) C_n^c(i) V_l' \right) + \Delta H_2 \left(\sum_{n=2}^{\infty} C_n^c(i) V_l' \right) \quad (11)$$

V_l' is a hypothetical volume such that the amounts of solutes fictitiously diluted and concentrated back are identical:

$$C_0^s V_l = C_0^c(i) V_l' \quad (12)$$

Combining eqs (1) and (9) to (12) yields the following expression:

$$Q(i) = -\Delta H K_2 K V_l \left[\frac{(C_1^s)^3}{(1 - K C_1^s)^2} - \frac{C_0^s (C_1^c(i))^3}{C_0^c(i) (1 - K C_1^c(i))^2} \right] - \Delta H_2 K_2 V_l \left[\frac{(C_1^s)^2}{1 - K C_1^s} - \frac{C_0^s (C_1^c(i))^2}{C_0^c(i) (1 - K C_1^c(i))} \right] \quad (13)$$

which is then introduced in eqs (8) and then (7). Finally, it is convenient to normalize the measured heat by the amount of solute injected:

$$\bar{Q}_{obs}(i) = \frac{Q_{obs}(i)}{C_0^s \Delta V_l} \quad (14)$$

Consequently, 5 unknown constants (K_2 , K , ΔH_2 , ΔH and Q_{dil}) are necessary to completely describe such a calorimetric experiment. Figure 1 shows the calculated evolution of $\bar{Q}_{obs}(i)$ for reasonable values of these constants. The curves have a sigmoidal shape. The magnitude of the step is directly related to the ΔH value, whereas ΔH_2 has a minor effect (Figure 1). The position of the step with respect to the concentration axis is mainly related to the K value, while K_2 influences only the slope of the curve (Figure 2).

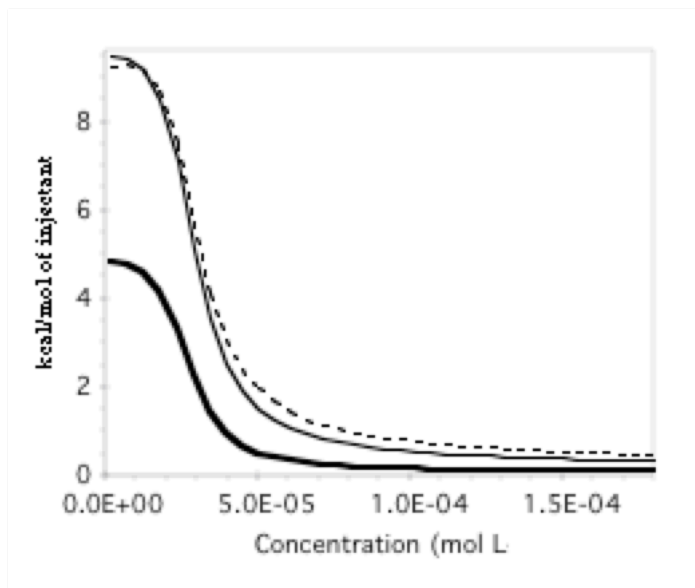


Figure 1. Theoretical enthalpograms calculated for $\Delta H_2 = \Delta H = -42 \text{ kJ mol}^{-1}$ (plain curve), $\Delta H_2 = -42 \text{ kJ mol}^{-1}$ and $\Delta H = -21 \text{ kJ mol}^{-1}$ (bold curve), $\Delta H_2 = -4 \text{ kJ mol}^{-1}$ and $\Delta H = -42 \text{ kJ mol}^{-1}$ (dotted curve). $K_2 = 500 \text{ dm}^3 \text{ mol}^{-1}$, $K = 30000 \text{ dm}^3 \text{ mol}^{-1}$ and $Q_{\text{di}} = 0$ for all curves.

