

Understanding the Cosolvation Effect of Dendrimers

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Abstract: Molecules that are virtually insoluble in certain solvents may be uploaded to “hostile” phases by dendrimers. Prime examples of this phenomenon are Eosin Y, EY, and Rose Bengal, RB, that are not soluble in CH_2Cl_2 where they can, however, be solvated through the interaction with a fourth generation dendrimer of polypropylene amine, POPAM-4D. The two dyes share the same carbon framework and differ for the pattern of halogenation, and yet their cosolvation varies over a factor of 4: six Eosin Y and ~ 25 Rose Bengals are solvated by the macromolecule. Leveraging on a previous report where molecular dynamics simulations of 12 EY@POPAM-4D in CH_2Cl_2 showed a reduction to the experimental limit of 6, we now perform similar calculations with an excess, i.e., 40, of RB@POPAM-4D. The simulations quantitatively reproduce the cosolvation effect. They also provide a microscopic understanding of its origin and of motions-interactions of the macromolecule and both of its guests.

Introduction

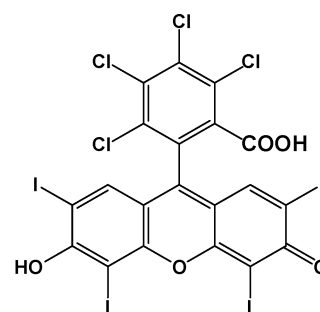
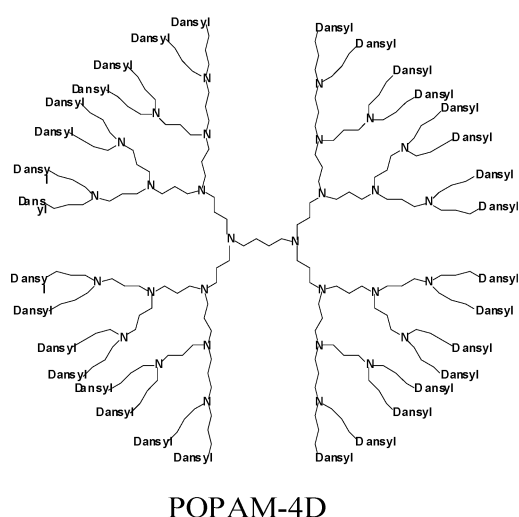
One of the several, potentially important, applications of dendrimers^{1–6} is the encapsulation of molecules. An important practical use of the entrapment could be transporting and delivering drugs to specific targets inside the body.⁷ To entrap a guest, the macromolecule must interact better with the guest than the surrounding environment. In practice, the carrier must be more “attractive” to the guest than the outside world. Another application of the same phenomenon is the increase of solubility, or even the solvation of molecules in solvents where it is usually not possible. Peculiarly, small variations of the chemical structure of the guests lead to substantial variations of their average number “inside” dendrimers.⁸ The case of a 4-th generation polypropylene amine dendrimer, in short POPAM-4D, and two rather similar dyes is illustrative. The dyes are water-soluble and CH_2Cl_2 insoluble; POPAM-4D is CH_2Cl_2 soluble but is water insoluble. When an aqueous solution of the dyes is shaken with an organic solution of the dendrimer, up to 6 Eosin Y molecules or ~ 25 molecules of Rose Bengal are transferred to CH_2Cl_2 .⁸ All the molecular structures are given in Scheme 1. Eosin Y and Rose Bengal share the same carbon framework and differ for the substitution of 4 hydrogens with

4 chlorines, and 4 bromines with 4 iodines, with Rose Bengal heavier by $\sim 50\%$. And yet, POPAM-4D uploads four times as many heavier molecules.⁸ *The relatively small structural change varies by half an order of magnitude the cosolvation effect of the dendrimer!*

