Nanometric Sponges Made of Water-Soluble Hydrophobic Dendrimers

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One of the new frontiers in chemistry concerns compounds of intermediate (nanometric) sizes between the molecular and the solid state, which should display unusual properties. In this perspective, dendrimers are one of the most promising types of nanometric compounds.[1] Indeed, dendrimers have highly tuneable architectures, which possess maximum interfaces for optimum interactions with their environment. A lot of properties were already demonstrated, mainly in the fields of catalysis, materials science, and biology. Intriguing new properties should be expected for some water-soluble "inorganic" dendrimers[2] as a consequence of the structural conflict between a hydrophobic interior and hydrophilic end groups. In this paper, we report that phosphorus dendrimers[3] solubilized in water behave like solid colloidal particles, which swell and "bloom" progressively like dried sponges, to afford micelle-like compounds when tetrahydrofuran (THF) is added. This state modification at the nanoscopic scale has dramatic consequences on the dendrimer environment at the nanoscopic level, but also at the macroscopic level.

The phosphorus dendrimers used in this study are built from an octaaldehyde metal-free phthalocyanine core, usable for sensing the internal behavior of dendrimers; the octasubstitution avoids complications due to regioisomers, previously shown for tetra-substituted phthalocyanines.[4] The synthesis was carried out using a divergent strategy,[3a] up to the fifth generation G_5, which is soluble in organic solvents such as THF. In the last step, 256 ammonium groups are grafted on the surface[5] of G_5 (Figure 1), to afford the dendrimer G_5N^+, which is soluble in polar solvents such as water. Surprisingly, the aqueous solution of G_5N^+ analyzed by UV−vis spectroscopy displays a very broad band with two main shoulders approximately at 675 and 720 nm, characteristic of the Q-band of a phthalocyanine in the solid state.[6] This special behavior of G_5N^+ evokes a frozen internal structure surrounded by solubilizing functions, reminiscent of a solid colloidal state in solution (a sol). A progressive addition of THF to the aqueous solution induces drastic changes of the Q-band, whose signals sharpen and increase, indicating the progressive solubilization of the core. A similar phenomenon is observed by ^{1}H NMR; G_5N^+ in D_2O gives only signals corresponding to ethyl groups, showing that only the external hydrophilic shell is solvated. The hydrophobic interior is unsolvated, and therefore rigid and anisotrope (Figure 1, left inset). Upon addition of THF-d_8, signals corresponding to the aryl internal groups ($b'b$) progressively appear (Figure 1, right inset).

To confirm and better understand this change of state at a nanoscopic level, solutions of G_5N^+ in D_2O, to which THF-d_8 was progressively added, were examined by means of high-field NMR experiments using the pulsed-field gradient spin−echo NMR technique. Such a technique was already used to probe size and geometrical parameters of dendrimers under the influence of pH,[7] temperature,[8] concentration,[9] or type of branching.[10] Our aim was to study the influence of the nanoscopic change of state induced by THF on the diffusion of G_5N^+ and on its size (hydrodynamic radius R_H), and to check the influence of such changes on its
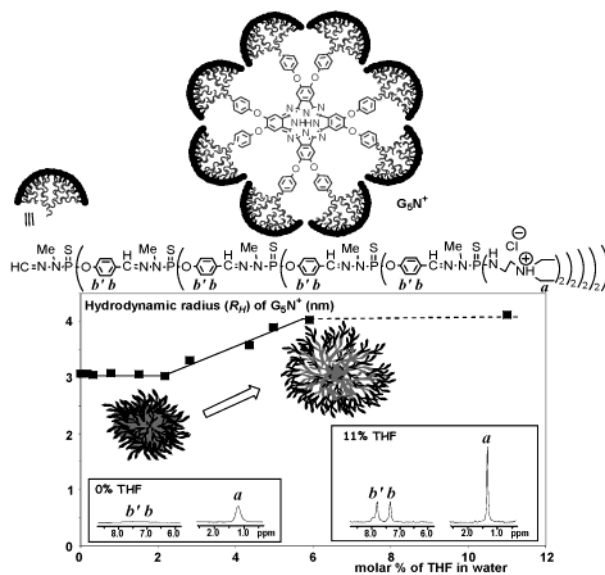

