SANS investigation of self-assembling dendrimers in organic solvents

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The self-assembly behaviour of tetraacids 1a–c and tetraester 4 in CDCl3, and [7H]tetrahydrofuran ([7H]THF) has been investigated by the small-angle neutron scattering (SANS) technique. The experimental SANS data were compared with simulated scattering data derived from structural models proposed previously for the aggregates. These studies suggest that dendritic monomers 1c self-assemble into cyclic hexameric aggregates, whereas 1a forms a large tubular aggregate in CDCl3. Further study on 1c in CDCl3, as a function of concentration suggests that the cyclic hexameric aggregates strongly interact with each other at higher concentrations. The control compound 4 was shown to be monomeric in both solvents.

There is significant current interest in organic compounds that self-assemble into cyclic hexameric aggregates, whereas 1a forms a large tubular aggregate in CDCl3. The synthesis and characterization of compounds 1a–c and 4 were described previously and material was available from the prior studies. [7H]Chloroform and [7H]tetrahydrofuran, purchased from Cambridge Isotope Laboratory, were used directly.

Materials and Methods

Materials

The synthesis and characterization of compounds 1a–c and 4 were performed in CDCl3. The self-assembly behaviour of compounds 1a and 4 was also investigated in [7H]THF to study the effect of this solvent, which is more competitive toward hydrogen-bonding interactions. The corresponding solution was injected into a Suprasil cylindrical cell with a 2 mm pathlength.

SANS measurements

SANS experiments of compounds 1a–c and 4 were performed in CDCl3. The self-assembly behaviour of compounds 1a and 4 was also investigated in [7H]THF to study the effect of this solvent, which is more competitive toward hydrogen-bonding interactions. The corresponding solution was injected into a Suprasil cylindrical cell with a 2 mm pathlength.

Small-angle neutron scattering

The differential scattering cross-section $f(Q)$ measured as a function of momentum transfer $Q$ by SANS is a convolution

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Fig. 1 (a) Dendritic tetraacids 1a–c and the proposed cyclic hexameric aggregate 2 and linear aggregate 3. (b) Tetraester 4
of two terms, namely, intraparticle correlations $P(Q)$ and interparticle correlations $S(Q)$.

$$I(Q) = nP(Q)S(Q)$$

(1)

In eqn. (1), $n$ is the number of particles per unit volume and $Q = 4\pi/\lambda \sin \theta$.

where $\lambda$ is the wavelength of neutrons and $2\theta$ is the scattering angle.

The intraparticle structure factor $P(Q)$ is defined as

$$P(Q) = \sum_{i,j} \delta_{ij} \exp(iQr_{ij})$$

(3)

and the interparticle structure factor

$$S(Q) = \frac{1}{N} \sum_{i \neq j} \exp(iQ(r_i - r_j))$$

(4)

In eqns. (3), $r_i$ and $r_j$ are the position vectors of the atoms in a particle and $\delta_{ij}$ and $\delta_{ij}$ are the scattering lengths of the atoms $i$ and $j$. The subscripts indicate that averaging is for all orientations of the particles is taken. In general, the scattering power of an atom depends on the isotope.\(^5\) Eqn. (3) can be used to calculate the scattering from the particle, if atomic coordinates are available. In eqn. (4), $R_i$ and $R_j$ are the position vectors of the particle centres and $N$ is the total number of particles.

In the case of dilute solutions the particles are far apart and $S(Q)$ in the low $Q$ region will oscillate around unity and hence $I(Q)$ is predominantly due to $P(Q)$. The $I(Q)$ data can be readily analysed to obtain the correct size, shape and molecular mass of the particle. At higher concentrations where the excluded volume effects become significant the size and molecular mass parameters derived from the low-$Q$ region become lower in values. This is due to the increased effect of $S(Q)$ on $I(Q)$ and one has to decompose $I(Q)$ to obtain the $P(Q)$ and $S(Q)$ terms prior to analysis. This step, however, requires information on the size and morphology of the particles as well as the interaction potentials. Under these conditions it is possible to obtain the surface potentials of the colloidal objects.\(^6\)

