

DMAEMA vs. DMAEA

By: Robert B. Login rloginconsulting.com

In my last pdf [ATRP Quats and Polyquats\(see my web page\)](#) I had proposed the need for DMAEA because it was not a methacrylate. I suggested that as a terminal monomer DMAEMA would not react with a ATRP terminal Br because of steric hindrance but that DMAEA would react to form a terminal quat. So I wondered how each monomer was employed in other capacities. Was there a significant difference between them?

When using these monomers, one must be cognoscente of their reactivity ratios. I believe both have similar reactivity ratios.

“The reactivity of NVP and methacrylates is different, and, therefore, the resulting cross-linked materials were not entirely homogeneous. Most likely, the cross-links do take part in the polymerization reaction much faster than the NVP molecules.”

Bruining, M. J., Blaauwgeers, H. G., Kuijter, R., Pels, E., Nuijts, R. M., & Koole, L. H. (2000). Biodegradable three-dimensional networks of poly (dimethylamino ethyl methacrylate). Synthesis, characterization and in vitro studies of structural degradation and cytotoxicity. *Biomaterials*, 21(6), 595-604.

NVP has a low reactivity ratio compared to methacrylates; therefore these workers switched from NVP to DMAEMA that had a reactivity ratio closer to their acrylate xlinkers.

As an example of this effect, patents to GAF describe the synthesis of copolymers of DMAEMA and NVP. They indicate that both are simply mixed together and polymerized with a free radical initiator in a suitable solvent. What this means is that the substantially faster DMAEMA will incorporate in the polymer before most of the NVP and even some of the NVP will homopolymerize.

Barabas, E. S., & Fein, M. M. (1975). *U.S. Patent No. 3,910,862*. Washington, DC: U.S. Patent and Trademark Office.

DMAEMA has numerous uses and when polymerized or copolymerized and quaternized, it is apparently hydrolysis resistant(is this true over time or temp. etc ?). So there are numerous patents based on its copolymers for various petroleum drilling applications. In reviews of ATRP, DMAEMA is used as a comonomer in various homo and copolymer motifs. DMAEMA has numerous references for numerous applications in a wide variety of copolymers.

Boyer, C., Corrigan, N. A., Jung, K., Nguyen, D., Nguyen, T. K., Adnan, N. N. M., ... & Yeow, J. (2016). Copper-

mediated living radical polymerization (atom transfer radical polymerization and copper (0) mediated polymerization): from fundamentals to bio applications. *Chemical reviews*, 116(4), 1803-1949.

Ribelli, T. G., Lorandi, F., Fantin, M., & Matyjaszewski, K. (2019). Atom transfer radical polymerization: Billion times more active catalysts and new initiation systems. *Macromolecular rapid communications*, 40(1), 1800616.

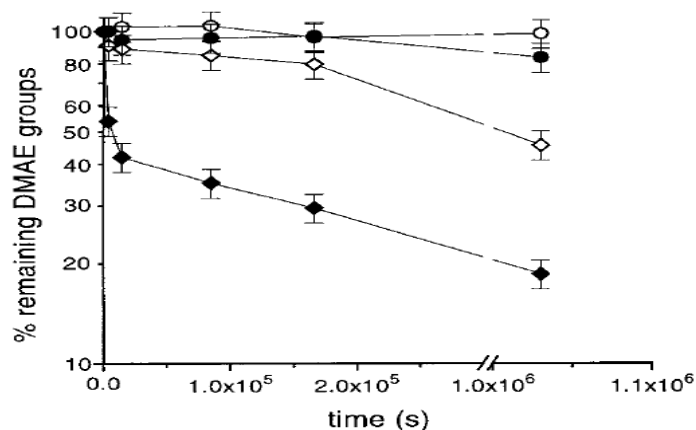


Figure 6. Degradation of p(DMAEMA) (circles) and p(DMAEA) (diamonds) at 80 °C and pH 1 (closed symbols) or pH 7 (open symbols).

Conclusions

This study shows that the ester in DMAEMA is rather unstable toward hydrolysis (at pH 7.4 and 37 °C, $t_{1/2} = 17$ h). However, after polymerization the ester groups in the polymer are quite insensitive toward hydrolysis, even under more extreme condition (80 °C, pH 1 and 7). This might be explained by the low dielectric constant in the microenvironment of the polymer backbone (including the ester groups) as demonstrated by fluorescence and pK_a measurements.