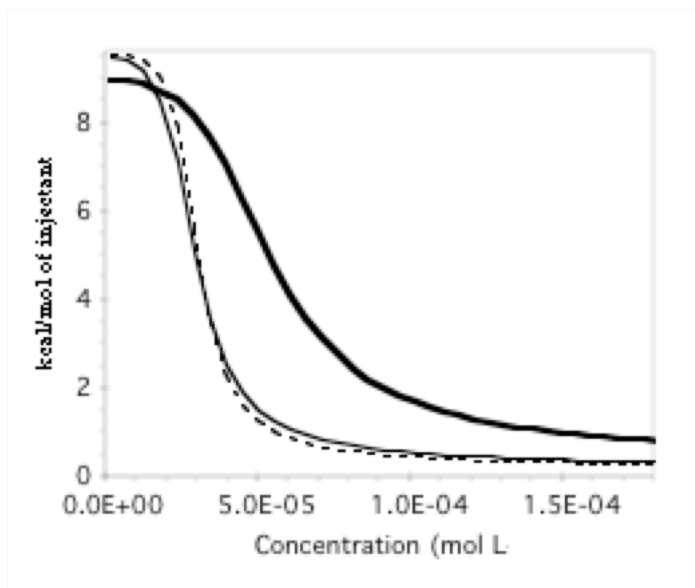


Figure 2. Theoretical enthalpograms calculated for $K_2 = 500 \text{ dm}^3 \text{ mol}^{-1}$ and $K = 30000 \text{ dm}^3 \text{ mol}^{-1}$ (plain curve), $K_2 = 500 \text{ dm}^3 \text{ mol}^{-1}$, $K = 15000 \text{ dm}^3 \text{ mol}^{-1}$ (bold curve), $K_2 = 250 \text{ dm}^3 \text{ mol}^{-1}$ and $K = 30000 \text{ dm}^3 \text{ mol}^{-1}$ (dotted curve). $\Delta H_2 = \Delta H = -42 \text{ kJ mol}^{-1}$ and $Q_{\text{di}} = 0$ for all curves.

Fit of experimental results. Starting with arbitrary values for the 5 constants (K_2 , K , ΔH_2 , ΔH and Q_{dil}), it is possible to calculate the free monomer concentrations C_1^s and $C_1^s(i)$ (eq (2)), and then the normalized heat (eqs (13), (8), (7) and (14)). Minimization of the distance between the experimental curve and the theoretical curve, with a standard non-linear curve fitting routine, should afford reasonable values for the 5 constants. However, two difficulties are encountered. Firstly, it is not possible to obtain the full sigmoidal curve in a single experiment, except for very cooperative systems. This results in a large uncertainty for the constants deduced. Consequently, we prefer to run at least 4 experiments with starting concentrations (C_0^s) differing by a factor of 2, and to perform the non-linear curve fitting procedure simultaneously on the 4 experimental curves (see part 4). Secondly, even this procedure yields unreliable values for ΔH_2 , because of the very small influence of this parameter (Figure 1). We checked that imposing an arbitrary value to ΔH_2 , and then adjusting the additional parameters to fit the experimental data, yields parameter values that lie within experimental uncertainty. Consequently, we impose $\Delta H_2 = \Delta H$, and perform the simultaneous curve fitting of the 4 curves. In this case, there are 7 constants: K_2 , K , ΔH and Q_{dil1} to Q_{dil4} which correspond to the heat of dilution for each measurement. Thus, experiments performed at a single temperature cannot yield a value for ΔH_2 . However, this parameter is accessible through van't Hoff analysis of variable temperature experiments (see part 4).

4. Results and Discussion

Confrontation with FTIR data. Figure 3 shows the heat flow curve obtained when a 6mM **EHUT** solution in $CDCl_3$ is incrementally injected into pure $CDCl_3$ at 20°C. The process is endothermic, in agreement with the fact that hydrogen bonds are dissociated during the dilution. The peaks decrease in intensity throughout the experiment, because the increasing **EHUT** concentration in the cell limits the extent of dissociation during the following injections. Integration of the heat flow peaks yields the enthalpograms presented in Figure 4 and 5 (5 experiments were performed with a different **EHUT** concentration in the syringe). The expected sigmoidal shape is obtained, and it can be seen that the lowest concentration experiment (3mM) reveals a plateau followed by a decrease. The plateau illustrates the fact