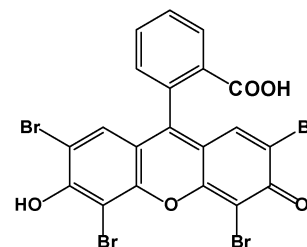
Recently,⁹ we studied the dynamics of this dendrimer with a varying number of eosins Y. The intent was to verify if computational methods could reproduce and provide insight into the 1:6 POPAM-4D:Eosin Y ratio. The initial “computer” encapsulation of twelve dyes evolved in less than a nanosecond to a stable arrangement with only six guests, while the other six fled away in the solvent.⁹ In practice, the host cannot harbor more than six Eosin Y’s and since this dye is not CH_2Cl_2 -soluble, this is the maximum number that can be uploaded to the organic phase per dendrimer molecule. The work focused mainly on dynamical aspects of the guest–host system and recorded a multitude of entrances and exits in the macromolecule. The origin of the hustle and bustle of molecules around the dendrimer is the “unfriendly” solvent environment. Low solubility arises — although not only — from weak intermolecular interactions with the solvent, which imply high mobility in it. If, after departure from POPAM-4D, a dye comes again in contact with the macromolecule, favorable stabilizing interaction forces “suck” it in. The molecule may then displace another

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Scheme 1



Rose Bengal



Eosin Y

guest, or, alternatively, if the closest guest molecule is solidly embedded in the macromolecule, it may be expelled again.

The ability of a simulation to reproduce the 4-fold increase of concentration of dye molecules caused by relatively small structural changes would broaden our understanding of the guest–host dynamics of the dendrimer (and strongly vouch for the accuracy of the computational model). Through the comparison of the results for the two types of guests, one could also understand the origin of the very different cosolvation effect obtained for the two structurally similar dyes. It is believed that the elucidation of the structural and dynamical properties of dendrimers and their guest–host systems can be partly achieved using computer modeling.¹⁰

Results and Discussion

The flexible branches that characterize the majority of dendrimers can rearrange to form a myriad of conformations. Their interconversion is rapid in a liquid, and this exchange can be partly transmitted to the solid, making the structural characterization very difficult (see, however, ref 11). Here we attempt to assist the process of developing a quantitative understanding of the geometrical and dynamical properties of their guest–host systems and of the cosolvation effect in particular. Before presenting the results of the simulations, it is worth summarizing the experiments. Aqueous solutions of water-soluble dyes that are not soluble in CH_2Cl_2 are shaken together with a CH_2Cl_2 +dendrimer solution. The dyes move from acidic water, $\text{pH}=5$, whose color fades, the CH_2Cl_2 solution, which becomes colored. The concentration of the dendrimer in CH_2Cl_2 is less than 2.5×10^{-6} M. The concentration of the dyes in water is 7.5×10^{-5} M. Aggregation and dishomogeneity due to concentration should therefore be unimportant on long time scales, although they may occur locally either at or around the dendrimer. The

measurements indicate that each molecule of dendrimer can interact, on average, with up to six eosin Y and ~ 25 Rose Bengal molecules.

In analogy with what done for the case of Eosin Y, we performed new molecular dynamics, MD, simulations of the dendrimer in CH_2Cl_2 solution with an excess number, i.e., 40, of molecules of Rose Bengal. The present comparison of the two sets of simulations for Eosin Y and Rose Bengal implies the assumption that the equilibria in water play a similar role for the two dyes.

The previous simulations with Eosin Y's⁹ showed that the excess of twelve dyes is rapidly reduced to the experimental limit of six. Rose Bengal behaves similarly. The 40 guests swarm around the dendrimer, Figure 1a, establishing and breaking contact several times. A clearer view of the behavior of selected few molecules is presented in Figure 1b.

The average number of guests in contact with the hyper-branched molecule is shown in Figure 1c. To assist the eye, the numbers represent averages over 5 ps of dynamics. Despite the highly dynamical evolution characterized by a series of departures and arrivals, the macromolecule is able to host between 21 and 27 Rose Bengals during the whole simulation.

The modeling reproduces the experimental observation of a substantial difference in the interaction with the macromolecule upon relatively small structural changes of the host. The calculations may also provide complementary information about three main aspects:

1. the shape of the macromolecule, and its variation, during the dynamics in the absence and in the presence of the guests,
2. the solvent molecules dynamics inside and around the macromolecule, both in the absence and in the presence of the guests,
3. the dynamics of the guest molecules.