Figure 1. Variation of the hydrodynamic radius of G_5N^+ in water with increasing amounts of THF, and "artist view" of swelling and blooming phenomena. Left inset: part of the ^{1}H NMR spectrum of G_5N^+ in D_2O. Right inset: part of the ^{1}H NMR spectrum of G_5N^+ in D_2O/THF 89/11.

environment. Self-diffusion measurements allow one to characterize the motion of separated entities (here G_5N^+) in solution; DOSY experiments give access to diffusion coefficients D using the Stejskal−Tanner equation.[11] The D value gives the R_H value of spherical particles (high generation dendrimers such as G_5N^+ can be approximate to spheres) using the Stokes−Einstein equation, provided the viscosity of the solution (η) is known. Because addition of THF to water[12] and addition of salts[13] modifies drastically the global viscosity, experiments were carried out in the presence of internal diffusion references. NMe_4Cl and PMe_4Cl were chosen as water-soluble references of constant R_H; a double reference system allows one to cross-check and validate the invariance of their hydrodynamic radius.[14] R_H as well as global viscosity fluctuations are calculated from the measured diffusion coefficients, using $\eta = k_BT/6\pi D_{ref}R_{Href}$ and $R_H = D_{ref}R_{Href}/D$.

Micromolar amounts of lyophilized G_5N^+ were dissolved in D_2O in the presence of NMe_4Cl and PMe_4Cl (5% molar for each/end groups). The DOSY data sets afford the diffusion coefficients of G_5N^+, using the signal corresponding to the external CH_3 groups ($\delta = 1.2$ ppm). A linear relationship is observed for the diffusion data of G_5N^+, indicating that this dendrimer is monodisperse within the limits of detection. Individual diffusion coefficients were deduced from each diffusion curve. Taking as invariant reference $R_{Href} = 2.9$ Å[15] for NMe_4^+, modification of the hydrodynamic radius of G_5N^+ upon addition of THF is plotted in Figure 1. Three domains are observed: at low amounts of THF, R_H remains constant; swelling begins from a critical value of approximately 2% (molar) of THF in water. A plateau is reached for larger amounts of THF
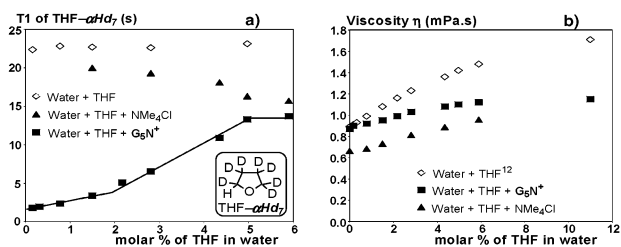
Figure 2. (a) Variation of the spin−lattice relaxation value T1 for THF-αHd7 in water with increasing amounts of THF. (b) Variation of the viscosity of water/THF solutions.

(5−6%). The diameter of G_5N^+ varies from ≅60 Å when it is contracted in pure water to ≅82 Å when it is expanded in D_2O/THF-d_8. These values correspond to single molecules (no aggregation) and are comparable to the diameter measured by electron microscopy for another fifth generation phosphorus dendrimer (90 ± 5 Å).[3c] Thus, addition of THF induces a dramatic increase of the dendrimer size (≅35% for its diameter and ≅150% for its volume). It is interesting to note that swelling is accompanied by "blooming"; the aryl signals corresponding to the internal structure begin to appear when the size of G_5N^+ begins to increase (Figure 1). Swelling of dendrimers in solution was previously reported,[7−10] but not "blooming". Surprisingly, the original behavior of G_5N^+ at the nanoscopic level, preceded by an induction period, is very reminiscent of the moistening of dried sea sponges at the macroscopic level and may raise the question of the persistence of the relation between structure and function at two very different scales.