that the first injections lead to the full dissociation of supramolecular chains into free monomers. This plateau is not visible in the high concentration experiments. However, the high concentration experiments are informative, because they reveal the leveling off of the curve at the end of the experiment. Two approaches were evaluated to fit the data. In a first simple approach, the 5 curves were simultaneously fitted with the isodesmic model described in part 3 ($K_2 = K$), with K , ΔH and Q_{dil} to Q_{dis} as adjustable constants (Figure 4). The quality of the fit is extremely poor, which is in agreement with previous results showing that the self-association of **EHUT** is not an isodesmic process.²³ In a second approach, the 5 curves were simultaneously fitted with the cooperative model described in part 3, with K_2 , K , ΔH and Q_{dil} to Q_{dis} as adjustable constants (Figure 5). The quality of the fit over this large concentration range is very satisfactory. The values of the constants obtained are listed in Table 1, together with the values previously determined by FTIR spectroscopy (first line in Table 1). The agreement between the two techniques is very good considering that (i) unlike the FTIR experiment, it is not possible to perform the ITC experiment in strict water-free conditions, and (ii) different assumptions inherent to each technique have been made. The coherence of these data validates the present procedure. The advantage of the ITC experiment is that enthalpy (and thus entropy) of association are simultaneously obtained, without running the measurement at several temperatures.

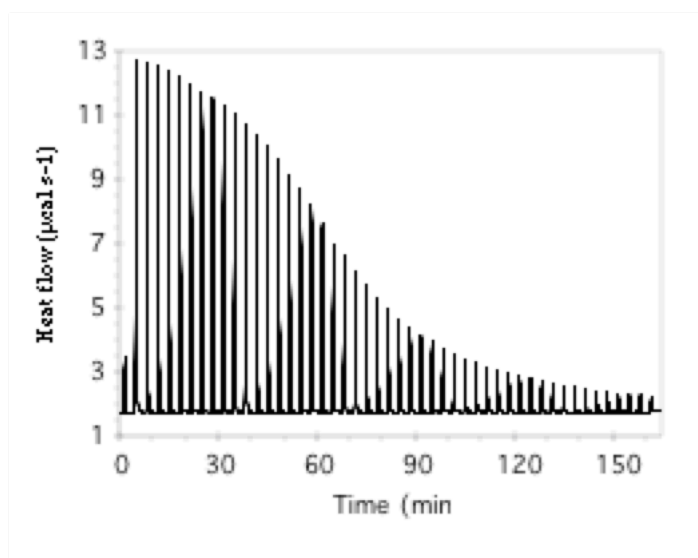


Figure 3. Heat effect produced by injecting 6 μ L aliquots of a 6mM **EHUT** solution in CDCl₃ into CDCl₃ (T=20°C).

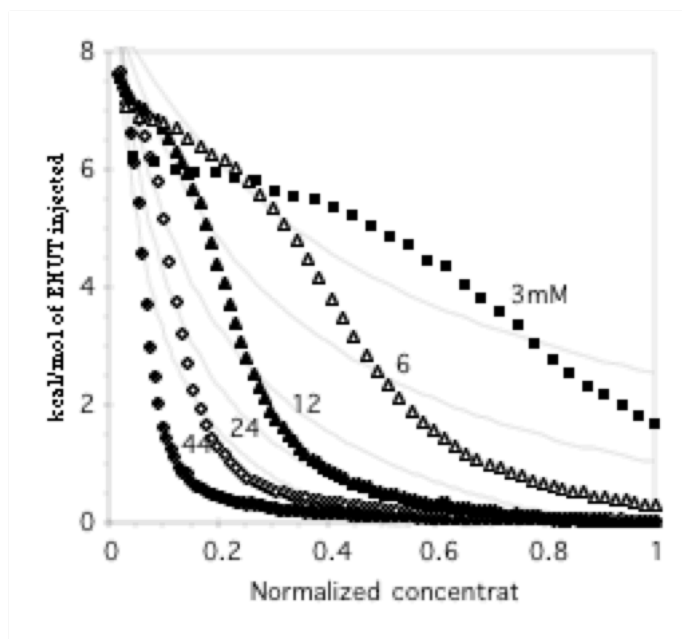


Figure 4. Enthalpograms of 44mM, 24mM, 12mM, 6mM and 3mM **EHUT** solutions in CDCl₃ versus concentration normalized by the final cell concentration (T=20°C). The plain curves are the "best" fits obtained with the isodesmic model ($K_i = K$) presented in part 3.

