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Molecular weight-controlled synthesis of polyamidoamines

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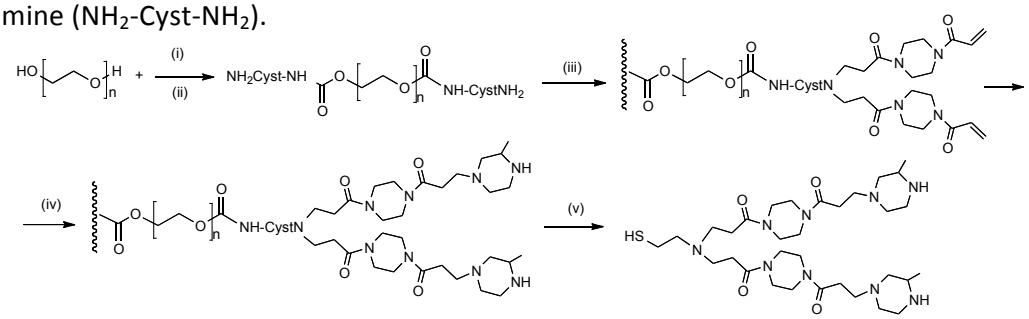
Polyamidoamines (PAAs) are biocompatibile and biodegradable synthetic polymers obtained by Michael-type stepwise polyaddition of *prim*- or *sec*-amines to bisacrylamides. They can be used, for instance, as drug and protein intracellular carriers, transfection promoters, antiviral and antimalarial agents [1,2]. The PAA synthesis is simple and environment friendly, but leads to highly polydisperse products. A process leading to monodisperse PAAs would be much welcome. The first attempts to synthesize a controlled molecular weight PAA by polyaddition of 2-methylpiperazine (2-MeP) with 1,4-bisacryloylpiperazine (BP) failed. Amino-functionalized polystyrene resins were used as solid supports for the controlled synthesis of a typical PAA by polyaddition of 2-MeP with BP. Bisacryloylcystine (BaCy) was covalently attached to the resin by reaction with of its amine groups. 2-MeP was then added, followed by BP. The double 2-MeP/BP addition was repeated three more times performing all steps at rt in water for 24 h. After each step the resin was exhaustively washed with water. Finally, a large excess of mercaptoethanol in water was added to cleave the BaCy disulphide bond and recover the product. However, the oligomer was not obtained, since the steric hindrance and hydrophobicity of the support biased the first addition steps and, possibly, the cleavage reaction. Then, a soluble support (α,ω-bis-imidazolyl polyethyleneglycol *MW* 8000) [3] was used (Scheme 1) and reacted with excess cystamine (NH_2-Cyst-NH_2).



Scheme 1. Controlled synthesis of the BP-2MeP PAA on water-soluble support: (i) carbonyldiimidazole; (ii) excess cystamine dihydrocloride (NH_2-Cyst-NH_2) + triethylamine; (iii) excess BP; (iv) excess 2MeP; (v) excess $HS(CH_2)_2OH$.

After each single step, the product was purified by ultrafiltration. The double-addition step was repeated three times, then N,N-dimethylacrylamide (DMA) was added to end-cap the residual amine terminals. The product was purified by ultrafiltration. The disulphide bond of the cystamine moiety connecting BP-2MeP to PEG was then reductively cleaved with excess 2-mercaptoethanol, the exhausted matrix separated by ultrafiltration through a membrane with cut-off 5000, a further amount of DMA added to the passed-through solution, which was then ultrafiltered through a membrane with cut-off 1000. The expected oligomer was recovered by lyophilizing the retained fraction**.** The NMR spectrum was consistent with the expected structure. MALDI-TOF analysis revealed an average *MW* 1945 (expected 2138) with polydispersity index 1.01, thus demonstrating that the PAA controlled synthesis is feasible.

References

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