Van de Wetering, P., Zuidam, N. J., Van Steenberg, M. J., Van Der Houwen, O. A. G. J., Underberg, W. J. M., & Hennink, W. E. (1998). A mechanistic study of the hydrolytic stability of poly (2-(dimethylamino) ethyl methacrylate). *Macromolecules*, 31(23), 8063-8068.

Polymeric DMAEA is another story when it comes to resistance to hydrolysis. There are articles that find the hydrolysis to the carboxylic acid as highly desirable.

(12) **United States Patent**
Burke et al.

(10) **Patent No.:** **US 10,407,527 B2**
(45) **Date of Patent:** **Sep. 10, 2019**

(54) **CHARGE-SHIFTING POLYMERS FOR TISSUE COMPATIBLE HYDROGELS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 223 days.

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Related U.S. Application Data

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C08L 33/24 (2006.01)
C08F 220/34 (2006.01)
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C08F 8/12 (2006.01)
C08J 3/075 (2006.01)
C08J 3/12 (2006.01)
C08J 3/24 (2006.01)

(52) **U.S. Cl.**

CPC **C08F 220/60** (2013.01); **C08F 8/12** (2013.01); **C08F 220/34** (2013.01); **C08J 3/075** (2013.01); **C08J 3/126** (2013.01); **C08J 3/245** (2013.01); **C08L 33/14** (2013.01); **C08L 33/24** (2013.01); **C08F 2438/03** (2013.01); **C08J 2333/14** (2013.01); **C08J 2333/26** (2013.01); **C08J 2433/14** (2013.01); **C08J 2433/26** (2013.01)

(58) **Field of Classification Search**

CPC **C08F 220/60**
See application file for complete search history.

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Zhang J.; Lynn, D.M. : “Ultrathin Multilayered Films Assembled from “Charge-Shifting” Cationic Polymers: Extended, Long-Term Release of Plasmid DNA from Surfaces”—Adv. Mater. 2007, 19, pp. 4218-4223.

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Chung et al.: “Tetrakis(hydroxymethyl) Phosphonium Chloride as a Covalent Cross-Linking Agent for Cell Encapsulation within Protein-Based Hydrogels”—Biomacromolecules 2012, 13, pp. 3912-3916.

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Primary Examiner — Michael F Pepitone

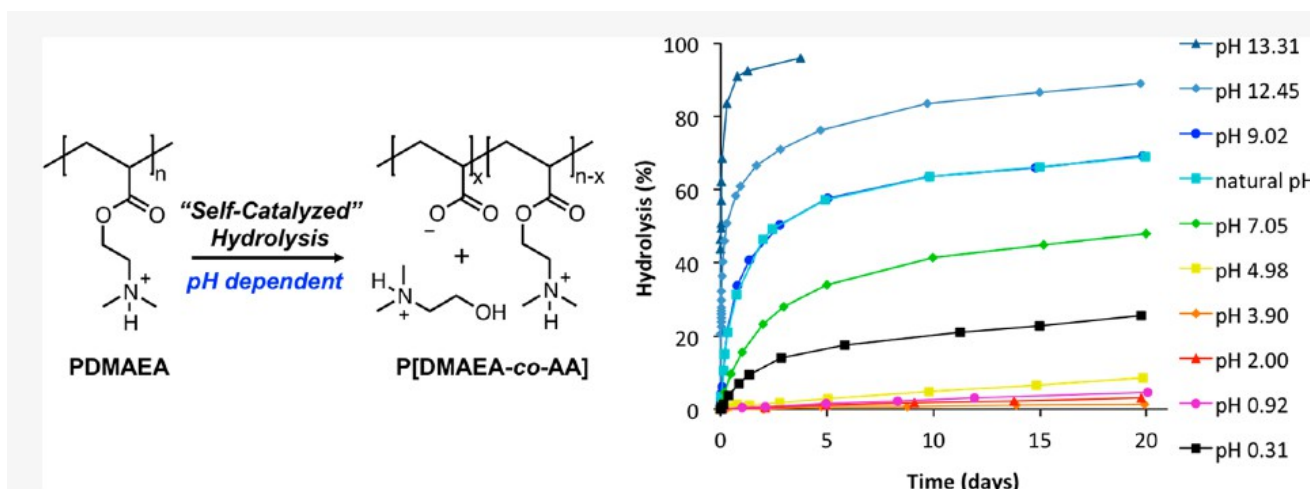
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(57) **ABSTRACT**

