Supplementary Material (ESI) for *PCCP*

Modeling of Hyperbranched Polyesters as Hosts for the Multifunctional Therapeutic Agent Shikonin

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Supplemental Material

Polyester Conformational Relaxation

Correlation functions of the squared fluctuations of the radius of gyration of the polyester molecules in each model were calculated according to the following expression

$$C_{R_g^2}(t) = \frac{\left\langle R_g^2(0) R_g^2(t) \right\rangle - \left\langle R_g^2 \right\rangle^2}{\left\langle R_g^4 \right\rangle - \left\langle R_g^2 \right\rangle^2}$$

The next figure illustrates the so-calculated correlations functions for the examined models.

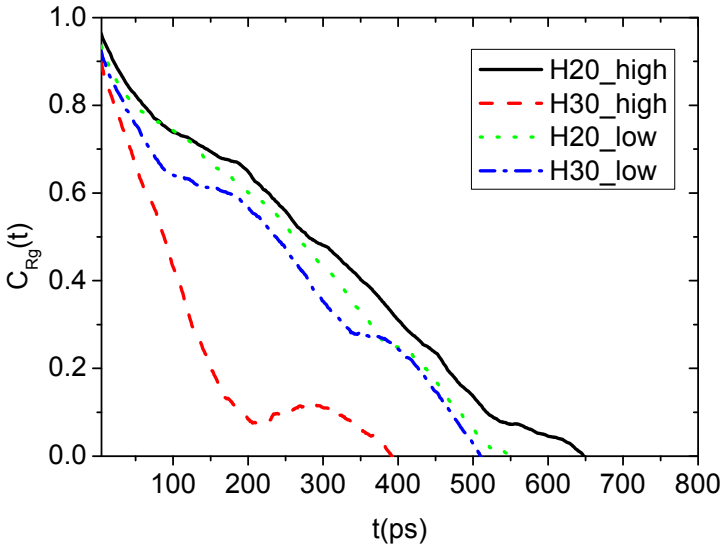

Figure S1: time correlation functions of the squared fluctuations of the radius of gyration of the polyester molecules, indicating the characteristic timescale for conformational relaxation

Evidently, for all systems the correlation functions decay well below the ns timescale. It is worthy noticing that in the H20 "low" system the conformational relaxation takes place at a larger timescale compared to the H20 "high", while the H30 systems decay in rather close timescales. This behavior is consistent with the one observed from the dynamic properties discussed in the text.

Snapshots of the examined systems

The figure below shows snapshots of the examined system (solvent molecules are omitted for clarity. The polyester and shikonin molecules appear in grey and green color respectively.