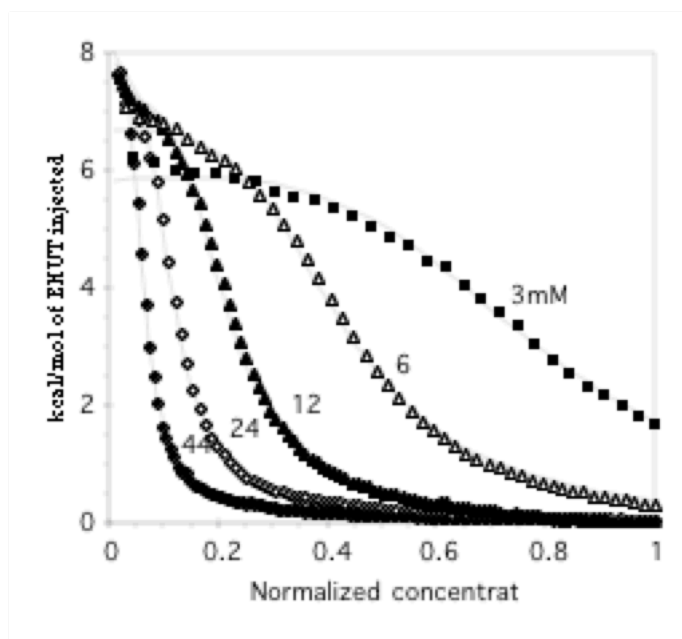


Figure 5. Enthalpograms of 44mM, 24mM, 12mM, 6mM and 3mM **EHUT** solutions in CDCl_3 versus concentration normalized by the final cell concentration ($T=20^\circ\text{C}$). The plain curves are the fits obtained with the cooperative model ($K_2 < K$) presented in part 3 and the parameter values reported in Table 1.

Table 1. Thermodynamic parameters determined by ITC, for solutions of **EHUT**.

solvent	T ^a	K_2 ^b	K ^c	K/K_2 ^d	K^2/K_2 ^e	ΔH ^f	$\Delta H_{2\text{vH}}$ ^g	C_{0h}^5
CDCl_3	<i>RT</i>	<i>21</i> ⁱ	<i>1400</i> ⁱ	<i>70</i> ⁱ	<i>1.0 10⁶</i> ⁱ	—	—	—
CDCl_3	20	57	1700	30	$5.1 \cdot 10^4$	-36	—	44/24/12/6/3
CHCl_3	10	74	2500	34	$8.6 \cdot 10^4$	-33	-16	44/24/12/6/3
CHCl_3	20	58	1700	29	$4.8 \cdot 10^4$	-35	-16	44/24/12/6/3
CHCl_3	30	54	1100	20	$2.1 \cdot 10^4$	-36	-16	44/24/12/6
CHCl_3	40	37	680	18	$1.2 \cdot 10^4$	-37	-16	44/24/12/6
toluene	40	430	28500	66	$1.9 \cdot 10^6$	-48	—	2/1/0.5/0.25

^a Temperature, in $^\circ\text{C}$.

^b Dimerization constant, in $\text{dm}^3 \text{mol}^{-1}$. Uncertainty $\pm 30\%$.

^c Oligomerization constant, in $\text{dm}^3 \text{mol}^{-1}$. Uncertainty $\pm 10\%$.

^d Measure of the cooperativity along the supramolecular chain.

^e Association constant between long oligomers, in $\text{dm}^3 \text{mol}^{-1}$.

^f Enthalpy of oligomerization, in kJ mol^{-1} . Uncertainty $\pm 10\%$.

^g Enthalpy of dimerization, determined by van't Hoff analysis, in kJ mol^{-1} . Uncertainty $\pm 30\%$.

^h Concentrations used, in $10^{-3} \text{mol dm}^{-3}$.