A novel charge-shifting copolymer is provided comprising a first charge-shifting monomer that is cationic under physiological conditions and which possesses cationic groups that may be converted into anionic groups under physiological conditions, a second monomer comprising at least one primary amine that is not convertible to an anionic group under physiological conditions, and optionally, one or more monomers which are polar uncharged monomers. A hydrogel system incorporating this copolymer, as well as a capsule system, are also provided.

13 Claims, 14 Drawing Sheets

I put this patent's first because it has a good literature review and is an fine example of this technology.

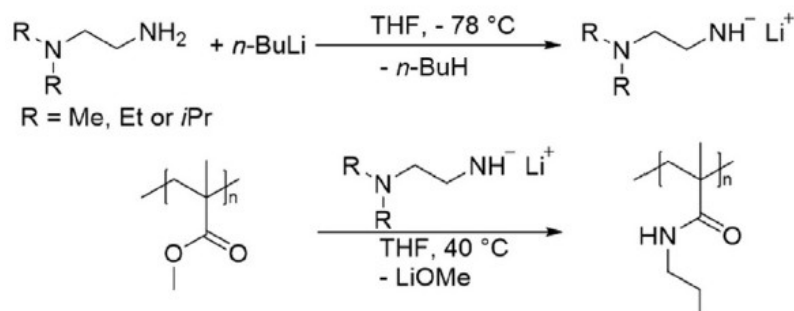


Ros, S., Wang, J., Burke, N. A., & Stöver, H. D. (2020). A Mechanistic Study of the Hydrolysis of Poly [N, N-(dimethylamino) ethyl acrylates] as Charge-Shifting Polycations. *Macromolecules*, 53(9), 3514-3523.

Charge-shifting polycations have emerged as a class of polymers attracting significant interest as transfection agents.^{18–31} These polymers have high cationic charge densities but undergo a charge-shifting process, making the polymer less cationic. The initial high cationic charge density enables efficient binding and protection of anionic nucleic acids from nucleases, forming polyplexes. Following cellular uptake, the polyplexes can dissociate because of the charge shift of the polycation, releasing the genetic payload for intracellular delivery. Both charge-shifting and reducible

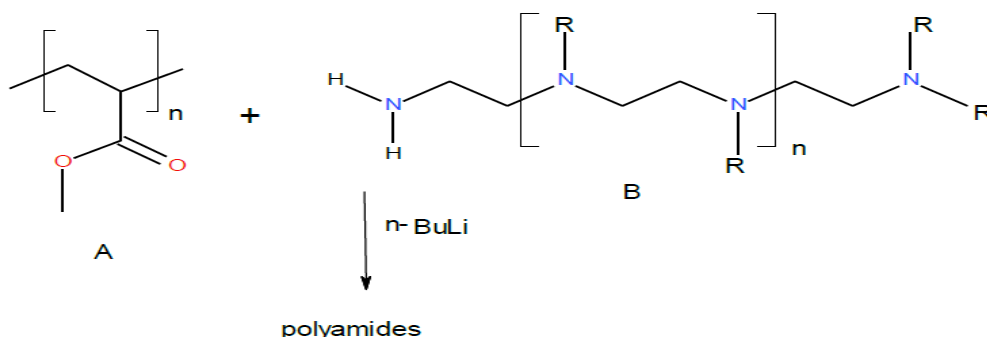
Ros, S., Freitag, J. S., Smith, D. M., & Stöver, H. D. (2020). Charge-Shifting Polycations Based on N, N-(dimethylamino) ethyl Acrylate for Improving Cytocompatibility During DNA Delivery. *ACS omega*, 5(16), 9114-9122.

The obvious question, are amide versions of these monomers hydrolytically stable. I would think they are the most hydrolytically stable as a monomer and in polymers.