To get a better understanding of the role played by THF in this phenomenon, the partially deuterated fraction of THF-d_8 (THF-αHd_7) is used as a probe. The diffusion coefficient of THF-αHd_7 is found constant either in or not in the presence of G_5N^+, whatever the concentration of THF in water is. However, the spin−lattice relaxation data (T_1) of THF-αHd_7 appear to be extraordinary sensitive to the presence of the dendrimer. Indeed, the T_1 value for THF-αHd_7 in water without dendrimer is constant (22 ± 1 s), whereas it is drastically modified in the presence of G_5N^+. This is not due only to the presence of charges, because NMe_4Cl has a totally different influence on T_1 (Figure 2a). The modifications of T_1 for THF-αHd_7 induced by the dendrimer G_5N^+ are parallel to the size modification of the dendrimer induced by increasing amounts of THF (Figure 1). The discrepancy found for THF-αHd_7 between its diffusion coefficient insensitive to the presence of G_5N^+, and its spin−lattice relaxation highly sensitive to the presence of G_5N^+, is extremely unusual. However, a related observation was made for water in polymer gels, whose diffusion is not affected by the degree of cross-linking, but whose T_1 decreases when the cross-linking increases.[16] Thus, the phenomenon observed in the presence of G_5N^+ could constitute a measurement of the degree of branches entanglement within each molecule of dendrimer. Indeed, the entanglement should be maxima for the "solid state" structure observed in water in the absence of THF, whereas it should decrease progressively and totally disappear at 5−6% mol of THF, when the dendrimer is totally opened out. In this latter case, only charges influence the T_1 value, which becomes close to that induced by NMe_4Cl.

In view of the modifications of its internal structure, G_5N^+ should act as a nanosponge for lipophilic drugs.[17] To demonstrate this assumption, tetramethylsilane (TMS) was used as a probe. Its ^{1}H NMR spectrum in the presence of G_5N^+ in water with or without THF revealed the presence of three signals, and DOSY experiments afforded three different diffusion coefficients. The most rapid diffusion corresponds to free TMS in water; the slowest is comparable to that of G_5N^+ and should correspond to TMS encapsulated within the dendrimer. The third diffusion, intermediate between both values, is presumably due to TMS species located at the frontier between the internal structure of the dendrimer and water. The presence of THF increases the diffusion of both TMS species in interaction with the dendrimer, indicating an increased porosity of the nanofrontier between the internal structure of the dendrimer and the external media, driven by THF.

Thus, the hydrophobic/hydrophilic character of G_5N^+ induces very original properties at the nanoscopic level, but it has also unexpected macroscopic consequences. Having quantified the size variations of G_5N^+ with increasing amounts of THF (Figure 1), it is possible to deduce the variation of the viscosity of the solution. The viscosity of water/THF mixtures alone is known[12] and is totally different (Figure 2b); it is also known that charges modify the viscosity of water. To check if the drastic modification observed is only due to charges, the viscosity of a solution of NMe_4Cl, at the same concentration in charges as was the dendrimer in the previous experiment, is also measured. As expected, the presence of charges has a large chaotrope effect, more pronounced for NMe_4-Cl than for G_5N^+ of the same ionic strength. Thus, G_5N^+ plays the original role of a buffer for regulating the viscosity of the solution, illustrating another facet of the interactions between the dendrimer and its environment. In fact, G_5N^+ acts as a highly singular and adaptable nanotool, able both to modify its environment and to be modified by it.

Supporting Information Available: Characterization of G_5N^+, DOSY data sets for G_5N^+, and part of a ^{1}H NMR spectrum, showing three types of TMS species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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