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Conformational Changes of Polyamidoamine (PAMAM) Dendrimers Adsorbed on Silica Substrates

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 Supporting Information

Numerous authors have suggested that dendrimers represent promising stimulus responsive drug delivery systems or gene vectors.^{1–6} The trapped compound could be released by inducing a conformational transition by changing the salt level, dendrimer charge, or nature of the solvent. These ideas were mostly scrutinized with polyamidoamine (PAMAM) dendrimers discovered by Tomalia and co-workers.⁷ Detailed scattering experiments have revealed that PAMAM dendrimers may swell in organic solvents, but in aqueous systems the swelling is marginal, even upon substantial changes of salt concentration or dendrimer charge.^{8–13} The charge can be tuned by solution pH due to the presence of weakly basic amine groups in the PAMAM scaffold.^{14,15} While earlier computer simulations suggested substantial swelling in aqueous solutions,^{16–19} recent atomistic molecular dynamics studies revealed that such conformational changes depend critically on the interaction potential between the amine groups and chloride ions.²⁰ With more accurate force fields derived from quantum mechanics, the simulations reproduce the experimentally observed minor variation in gyration radii with pH but further suggest the existence of an internal conformational transition. Such internal rearrangements within dendrimers were scrutinized recently, as they may provide an alternative mechanism to trigger the release of trapped compounds.^{13,20,21}

Here, we report that major conformational changes of PAMAM dendrimers can be induced in aqueous solution by variations in salt level and pH, provided the dendrimers are adsorbed on a charged substrate. Adsorbed dendrimers at the water–silica interface swell substantially with increasing salt level and decreasing pH as shown by in-situ atomic force microscopy (AFM) and quartz crystal microbalance (QCM). Earlier AFM studies have revealed that adsorbed dendrimers flatten,^{22–24} and their shape was suggested to depend on the substrate or solvent.^{25,26} However, these results are difficult to interpret since imaging was mostly performed in dried state ex-situ, and systematic in-situ studies in solution were not carried out.

AFM images of PAMAM G10 dendrimers adsorbed on silica from salt-free aqueous solution adjusted to pH 4 are shown in Figure 1 (top row). The dendrimers adsorb in a low-coverage monolayer with a liquidlike structure, which is generated by the long-ranged electrostatic repulsions between the charged dendrimers.²⁷ The height of the adsorbed dendrimers is ~10 nm in

solution and ~9 nm in air. By deconvoluting the images to correct for the finite size of the AFM tip, one obtains a molecular volume of ~1400 nm³ in dried state. The quantitative AFM results were obtained by statistical analysis of 3–4 different substrates and counting 30–100 dendrimers on each substrate. When compared to the known molecular mass and density, this value suggests a small content of residual water. The larger volumes in the wet state indicate a water content of ~50%. The latter number is rather approximate due to the residual water in the dried dendrimers but is still well comparable to the water content of dendrimers measured in solution by NMR and small-angle neutron scattering.^{28,29}

When the silica substrate with adsorbed dendrimers is incubated in 100 mM KCl solution of lower pH, substantial swelling of the dendrimers is observed by in-situ AFM imaging in solution (Figure 1, bottom row). In-situ imaging in a pH 3 solution shows that dendrimer heights increase by ~30%, while their volumes almost double (Figure 1, left column). We interpret these results by a conformational change accompanied by swelling and incorporation of water into the dendrimer. A similar change can be observed by ex-situ AFM imaging in air after drying (Figure 1, right column). The fact that this change still occurs in dried state is probably related to the presence of residual water or quenching of the conformation during the drying process.

Independent confirmation of the swelling process can be obtained by QCM. Adsorption processes can be detected through a frequency shift. This shift is sensitive to the wet mass, which includes the mass of trapped water. PAMAM G10 dendrimers were adsorbed on a silica-coated QCM crystal from a salt-free pH 4 solution, and a wet mass of ~0.92 mg/m² is obtained (Figure 2a). When the substrate is rinsed, one confirms that the adsorbed layer is stable. When a dendrimer-free 100 mM KCl solution of pH 4 is injected, swelling of the adsorbed dendrimers is detected by an increase of the signal of about 40%. This change corresponds approximately to the relative change in the water content of the adsorbed dendrimers and reflects the conformational change observed by AFM. Repeating the same sequence of

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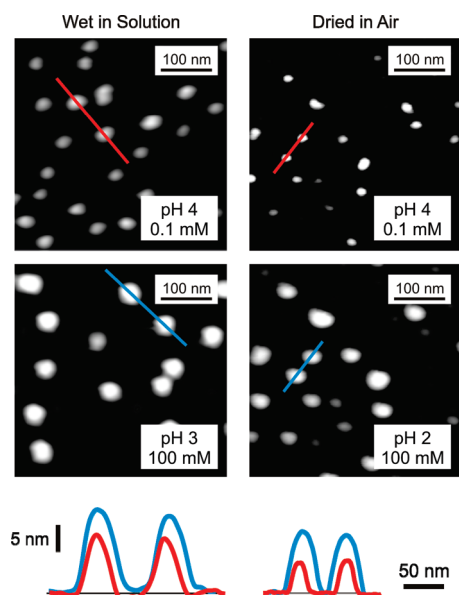


