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Letter to the Editor

Dear Editor,

We would like to bring to your attention one matter of great concern to our group, namely similarities found between our work published in Biomacromolecules (doi:10.1021/bm800158c) and one of the papers recently published in Carbohydrate Polymers (CP). The article in question by Yaping Li and coworkers is entitled "One-step synthesis of amino-reserved chitosan-*graft*-polycaprolactone as a promising substance of biomaterial" (doi:10.1016/j.carbpol.2009.12.013).

To the informed reader, the Li et al. article closely resembles our Biomacromolecules paper published in 2008. Our experiments were reproduced in great detail and the only significant difference is the source of lactone used: ε-caprolactone and L-lactide, in Li's work and in our contribution, respectively. It is worth noting that the polymerization chemistry of these two lactones is very similar. Our synthetic procedure is literally identical to the one proposed by these authors, and the same can be said with regard to most of Li and co-workers' choices of characterization methods.

While we are very appreciative of the fact that our published work inspired Li and collaborators to conduct similar research, we feel that proper credit to our publication is not given by these authors. In our view their claim that a new synthetic method to graft chitosan with ε-caprolactone has been advanced by their team is a misrepresentation of the facts. Our work was published more than a year earlier (Ref. Skotak, Leonov, Larsen, Noriega, and Subramanian, 2008 in Li's paper).

One major challenge we faced in our research was to develop an efficient method to isolate the reaction product. Our procedure was copied in Li's paper, and these authors venture a claim in their paper's abstract that reads: "One-step approach was developed to synthesize amino-reserved chitosan-graft-polycaprolactone (CS-g-PCL) by grafting e-CL oligomers onto the hydroxyl groups of CS via ring-opening polymerization by using methanesulfonic acid as solvent and catalyst." This situation is further aggravated by another, more disturbing set of facts: Paragraph 3.1 describing the synthesis of CHIT-g-CL polymers is composed of rephrased excerpts from our manuscript. On page 501, paragraph 3.1 one reads: "The buffering properties of the monobasic phosphate ion avoid rapid and uncontrolled pH changes during the quenching of the reaction". This sentence is exactly the same as the one found in our paper on page 1903 of the experimental section. The probability for an exact replica of a 20-word string from our article to appear in Li et al.'s paper through no fault on their part is essentially zero.

After a detailed inspection of their paper we noticed many inconsistent conclusions that the reported data simply does not support. We list these in Appendix A, and offer our specific comments. The authors did not make sufficient effort concerning the additional experiments necessary to elucidate the chemistry of caprolactone polymerization in methanseulfonic acid and the resulting polymer structures. Instead, they propose only superficial explanations for their results from the characterization methods they adopted.

We would therefore like to request that you ask Li and collaborators to correct their various mistakes, possibly asking them to furnish additional experimental data that would address some of our points below, and to give proper credit were credit is rightfully due. Each member of our team is an ardent believer of second chances. We certainly do not question the intellectual prowess of Li and coworkers, and wholeheartedly wish that they advance and refine our original work to the next level. We are just a group of concerned scientists that feel that certain principles must stand the test of time, and are not to be compromised in this day and age of rapid publication and high-volume information access.

Appendix A.

We have noticed numerous basic mistakes in Li et al.'s data interpretation. The most salient ones are listed below:

1. In the ^{1}H NMR spectrum presented in Fig. 2 for the CS-g-PCL(1:12) sample, the proton peaks of glucosamine monomeric unit marked as 3,4,5,6,6′ have higher intensities than those of the methylene protons of PCL sidechains. This provides direct evidence for the occurrence of a very low degree of polymerization. This in turn, would be in contradiction with the following data and observations made by the authors:
   a. Reaction yields in Table 1: These results suggest high degrees of polymerization: at a yield of 80% for sample CS-g-PCL(1:12), a side-chain length of average 9.6 caprolactone monomers would be expected, instead of the 2.5 reported in the paper.
   b. It is a well-known fact that caprolactone (CL) has a more favorable thermodynamics for polymerization than L-lactide (LLA), and methanesulfonic acid is a superior catalyst for this reaction.
   c. FTIR data reported by Li and co-workers (see criticism 5 below): No signals from chitosan can be detected with this characterization method, which is rather disconcerting.
   d. Their GPC data: Taking into consideration 1.c, and that some level of degradation of chitosan will inevitably take place in a strongly acidic medium (similar to that observed in our experiments with LLA grafting of chitosan reported in Biomacromolecules), their resulting polymers must be composed predominantly of PCL.
2. There is no assignment for the ε′ methylene protons of the terminal CL unit (adjacent to the terminal hydroxyl group), i.e. the signal at 3.40 ppm is incorrectly attributed to the glucosamine ring proton. The ratio of integrals of terminal (ε′) to internal (ε) methylene protons should be used to calculate an average chain length for any oligomeric PCL dangling group. Likewise,