ⁱ Determined by FTIR.²³

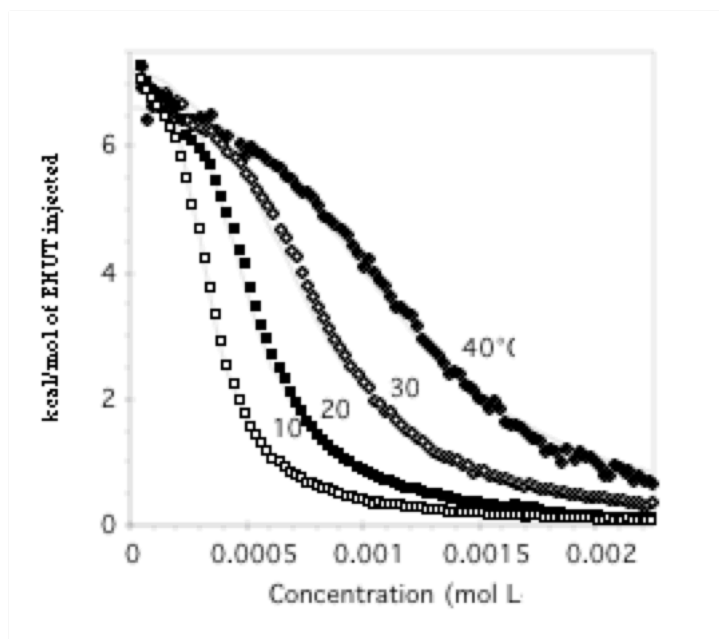


Figure 6. Enthalpograms of a 12mM **EHUT** solution in CHCl₃, at T=10°C, 20°C, 30°C and 40°C.

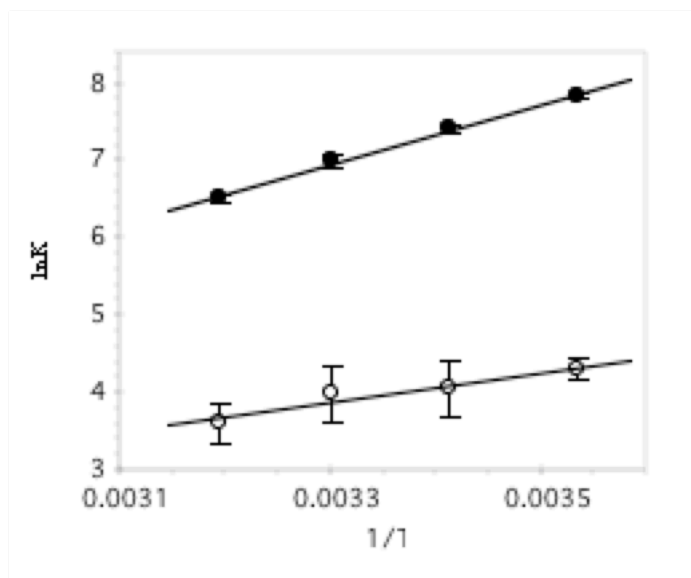


Figure 7. van't Hoff plot for **EHUT** in CHCl₃.

Influence of temperature. As explained in part 3, the present method cannot be used to determine ΔH_s directly. Consequently, measurements at several temperatures were performed in order to see if a van't Hoff analysis of the temperature variation of K_s could yield an estimate of ΔH_s . Figure 6 shows the enthalpograms obtained between 10 and 40°C, when the same 12mM **EHUT** solution in chloroform is diluted into pure chloroform. The shift of the curves to higher concentrations is indicative of a decrease

of the association constant (K) with increasing temperature. The fit, which was performed at each temperature simultaneously on at least 4 experiments, yielded the values listed in Table 1. It can be seen that the same values are obtained at 20°C in CDCl_3 and CHCl_3 . In order to comment the other experiments, it is more informative to consider the values of K/K_2 , which is a measure of the cooperativity of the association; and K^2/K_2 , which is the association constant between 2 oligomers.²³ K^2/K_2 is more relevant than K_2 or K in the high concentration regime where the chains are long.²³ There is not only a clear decrease in K^2/K_2 with increasing temperature (the strength of the association is divided by 2 when the temperature is increased by 10°C), but the cooperativity is also reduced. The van't Hoff plot (Figure 7) also shows the smooth variation of K_2 and K . The slope of the straight lines affords the corresponding enthalpy of association: $\Delta H_{\text{vH}} = -32 \text{ kJ mol}^{-1}$ and $\Delta H_{2\text{vH}} = -16 \text{ kJ mol}^{-1}$. The first value is in perfect agreement with the values directly determined at each temperature (Table 1), which further validates our approach. Concerning $\Delta H_{2\text{vH}}$, the low value obtained is reasonable, considering the fact that $K_2 < K$.