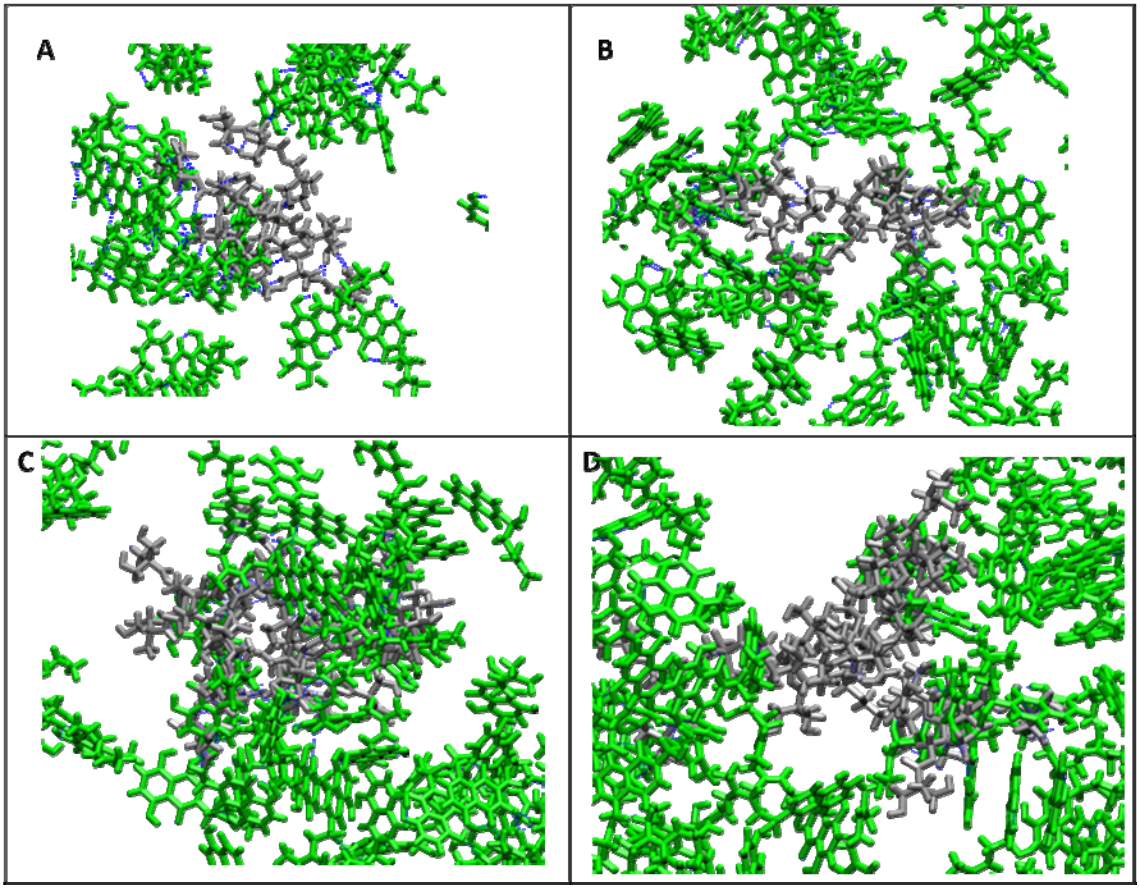

Figure S2: Snapshots of the examined systems: A) H20 "low" B) H20 "high" C) H30 "low" D) H30 "high". Ethanol molecules are omitted for clarity. Shikonin molecules appear in green, polyester molecules in grey, while short dotted lines indicate hydrogen-bonds

In all systems clustering of shikonin molecules is observed, either close to the polyester, or in the solution. Both, intra- and intermolecular hydrogen bonding can be

observed in all systems. The conformations corresponding to "high" systems appear to be somewhat more "open" compared to their respective "low" analogues.

Static structure factor of the center of mass of the drug molecules

The figure below depicts the static structure factor arising from the centers of mass of the drug molecules. The presence of second-order peaks in all systems indicates the existence of partial order in the arrangement of drug molecules at different spatial scales. The second order peaks corresponding to distances of the order of 10-15Å would be consistent with the separation between drug molecules located at diametrically opposite sides of a drug cluster or of the polyester molecule, while the lower-q maxima (corresponding to separations of 20 to 35 Å) could be associated with the average distance between the formed drug clusters

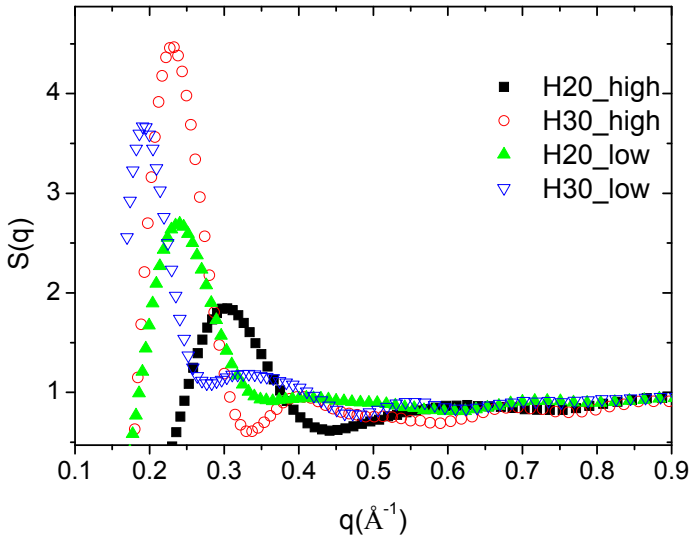

Figure S3: Static structure factor arising from the centers of mass of the drug molecules

Partial charges and atomtypes according the GAFF forcefield (ref 50 of the manuscript) for shikonin