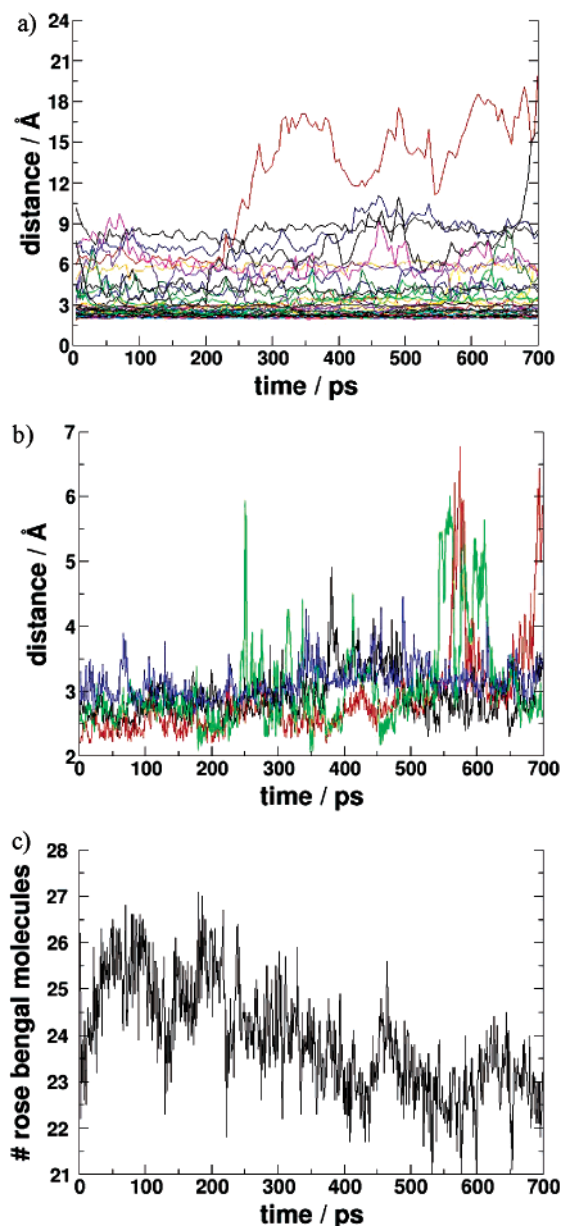


Figure 1. Simulation of an excess of Rose Bengal molecules in a CH_2Cl_2 box with POPAM-4D: (a) instantaneous shortest distance between an atom of each of the 40 Rose Bengals and one of the dendrimer; (b) zoom on four of the guests, which show multiple entrances and exits from contact with the dendrimer; (c) average number over 5 ps of the Rose Bengal molecules in contact with the dendrimer.

Shape Variation of POPAM-4D. In solvents, dendrimers tend to have collapsed, compact conformations¹² that are characterized by high internal mobility. The presence of guests may affect the conformational equilibria. Figure 2a shows the instantaneous ratios of the largest moment of inertia divided by either one of the other two, together with the gyration ratio. A spherical, static dendrimer would have both ratios constant and equal to one; a cylindrical dendrimer would have only one of the ratios equal to one, see computational section for details. Figure 2b displays the deviations from perfect spherical and cylindrical shapes as a function of time.