**Analysis of SANS data**

At the low-$Q$ region, the experimental scattering intensity $I(Q)$ vs. $Q$ data can be used to obtain size information by using eqns. (5)\(^7\) which is an approximation of eqn. (1) in the low-$Q$ region.

$$I(Q) = 10^6 \exp(-Q^2R^2 \ell^3)$$

(5)

where

$$I(0) = 10^6 \ell^3$$

(6)

In eqns. (6), $\ell$ and $\ell$ are the scattering length densities $\ell = \frac{\sum \rho_i}{1}$ of the particles and the solvents, $V$ is the volume of the particle, and $b_i$ is the scattering length of individual atoms.

The radius of gyration, $R_g$ is the root-mean-squared distances of all of the atoms to the centroid of the scattering volume of the particle. This parameter is shape independent and one needs to know the shape of the particle in order to derive sizes in terms of the familiar physical dimensions. For example, for a sphere with a radius of $R$, $R_g^2 = 0.6B^2$ and for an ellipsoid, $R_g^2 = a^2 + b^2 + c^2/5$ where $a$, $b$, and $c$ are the semi-axes of an ellipsoid. The value of $R_g$ is obtained from the absolute value of the slope $(d)$ of a line in the natural log of $I(Q)$ vs. $Q^2$ plot (Guinier plot)\(^8\) in the $Q$ region where $\Re \# 10$, $R_g^2 = 3k$.

In dilute solutions where the interparticle interactions are either nonexistent or minimal, this value will represent the true size of the particle. However, in the presence of interparticle interactions the value of $R_g$ will be smaller and this value has to be denoted as apparent value. In the absence of any other concentration dependent effects, such as aggregation, it is possible to obtain the true $R_g$ of the particle by the linear extrapolation of measured $R_g^2$ values at several concentrations.

The magnitude of the slope of the curve (second virial coefficient) in the apparent $R_g$ vs. concentration plot yields qualitative information on the interparticle interactions.

In the case of polydisperse systems, the $R_g$ and $I(0)$ values are respectively the $Z$-averaged and mass-averaged quantities. For example, the $Z$-averaged $R_g$ value is defined as

$$R_g^2 = \sum N_i M_i R_g^2 / \sum N_i M_i$$

(7)

where $N_i$ and $M_i$ and $(R_g)$ are the number density, molecular mass, and radius of gyration of the aggregates of type $i$, respectively.

The shape of the scattering particles can be analysed by fitting the scattering pattern in the whole $Q$ range by either using the analytical functions for the form factors of different geometrical objects,\(^9\) or by calculating the scattering pattern using a suitable molecular model, as was done for proteins using eqn. (3).\(^10\) The molecular models of compounds 1a–c and 4 and their possible aggregate structures were constructed with the Macromodel program\(^11\) on a Silicon Graphics workstation. Because of the limitations on the number of atoms used, the dendrimer substructures and the tetraacrid core unit were minimized separately and then covalently linked. Each structure was first minimized using molecular mechanics: MM2 force field with the Polak–Ribier conjugate gradient method of optimization. These minimized structures were then further minimized by molecular dynamics with automatic set-up parameters of 300 K, initial temperature, 10 ps run with a 15 fs timestep using SHAKE and zero momentum.

The atomic coordinates of the structures used from the modelling studies were used to calculate the scattering patterns. It is important to state that we used only the atomic coordinates of the molecular models for calculating the scattering curves, but did not use the neutron scattering cross-sections of individual atoms. What this means is that the shape of the scattering curve for a given system is appropriate, but the scaling is not. We arbitrarily scaled the calculated scattering data and compared the shapes with the experimental data to test the validity of the proposed models. In the case of 10.6 mM CDCl\(_3\) solution of 1a none of the aggregate models generated by the Macromodel program could explain the measured scattering data (discussed later) and hence modelling using the form factor for a hollow cylinder was used. The form factor of a cylindrical shape particle with or without a hollow inner portion (tube vs. rod) can be written as

$$A(Q) = \frac{2 \sin(QL/2)}{Q^2/4} \frac{A(R_g/R_c) \exp(2Q g^2 |R_c - R_o|)}{V}$$