Influence of solvent. In order to test if this ITC procedure can be applied to more strongly associated systems, the dissociation of the same bis-urea supramolecular polymer was studied in toluene, where the association is known to be stronger than in chloroform, although no quantitative determination of the association has been reported. Figure 8 shows the heat flow measured during injection of a 1mM **EHUT** solution into toluene. This result is very similar to the data in CDCl_3 (Figure 3), except that the signal intensity is an order of magnitude lower, because the concentration in the syringe had to be decreased, in order to obtain significant dissociation. The parameters of the model were determined by a simultaneous fit of 4 enthalpograms (Figure 9). The fit quality is satisfactory, although the lower signal to noise ratio (compared to Figure 5) is visible. It is worth mentioning that we had not previously been able to determine the association constant of this system (**EHUT** in toluene) by FTIR or NMR spectroscopy, thus showing the potential of ITC. The parameter values (Table 1) show that the association (K^2/K_2) is 2 orders of magnitude stronger in toluene than in chloroform at the same temperature. This increase in strength goes together with an increase in cooperativity (K/K_2) and enthalpy of association.

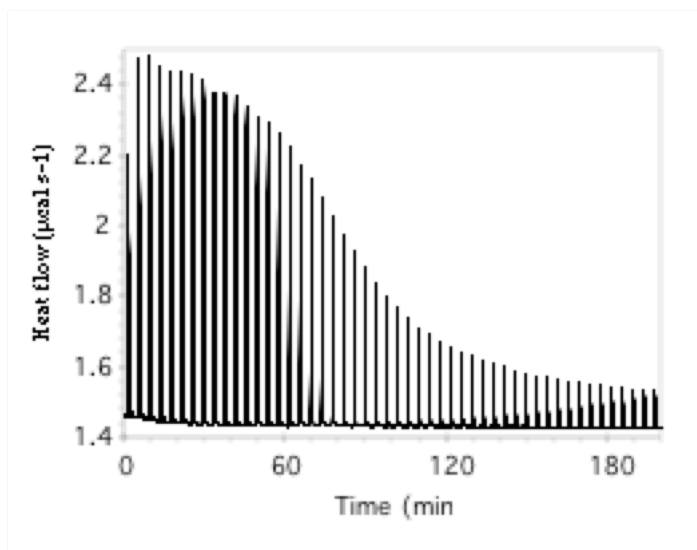


Figure 8. Heat effect produced by injecting 2 μ L aliquots of a 1mM **EHUT** solution in toluene into toluene (T=40°C).

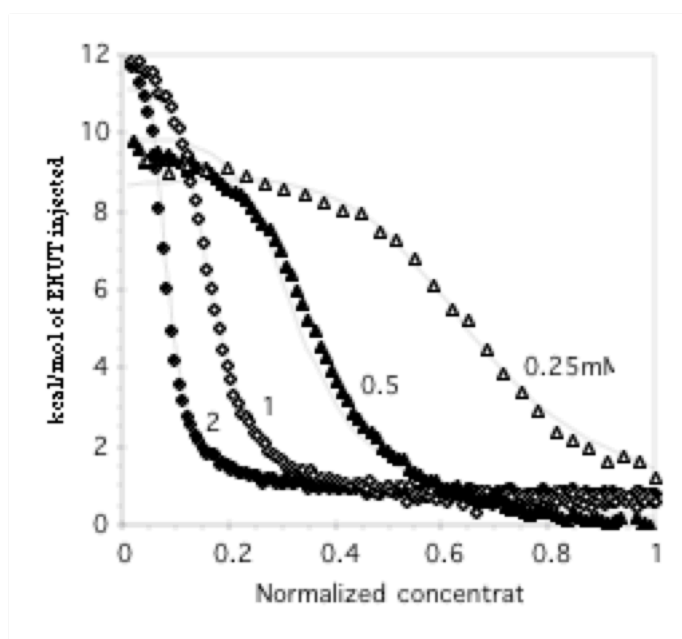


Figure 9. Enthalpograms of 2mM, 1mM, 0.5mM and 0.25mM **EHUT** solutions in toluene versus concentration normalized by the final cell concentration (T=40°C).

5. Conclusion

We have demonstrated that ITC is a powerful tool to characterize the self-association of supramolecular polymers. Association constants in the range 10^4 to 10^6 dm³ mol⁻¹ have been successfully determined from the heat exchange occurring when a solution of supramolecular polymer is injected into the calorimetric cell containing pure solvent. Compared to other techniques (such as NMR or FTIR spectroscopy), the use of ITC presents several advantages: (i) the enthalpy of association is obtained together with the association constant from the same experiment, (ii) the measurements can be performed in almost any solvent, and (iii) systems with higher association constants can be characterized.

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