Supplementary Information for "An introduction to zwitterionic polymer behavior and applications in solution and at surfaces"

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Supplementary Figures

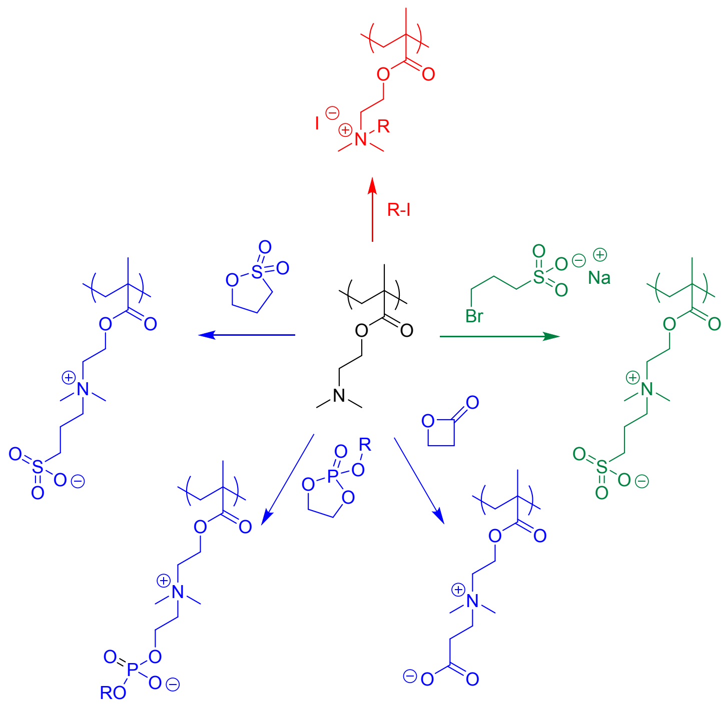

Figure S1. Various post-polymerization modifications of PDMAEMA. S_N2 alkylation with neutral alkyl halides to form a cationic polyelectrolyte (red arrow). S_N2 alkylation with anionic alkyl halides to form betaines, in this case a poly(sulfobetaine) (green arrow). Ring opening of sultones, 2-*oxo*-1,3,2-dioxaphospholanes and strained lactones (blue arrows) to form the corresponding poly(sulfobetaine), poly(phosphobetaine) and poly(carboxybetaine). Note that the 2-*oxo*-1,3,2-dioxaphospholane in question must be first prepared from 2-chloro-2-*oxo*-1,3,2-dioxaphospholane and the corresponding alcohol. For a more detailed discussion of these reactions, including their limitations, the reader is referred to the following texts.[1, 2]

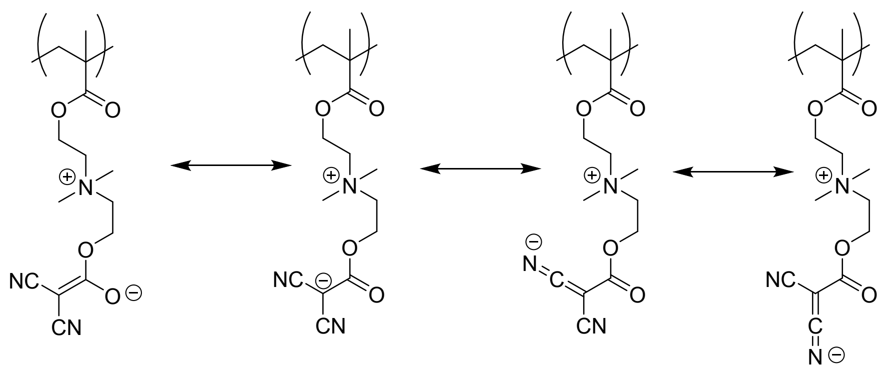

Figure S2. Structure and resonance forms of the poly(ammonio alkoxydicyanoethenolate)s studied by Pujol-Fortin and Galin.[3]