(8)

where $L$ is the length of the cylinder, $R_c$ is the outer radius of the cylinder, $R_o$ is the inner radius of the cylinder, $Q$ is the component of $Q$ in the axial direction, $Q$ is the component of $Q$ in the cross-section plane, and $\gamma$ is the first-order Bessel function of the first kind. The orientationally averaged particle structure factor used to fit is

$$P(Q) = \frac{1}{V} \sum_{\alpha} \sum_{\pm} \delta_{\nu} \delta_{\nu \nu} A(Q)^2 \exp(2Q g^2 |R_c - R_o|)$$

(9)

where $V = \pi R_o^2 L$.

**Results and Discussion**

Fig. 2 shows the measured SANS data for 1c in CDCl\(_3\) at three concentrations. Each curve is superimposed by the calculated SANS data from the coordinates generated for the cyclic hexamer 2 (see Fig 1) proposed for this system. It is

The experimental SANS data for 1c in CDCl₃ at three concentrations: (a) 12 mg ml⁻¹, (b) 24 mg ml⁻¹, and (c) 50 mg ml⁻¹. The calculated scattering pattern (—) from the coordinates generated for the cyclic hexamer model proposed for this system is superimposed on the experimental data.

The calculated SANS data for the cyclic hexamer yields an $R_g$ of 33.6 Å, while the apparent $R_g$ values for the measured samples with a monomer concentration of 3.8 mM (12 mg ml⁻¹), 7.6 mM (24 mg ml⁻¹), and 15.7 mM (50 mg ml⁻¹) are 30.4, 28.9, and 23.7 Å, respectively. The linear dependence of apparent $R_g$ as a function of concentration. The $R_g$ value at infinite dilution from Fig. 4 is 33.1 Å which agrees quite well with the expected value of 33.6 Å on the basis of the proposed model. Thus the cyclic hexamer model (see Fig. 1) proposed for 1c in CDCl₃ is consistent with the SANS results. However, it is noteworthy to mention that SANS also suggests the presence of concentration-dependent interactions between these aggregates at the high concentration range investigated here.

The corresponding Guinier plots for the data in Fig. 2. The Guinier calculated scattering pattern (—) from the coordinates generated for the cyclic hexamer model proposed for this system is superimposed on the experimental data.

The Guinier plots for the calculated curves (+) are shown in each case. The value of the slopes in the experimental data (---) decreases with increasing concentration; all of them are smaller than that for the calculated data.

The linear dependence of apparent $R_g$ as a function of concentration. The $R_g$ value at infinite dilution agrees well with the $R_g$ value calculated for the cyclic hexamer.
When 1c is dissolved in $[^7\text{H}]$THF, the aggregation properties change. The $I(Q)$ data and the corresponding Guinier curves for a solution of 1c in $[^7\text{H}]$THF at a concentration of 8.2 mm are shown in Fig. 5. Compound 1c was proposed to exist as a monomer in this media as THF competes with the hydrogen-bonding contacts thus preventing aggregate formation. The measured $I(Q)$ data for this is compared with the calculated SANS data for a monomer. The $R_g$ value of 13.5 Å for the calculated SANS curve agrees reasonably well with the experimental $R_g$ value of 14.6 ± 1 Å obtained from the middle-$Q$ region of the data. Also the data in the high-$Q$ region for both the experimental and the calculated data for a monomer agree quite well. However, in the low-$Q$ region, the two data sets do not agree. Interestingly, the low-$Q$ region of the experimental data exhibits a power law $I(Q) \sim Q^{-1.8}$ which points to extremely large structures resembling mass fractals.

Nevertheless this unusual SANS curvature in the low-$Q$ region is not reproducible. For example, in a different run, the experimental SANS data fit to the calculated value for a dimeric structure. The differences between runs may originate from a slow disassembly process of the hexameric aggregate.

To demonstrate the appropriateness of the SANS technique for examining this class of macromolecules, as well as to probe the effect of solvent on conformation, tetraester 4 was investigated in both CDC$_3$ and $[^7\text{H}]$THF. Tetraester 4, a close analogue of 1c, was shown previously to exist as a monomer in both solvents due to the absence of hydrogen-bonding sites.