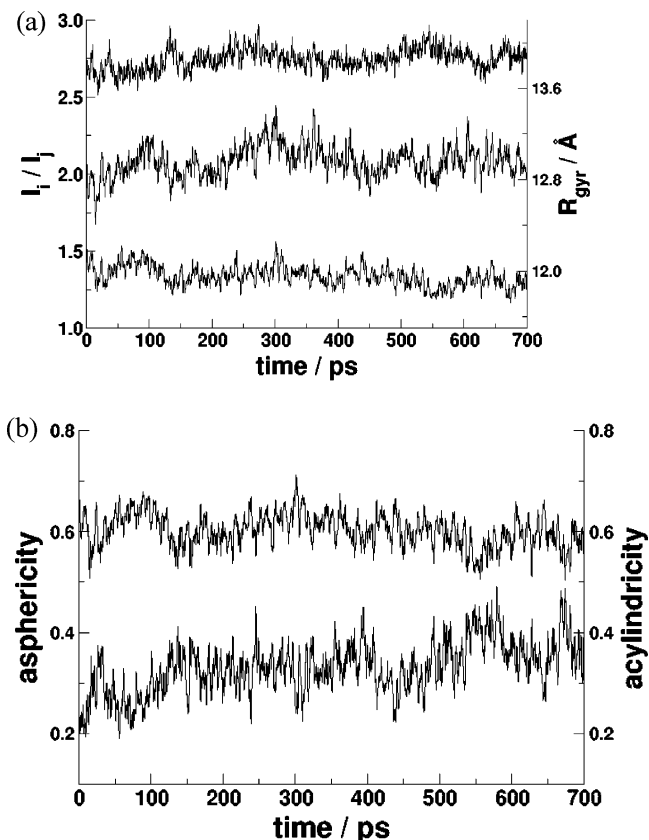


Figure 2. Dynamics of POPAM-4D in CH_2Cl_2 solution in the presence of an excess of Rose Bengal molecules: (a) instantaneous ratios of moments of inertia I_1/I_2 and I_1/I_3 , with $I_1 > I_2 > I_3$, the top curve is the gyration radius; (b) top, deviation from spherical shape, bottom, deviation from cylindrical shape.

During the dynamics I_1/I_2 ranges between 1.25 and 1.5, while I_1/I_3 ranges between 1.7 and 2.5: the macromolecule is hardly spherical. The average values of r_{gyr} give additional information. For POPAM-4D, EY@POPAM-4D, and RB@POPAM-4D, they were 17.17, 15.93 and 13.86 Å with largest instantaneous deviations from the average values of 2.23, 1.27, and 0.40 Å. Therefore the guests tend to make the macromolecule more compact. Because of the lower r_{gyr} , one of the results of the presence of Rose Bengal is the effective decrease of the size and number of the pockets that can encapsulate the guests inside the macromolecule. It can be surmised that the increased solubility of RB must have an origin different from the direct interaction between guest and host. So far as one can think of a dendrimer as a box, the presence of guests effectively close the dendrimer box (It may even be thought that the molecules pull the door with them after entering!).

The nonspherical shape of the macromolecule appears in the top line of Figure 2b. In the same order as above (POPAM-4D, EY@POPAM-4D, RB@POPAM-4D), the average values are 0.62, 0.50, 0.60 with largest instantaneous deviations of 0.19, 0.19, 0.11. The macromolecules are therefore hardly spherical. A better description of the dendrimer is as a cylinder. Indeed, the values of departure from the perfect cylindrical shape are small and are 0.36, 0.27, 0.33. The relative largest instantaneous deviations are

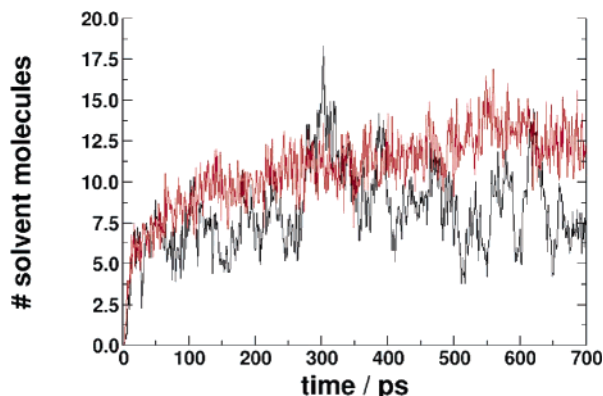


Figure 3. Number of solvent molecules, averaged over 5 ps, around POPAM-4D in CH_2Cl_2 solution in the presence of an excess of Rose Bengal molecules: the red line is the number of solvent molecules with at least one atom less than 2.8 Å away from an atom of the dendrimer, and the black line is the number of solvent molecules inside r_{gyr} .

0.29, 0.22, 0.16. Overall, it appears that the general shape of empty POPAM-4D and RB@POPAM-4D departs from that of EY@POPAM-4D.

The conclusion of this subsection is that the presence of the guests is a way to manipulate the structure of the dendrimer, which becomes more cylindrical and denser.