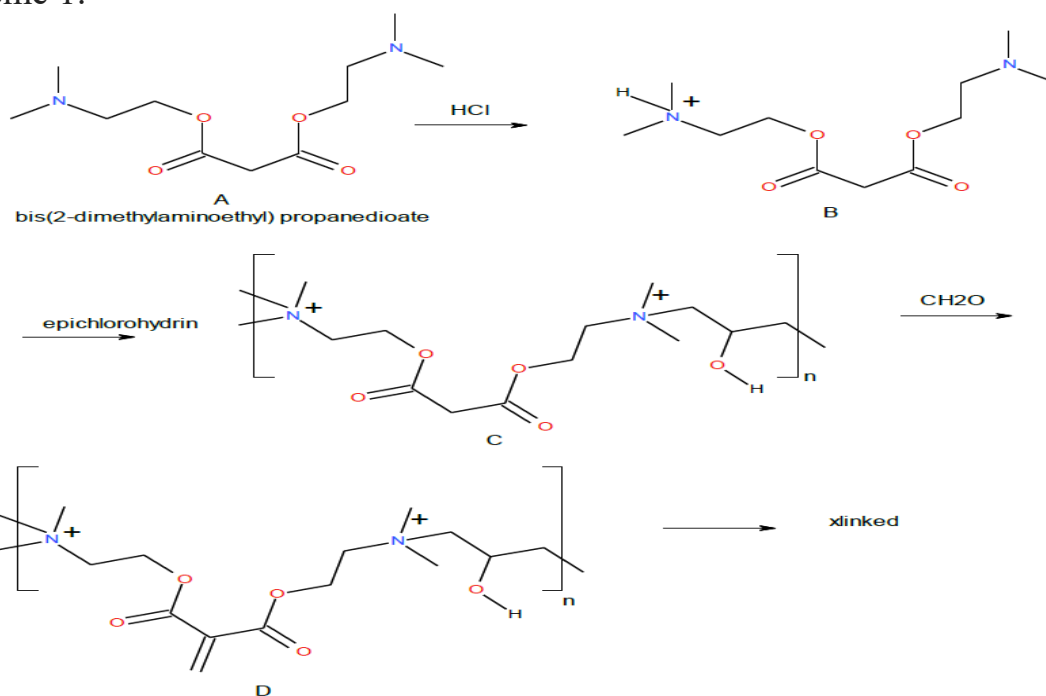


Hils, C., Fuchs, E., Eger, F., Schöbel, J., & Schmalz, H. (2020). Converting poly (methyl methacrylate) into a triple-responsive polymer. *Chemistry—A European Journal*.

I didn't know that primary amines will readily react with polyMMA to form amides but this makes sense if the amine is anionic. This is very clever and avoids other problems with preparing the amide monomer. Why not expand this reaction as follows:

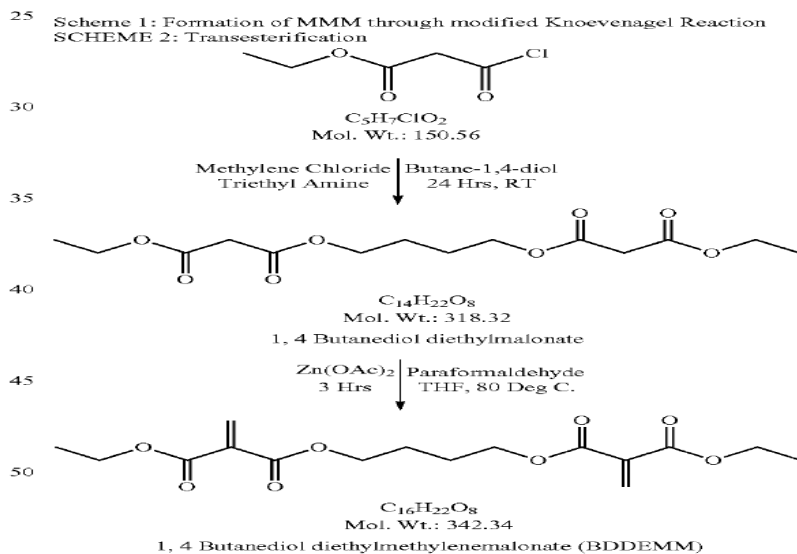


Scheme 1:



Scheme 2: An idea for a cross-linked quat polymer that will readily hydrolyse releasing its DNA load. I show the quat but the tertiary amine version as "D" a DMAEA analog would also be an interesting monomer.