Discussion concerning the immunogenicity of polyzwitterions vs PEG

With the rise of PEGylated therapeutics being used in the clinic, there has been growing concern regarding the immunogenicity of PEG, with PEG antibodies being observed in human patients, leading to reduced activity of the therapeutic and adverse side effects.[4] There is evidence to suggest that polyzwitterions such as polycarboxybetaine (PCBs) lead to an overall reduction in polymer-specific antibodies (anti-PCB), compared with PEG (anti-PEG).[5] However one study by Elsabahy and Wooley *et al*. showed that both PCB and PEG-coated nanoparticles could induce the expression of cytokines *in vitro* and *in vivo*, with PCB being more immunotoxic than PEG.[6] Therefore, whilst polyzwitterions do show some promise as PEG alternatives, further detailed studies, such as those discussed here, are required to fully elucidate their potential application and risk in nanomedicine and biotechnology.

Related Additional Reading

Nomenclature of polyampholytes and zwitterionic polymers:

IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A.Wilkinson. Blackwell Scientific Publications, Oxford, 1997. ISBN 0-9678550-9-8.

Worked example of equation ***(1)*** *at R = 1 and R = 0.5 and when R<<1 and R>>1:*

Polypeptide Amino Acid Composition and Isoelectric Point: 1. A Closed-Form Approximation. C. S. Patrickios, *J. Colloid. Interface Sci.* 1995, **175**, 256.

Recent stimuli-responsive zwitterionic polymer articles

Salt-responsive zwitterionic polymer brushes with anti-polyelectrolyte property. S. Xiao, B. Ren, L. Huang, M. Shen, Y. Zhang, M. Zhong, J. Yang and J. Zheng, *Curr. Opin. Chem. Eng.*, 2018, **19**, 86-93.

Environmentally responsive polyelectrolytes and zwitterionic polymers. M. T. Bernards, in *Switchable and Responsive Surfaces and Materials for Biomedical Applications*, ed. Z. Zhang, Woodhead Publishing, Oxford, 2015, 45-64.

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Temperature-responsive methacrylamide polyampholytes. L. G. Weaver, R. Stockmann, S. H. Thang and A. Postma, *RSC Advances*, 2017, **7**, 31033-31041.

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Non-toxic antifouling strategies. C. M. Magin, S. P. Cooper and A. B. Brennan, *Materials Today*, 2010, **13**, 36-44.

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Synthesis and Properties of Alternating Polypeptoids and Polyampholytes as Protein-Resistant Polymers. Y. Tao, S. Wang, X. Zhang, Z. Wang, Y. Tao and X. Wang, *Biomacromolecules*, 2018, **19**, 936-942.

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Self-Healing Hydrogels. D. L. Taylor and M. in het Panhuis, *Adv. Mater.*, 2016, **28**, 9060-9093.

Reversible interactions in self-healing and shape memory hydrogels. B. Gyarmati, B. Á. Szilágyi and A. Szilágyi, *Eur. Polym. J.*, 2017, **93**, 642-669.

Self-Healable Antifouling Zwitterionic Hydrogel Based on Synergistic Phototriggered Dynamic Disulfide Metathesis Reaction and Ionic Interaction. S. L. Banerjee, K. Bhattacharya, S. Samanta and N. K. Singha, *ACS Appl. Mater. Interfaces*, 2018, **10**, 27391-27406.

Responsive Hydrogels from Associative Block Copolymers: Physical Gelling through Polyion Complexation. C. Papadakis and C. Tsitsilianis, *Gels*, 2017, **3**, 3.

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Clickable-Zwitterionic Copolymer Capped-Quantum Dots for in Vivo Fluorescence Tumor Imaging. L. Trapiella-Alfonso, T. Pons, N. Lequeux, L. Leleu, J. Grimaldi, M. Tasso, E. Oujagir, J. Seguin, F. d'Orlyé, C. Girard, B.-T. Doan and A. Varenne, *ACS Appl. Mater. Interfaces*, 2018, **10**, 17107-17116.

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5. S. Liu and S. Jiang, *Nano Today*, 2016, **11**, 285-291.
6. M. Elsabahy, A. Li, F. Zhang, D. Sultan, Y. Liu and K. L. Wooley, *J. Control. Release*, 2013, **172**, 641-652.