Solvent Dynamics inside POPAM-4D. In solution, the free dendrimer has ~ 30 CH_2Cl_2 molecules in contact with it at any one time. They can be either on the surface or inside. The formation of the guest–host system with 6 Eosin Y decreases them to about 24. Figure 3 shows that in the case of Rose Bengal, they undergo a further drop to ~ 12 . Because of the way the simulation is set up, CH_2Cl_2 molecules are not initially present inside POPAM-4D. However, the solvent molecules penetrate very rapidly inside the dendrimer and, in 200 ps, reach an average number of 12. The process corresponds to a rather fast equilibration: during this time the dynamics also reaches a near constant value of the potential energy. This percolation process does not correspond to a real physical process. It is, however, useful to understand the rapidity of the solvent movements inside the dendrimer. In the case of Eosin Y, the same equilibration, with more molecules was reached in ~ 60 ps. The different time frames agree with the more compact structure of POPAM-4D in the presence of Rose Bengal, which, in turn, makes movements inside it slower.

The solvent molecules inside r_{gyr} tend to be fewer than those in contact with the hyper-branched system. The trend is opposite to that recorded when the guests are Eosin Y's.⁹ Although r_{gyr} does not perfectly match the surface of the dendrimer (the nonspherical shape makes the radius include regions where there may not be dendrimer atoms and exclude zones where they are still present), the inversion with respect to the case of Eosin Y signals that Rose Bengal displaces CH_2Cl_2 in the neighborhood of the surface (see below).

Dynamics of the Guest Molecules. While the number of “permanent” guests at POPAM-4D is roughly constant, their position is hardly stationary. Figures 4a and 4b give more details. Figure 4a shows the evolution of the distances

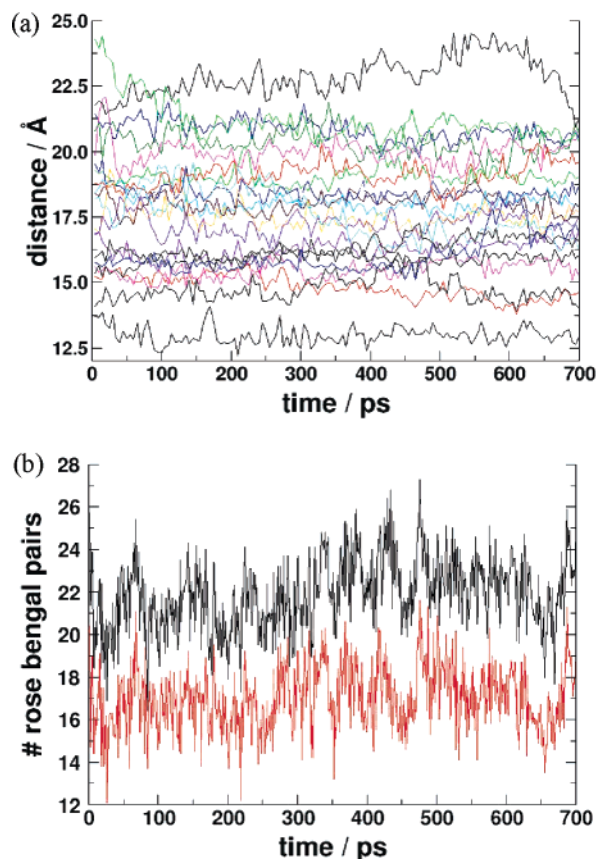


Figure 4. (a) Instantaneous Rose Bengals-POPAM-4D center-to-center of mass distance for the dyes in contact with the dendrimer; (b) Rose Bengal physical dimerization: in black the total number of pairs, in red the number of dimers in contact with the dendrimer.

between the centers of mass of the guest Rose Bengals and that of the dendrimer. At odds with the case of the Eosins where two molecules resided in the inner core of the dendrimer (5–10 Å from the center of mass),⁹ RB's distribute rather evenly. This agrees with the more tightly packed structure of the macromolecule, which does not allow the dyes to percolate inside it although they do show a substantial mobility.

Figure 4b shows that a number of guest pairs (or even trimers) are instantaneously formed. Some of the pairs permanently leave the macromolecule. The physical dimerization of the guests indicates that in CH_2Cl_2 , Rose Bengal prefers to interact with itself rather than with the solvent.

Origin of the Cosolvation. The simulations satisfactorily describe the different nature of the guest–host systems of POPAM-4D with the two dyes and reproduce their different amount of solvated molecules. A single bottom line able to explain the larger solvation of RB's is, however, still required.