Figure 1. AFM images of adsorbed PAMAM G10 dendrimers on silica in solution (wet, left column) and in air (dried, right column). Initial situation of dendrimers adsorbed from a solution of pH 4 and 0.1 mM (top row). When the sample is incubated in a KCl solution of 100 mM of lower pH, the dendrimers swell substantially (middle row) as also indicated in cross sections (bottom row). The incubating solution had pH 3 for the image in solution (middle left) and pH 2 for the image in air (middle right). Note that identical dendrimers before and after swelling were imaged in air and that pH 2 was used to make the effect more visible.

solutions demonstrates that the conformational change is reversible and that no desorption takes place. Independent optical reflectivity measurements corroborate the absence of desorption, as this technique is insensitive to trapped water and yields a dry mass of $\sim 0.12 \text{ mg/m}^2$. The latter value of the dry mass and lack of desorption are consistent with previous dendrimer adsorption studies with reflectivity.^{27,30,31} By comparing reflectivity and QCM data, we find that the layer contains about 80% of water. When exposed to 100 mM KCl solution of pH 4, the water content increases to $\sim 90\%$. The differences between the water contents determined by the different techniques are probably due to the response of the QCM to roughness of the dendrimer layer, deformation of the dendrimers by the AFM tip, or minor differences in the surface composition of the silica substrates.

Adsorbed dendrimers were incubated in various solutions and the relative changes in wet state obtained by QCM or AFM reveal congruent trends (Figure 2b). The dendrimers are always adsorbed from a salt-free solution of pH 4, and swelling is observed in solutions containing 100 mM KCl of pH 3, 4, or 6. Swelling is most pronounced in acidic conditions. Conversely, adsorbed dendrimers shrink when they are incubated in a 0.1 mM KCl solution of pH 6. While a quantitative comparison of these experimental results appears nontrivial, qualitative trends obtained from the two independent techniques agree strikingly well. The molecular volumes determined by AFM in solution follow the same trend. However, we prefer to report the heights of the dendrimers, which can be determined from the AFM images directly. The heights do reflect the conformational changes but are unaffected by tip convolution. From reflectivity measurements we further conclude that different incubating solutions

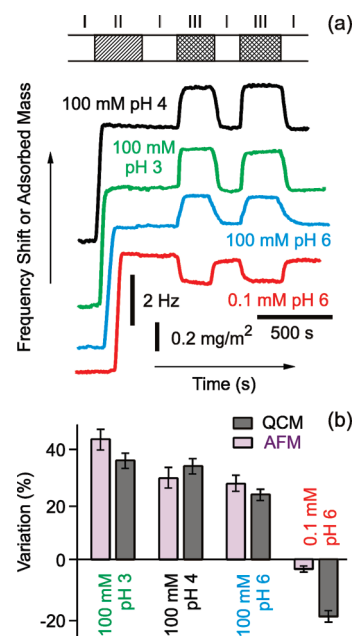


Figure 2. Conformational changes of adsorbed PAMAM G10 dendrimers. (a) Negative frequency shift measured by QCM as a function of time along a sequence of different incubating solutions indicated in the upper bar. (I) Background salt-free solution of pH 4. (II) Dendrimer solution of a concentration of 3 mg/L at pH 4. (III) The composition of the incubating solution is indicated in the figure. (b) Comparison of the relative variation of change in the wet adsorbed mass obtained by QCM and in the height obtained by AFM in wet state relative to the values in a salt-free solution of pH 4. The error bars represent the standard deviation of the mean.

induce only minor changes in the content of trapped ions in the adsorbed dendrimers.

The observed behavior can be qualitatively rationalized by attractive electrostatic interactions between the positively charged dendrimers and the negatively charged water–silica interface. The surface charge of silica originates from dissociation of the silanol groups, which becomes more pronounced with increasing pH.³² At low salt levels, the dendrimers are flattened by strong electrostatic attractions between the positive amine groups and the negative silanol groups. At higher salt levels, this attraction is screened, the dendrimers are attracted to the substrate more weakly, and therefore they swell. The swelling is maximal at low pH, where the interface is negligibly charged. With increasing pH, the attraction becomes stronger, since the silanol groups dissociate, and the respective swelling is smaller. These conformational transitions seem to be mainly driven by dendrimer–substrate interactions and to a lesser extent by intramolecular interactions within the dendrimer. The fact that forces between the dendrimers and the substrate may control conformations of adsorbed dendrimers was suggested earlier on the basis of computer simulations.^{26,33} The negligible role of intramolecular interactions is further evidenced by the fact that dendrimers in solution swell very little upon variations of the salt level or pH.^{8–13}

We conclude that conformation of adsorbed dendrimers on water–silica interfaces can be substantially influenced by the salt level in solution and the charge of the substrate. Changes in volume of up to a factor of 2 could be observed. This effect is mainly driven by electrostatic attraction between the dendrimers

and the substrate. Therefore, adsorbed dendrimers swell with increasing salt level and with decreasing pH. Similar effects can be expected for oxides surfaces, provided their surface charge varies with pH. The present findings could be of substantial importance for the engineering of novel dendrimer-based responsive nanocarrier systems driven by conformational transitions, which would be triggered by dendrimer–substrate interactions. Therefore, an alternative strategy to design drug or gene delivery systems could be based on adsorbing or grafting dendrimers to planar substrates,^{1,27} porous scaffolds,^{3,5} or nanoparticles.³⁴

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details and further information on reflectivity experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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