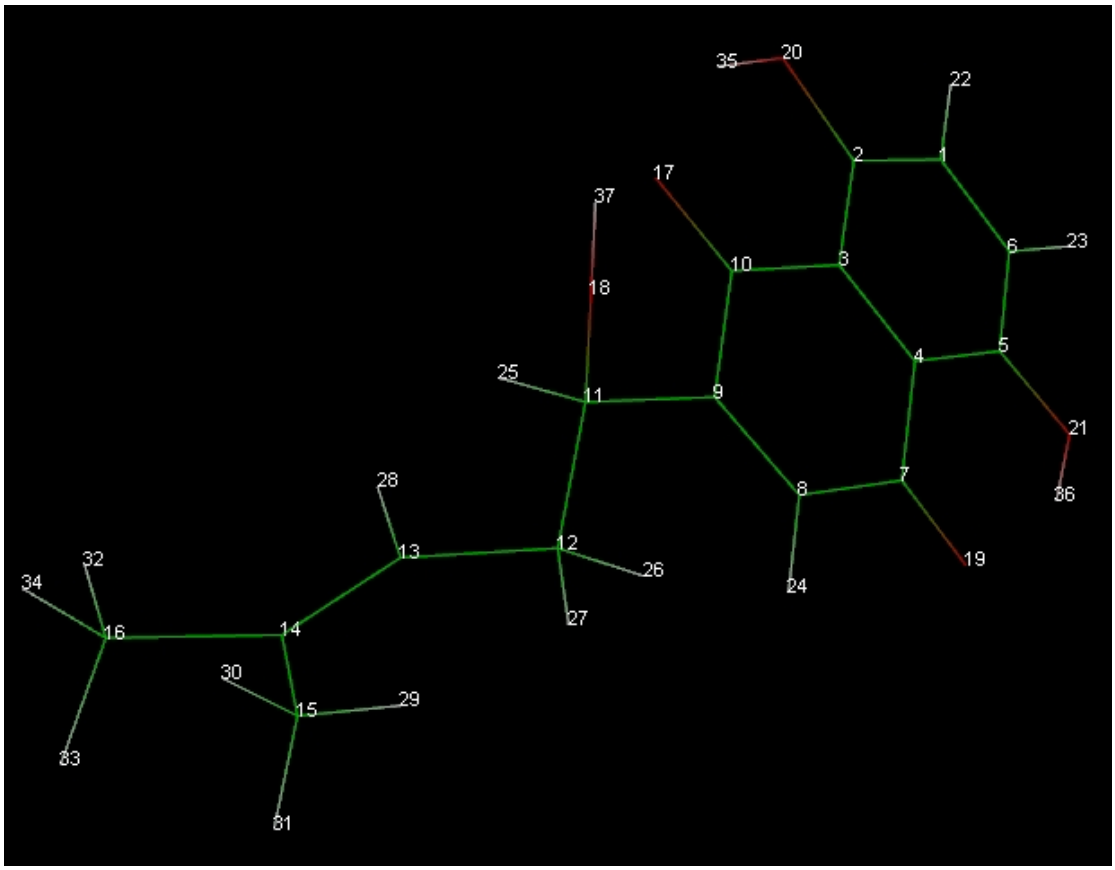

Figure S4: atom indexing for the shikonin molecule.

Table S1: Atomtypes and partial charges of the shikonin molecule according to the GAFF forcefield (ref. 50 of the manuscript). Atom indexing follows that of figure S4.

Number	Atomtype	Partial Charge	Number	Atomtype	Partial Charge
1	CA	-0.029	19	O	-0.287
2	CA	0.084	20	OH	-0.359
3	CA	0.065	21	OH	-0.359
4	CA	0.065	22	HA	0.064
5	CA	0.084	23	HA	0.064
6	CA	-0.029	24	HA	0.066
7	C	0.190	25	H1	0.065
8	CC	-0.005	26	HC	0.034
9	CD	0.032	27	HC	0.034
10	C	0.195	28	HA	0.057
11	C3	0.087	29	HC	0.028
12	C3	-0.004	30	HC	0.028
13	C2	-0.083	31	HC	0.028

14	C2	-0.080	32	HC	0.028
15	C3	-0.0044	33	HC	0.028
16	C3	-0.044	34	HC	0.028
17	O	-0.287	35	HO	0.217
18	OH	-0.388	36	HO	0.217
			37	HO	0.210