To obtain it, we calculated the average energies, over time, of guest–host, guest–solvent, and guest–guest interactions for each one of the dyes of 12EY@POPAM-4D and 40RB@POPAM-4D. A table with the results is given in the Supporting Information. Both $\langle V_{\text{guest–host}} \rangle$ and $\langle V_{\text{guest–solv}} \rangle$ resulted quite similar, while $\langle V_{\text{guest–guest}} \rangle$ is substantially larger for Rose Bengal. Indeed, the average of the time-averages

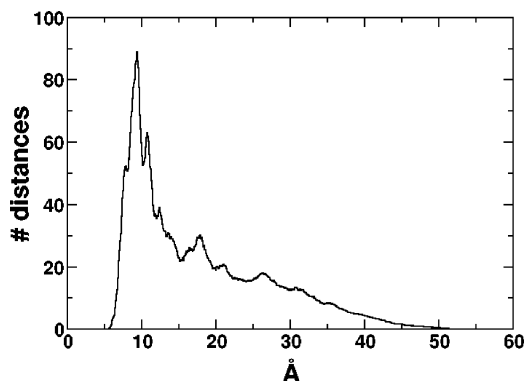


Figure 5. Radial distribution of the distance of the centers of mass of the Rose Bengals. The peak of the dimers ~ 10 Å is a doublet due to the presence of two types of aggregates.

of the interactions for the two dyes are

$$\text{for EY, } \langle V_{\text{guest-host}} \rangle = -13.9; \langle V_{\text{guest-solv}} \rangle = -35.0; \langle V_{\text{guest-guest}} \rangle = -4.37 \text{ kcal mol}^{-1}$$

$$\text{for RB, } \langle V_{\text{guest-host}} \rangle = -12.3; \langle V_{\text{guest-solv}} \rangle = -32.6; \langle V_{\text{guest-guest}} \rangle = -25.3 \text{ kcal mol}^{-1}$$

It appears that the most remarkable difference between the two dyes arises from $\langle V_{\text{guest-guest}} \rangle$, with a factor of 5–6 in favor of Rose Bengal. Even discounting the larger number of Rose Bengals in the simulations, it can be concluded that the origin of the larger cosolvation effect for this dye arises from its tendency to form pairs in CH_2Cl_2 . In practice, POPAM-4D solvates some RB molecules, which subsequently assist the solvation of other molecules giving a true collective cosolvation effect. Interestingly, the radial distribution of the relative distances of the centers of mass of the Rose Bengals, Figure 5, shows that the dimers are of two types. The more abundant type is due to the formation of a hydrogen bond between the carboxylic hydrogen and a carbonyl located between the two Iodine atoms, see Scheme 1. The less abundant dimer is due to π -stack formation, which is hindered by the nonplanar conformation of the molecule.

To support further the results, we also estimated the free energy of cavitation in CH_2Cl_2 ^{17f} which resulted in 22.8 kcal mol⁻¹ for the monomer and 37.8 kcal mol⁻¹ for the dimer. The sum of electrostatic and van der Waals terms gives -69.9 kcal mol⁻¹ for the monomer and -74.6 kcal mol⁻¹ for the dimer. Solubilizing a RB dimer involves a stabilization of $(37.8 - 2 \times 74.6) - 2 \times (22.8 - 69.9) = -17.2$ kcal mol⁻¹.

Finally, we calculated the rates of entrance-exits or better contact formation and breaking, k_{e-e} , of the guest molecules using a time-honored approach.¹³ As a rule, the kinetic constants are related to thermodynamics only when the forward and backward processes are considered at the same time. However, some general information can still be acquired from their analysis. Only molecules that spent between 30 and 70% of their time at POPAM-4D were considered. The results must be considered semiquantitative. For EY, $k_{ee} = 1.5 \times 10^{11} \text{ s}^{-1}$, while for RB, $k_{ee} = 4.4 \times 10^{11} \text{ s}^{-1}$. These high rates are compatible with molecular

motions in solvents and imply that the behavior of the macromolecule with respect to its guest is analogous to that of a real solvent. The larger rate for RB originates from the presence of dye molecules external to the dendrimer, which facilitate the extraction of the guests (see below).