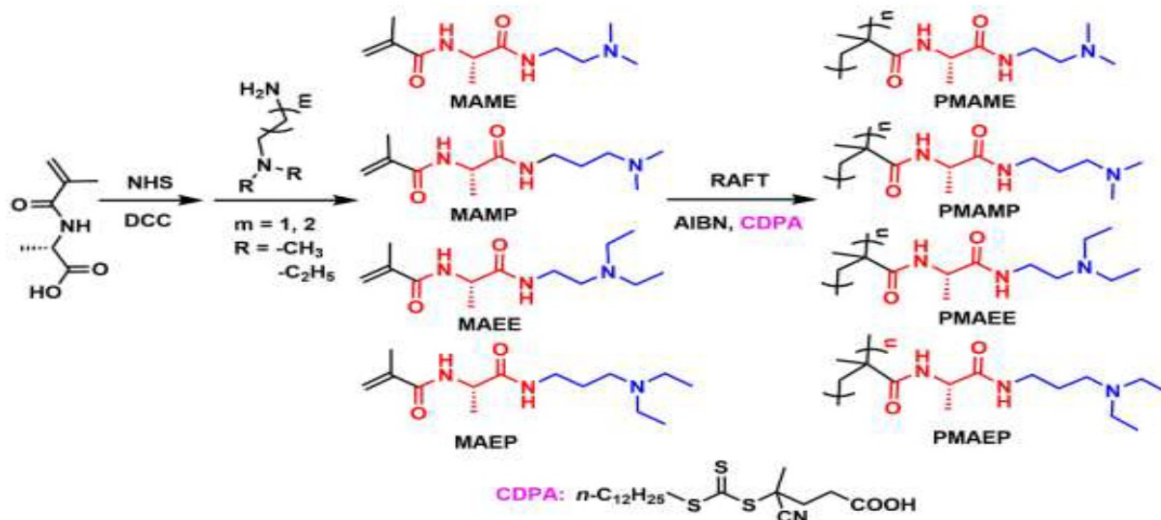
Login, R. B. (1989). *U.S. Patent No. 4,812,263*. Washington, DC: U.S. Patent and Trademark Office.



Malofsky, B. M., Malofsky, A. G., Dey, T., Ellison, M. M., & Hines, L. (2020). *U.S. Patent No. 10,604,601*. Washington, DC: U.S. Patent and Trademark Office.

These methylene malonates can be polymerized by both anionic and FR mechanisms.

Stimuli Responsive Polymers:



Scheme 1. Synthesis of tertiary amine-modified *L*-alanine-based methacrylamides and corresponding polymethacrylamide homopolymers prepared by reversible addition-fragmentation chain transfer polymerization.

The idea here is that polymers with LCST and sensitivity to CO₂ can be designed.

Luo, C., Fu, W., Li, Z., & Zhao, B. (2016). Multi-responsive polymethacrylamide homopolymers derived from tertiary amine-modified *L*-alanine. *Polymer*, 101, 319-327.

Abstract:

CO₂-Responsive polymer materials have received enormous attention in recent years, since CO₂ as a new trigger has many advantages such as abundant availability, low cost, energy-saving, environment-friendly, non-toxic, good reversibility as well as great biocompatibility. In this review, we first discuss the virtues of

CO₂-responsiveness by comparing with traditional stimuli-sensitive materials that respond to pH, light, or redox stimuli. Then, the chemical fundamentals of CO₂-responsive polymer materials are revealed including recently discovered “unexpected” CO₂-sensitive features. Recent progress of CO₂-responsive polymer materials is highlighted followed by various CO₂-responsive “smart” polymer systems. Finally, challenges and outlooks in this area are discussed

Liu, H., Lin, S., Feng, Y., & Theato, P. (2017). CO₂-Responsive polymer materials. *Polymer Chemistry*, 8(1), 12-23.

Searching this topic on Google scholar resulted in 581 hits just from 2017-2021!

Thank you for reading these proposals.

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