The SANS data collected for 4 in CDC$_3$ and $[^7\text{H}]$THF at a concentration of 8.0 mm are shown in Fig. 6. These results validate the monomer model proposed for this system (see Fig. 1). Thus, these data show that the experimental scattering patterns are identical to the calculated ones for the monomer. The large difference in the scaling of data for 4 in CDC$_3$ and

Fig. 5 (a) Experimental SANS data of a 8.3 mm solution of 1c in $[^7\text{H}]$THF (A) along with the calculated data for a monomer (B). (b) Guinier plots for the data in (a).

Fig. 6 Experimental SANS data for 16 mg ml$^{-1}$ 4 in $[^7\text{H}]$THF (A) and in CDC$_3$ (B). The lines are the calculated scattering patterns for the monomer. The different scaling between these data sets is due to the difference in contrast provided by the solvent for the scattering from the monomer.

$[^7\text{H}]$THF is due to different contrasts (see eqn. (6)) provided by the different scattering length densities of the solvents CDC$_3$ (3.16 × 10$^{10}$ cm$^{-2}$) and $[^7\text{H}]$THF (6.36 × 10$^{10}$ cm$^{-2}$). It is evident that the contrast for neutron scattering from these particles is higher in $[^7\text{H}]$THF when compared to that in CDC$_3$, as seen from the low signal intensity and large error bars for the latter, even though both samples used similar beam times.

Tetraacids 1 with second- and first-generation dendritic substituents were also investigated. Experimental SANS data for an 8.5 mm solution of 1b in CDC$_3$ along with the calculated data derived from a cyclic hexameric aggregate are shown in Fig. 7. The experimental $R_g$ of 27.1 ± 1 Å agrees quite well with that from the calculated data ($R_g$ = 28.6 Å). The shapes of the scattering patterns also agree well in the whole $Q$ region thus validating the correctness of the proposed model for this system.

Previous SEC dilution study in methylene chloride showed that the aggregation of tetraacid 1a is concentration dependent. This behaviour, as well as the breadth of the SEC peak, suggested that 1a forms a series of linear aggregates. Molecular modelling studies suggested that this preference resulted from hydrogen-bonding contacts thus preventing aggregate formation. The measured $I(Q)$ data for a solution of 1a in CDC$_3$ is concentration dependent. Non-specific aggregation was also observed in the SANS studies which suggest the formation of large and polydisperse aggregates in a 10.6 mm CDC$_3$ solution of 1a (Fig. 8). This Fig. shows the measured SANS data and calculated form factors for linear aggregates with 8 and 20 monomers. The Guinier plot for the measured data has at least two different
systems in different solvents. Scattering data were calculated from an extremely flat and extended monomer. Further SANS studies provide strong support for the cyclic hexameric aggregates. The ester analogue was studied in both THF and CDCl$_3$ and found to exist as a monomer, as expected. Compound 1a seems to form large and non-discrete aggregates. However, the previously proposed linear aggregate model could not explain the experimental data rather the aggregate may have a thin, hollow, cylindrical structure.

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References

Conclusions

Hydrogen-bond mediated self-assembling dendrimers have been studied by a variety of techniques and structural models have been proposed based on the results of SEC, NMR and VPO studies. Small-angle neutron scattering (SANS) was shown to be a direct and powerful technique for studying these systems in different solvents. Scattering data were calculated from the atomic coordinates generated from the proposed models and compared with the measured scattering data. This offers a direct way to compare the validity of the models and thus increase our understanding of these systems.

The SANS studies provide strong support for the cyclic hexamer model previously proposed for 1ke in CDCl$_3$. SANS further suggests a concentration dependent interaction between these hexameric aggregates. The ester analogue was studied in both THF and CDCl$_3$ and found to exist as a monomer, as expected. Compound 1a seems to form large and non-discrete aggregates. However, the previously proposed linear aggregate model could not explain the experimental data rather the aggregate may have a thin, hollow, cylindrical structure.