Conclusion

MD calculations find that POPAM-4D is a flexible system where a large number of solvent molecules move nearly freely. Introduction of extra dye molecules in a thought-experiment performed using Molecular Dynamics shows that they tend to leave the macromolecule, first tentatively with several returns and then permanently, until they reach the experimental limit of six for Eosin Y and >20 for Rose Bengal. The presence of the guest molecules compacts the dendrimer structure and dislodges the solvent molecules inside it. The guest molecules can still move inside and around POPAM-4D substantially, but Rose Bengal tends to form pairs. They swarm in and out of the dendrimer very rapidly, with similar rate constants, of the order of what is expected for solvent-solute interactions. It is the tendency of Rose Bengal molecules to undergo physical dimerization, which is due to their higher interaction energy, that ultimately makes POPAM-4D extract more than 20 of them from the aqueous solution, compared to the lower number reported for Eosin Y.

Computational Details

All the calculation were performed with the MM3 force field that has been found to be accurate for organic systems¹⁴ and is parametrized explicitly to describe the π - π stacking interactions that govern a sizable part of the interactions in this system. The parametrization of the S-C and S-N torsional potential energy curves of the sulfonamide of the dansyl units that terminate the branches of POPAM-4D was presented before.⁹ The molecular dynamics calculations were run at constant volume and at a temperature equal to 300 K, using periodic boundary conditions (PBC), with the Tinker program.¹⁵ The temperature was kept constant using the algorithm proposed by Berendsen et al.¹⁶ Periodic boundary conditions were used throughout with a cubic box with a linear dimension of 80.58 Å. The approach based on MM3 implemented in the Tinker program has been rather successful in a variety of applications carried out by our group.¹⁷ As in the previous work, solvent molecules of CH_2Cl_2 were treated explicitly as dipoles.⁹ Optimized geometries of POPAM-4D and 40 Rose Bengal molecules were inserted in an equilibrated box of solvent molecules. All solvent molecules with center of mass less than 4.2 Å away from any atom (hydrogens included) of the dendrimer were removed. The 4.2 Å value was determined by trial and error to replace an equal number of atoms, which makes for the most stable simulation box. This leads to a system of 3880 CH_2Cl_2 molecules plus the guest-host system. Equilibration was performed in the NVT ensemble at 300 K until the potential energy converged. During the simulation a plateau for the total energy is reached (see Figure 1 in the Supporting Information). This condition is not sufficient per se to prove that the guest-host arrangement is stable, but it shows that

the guest dynamics do not involve strong nonequilibrium conditions. We also verified that the rotational autocorrelation function of the molecules of Rose Bengal that form and break contacts with the dendrimer gives a lifetime shorter than the simulation time. The correlation time for these motions is shorter than 200 ps (see Figure 2 in the Supporting Information). This is less than one-third of the time of the simulations and is the time needed by the guests, which wander the most, to explore the different interactions both with the macromolecule and the solvent. A simulation three times as long should acquire sufficient statistics.

To analyze quantitatively the results, one can use two distances. The first is the gyration radius, r_{gyr} ,

$$r_{\text{gyr}} = \left[\frac{\sum_i^{N_d} m_i (r_i - r_{\text{CM},d})^2}{M_d} \right]^{1/2} \quad (1)$$

where m_i and r_i run over all the masses and the positions of the atoms of the dendrimer, $r_{\text{CM},d}$ is the location of the center of mass of the dendrimer, and M_d is the dendrimer mass; the second and more relevant distance is the shortest distance between an eosin atom and a dendrimer atom. Two other useful quantities are the departure from perfect spherical shape, b , and from perfect cylindrical shape, c ,

$$b = I_1^2 - \frac{1}{2}(I_2^2 + I_3^2) \quad (2)$$

$$c = I_2^2 - I_3^2 \quad (3)$$

where the three components of moments of inertia, I , are $I_1 \geq I_2 \geq I_3$; in the ideal shape, both b and c are zero.

Finally, the evaluation of the rates of multiple entrance-exits was calculated using the time correlation model of Allen and Schofield.¹³

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Supporting Information Available: A file with 1) a figure with the energy in time during the simulation; 2) the autocorrelation function of the rotational motions of the RB that move the most during the simulation; and 3) a table with quantitative details of the energies of guest–host, guest–solvent, and guest–guest interactions of 12EY@POPAM-4D and 40RB@POPAM-4D and two animations with EY@POPAM-4D and RB@POPAM-4D where the solvent molecules have been removed. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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