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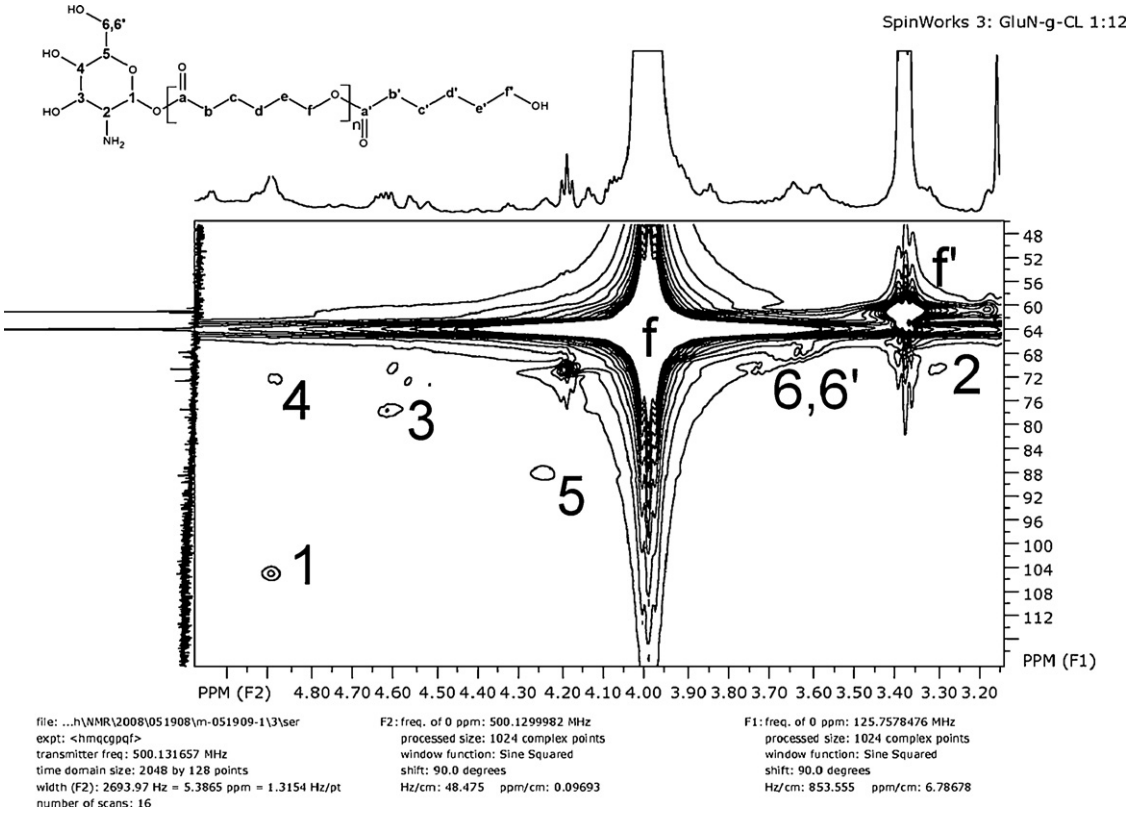
the ratio of integrals of signals of terminal PCL methylene (ε') to glucosamine ring protons should be used to estimate the average number of PCL chains per chitosan monomer unit. Instead, a parameter labeled as CLn of mysterious origin is used Table 1.

3. The authors do not present any credible statement as to how peak assignments were carried out. There are no 2D NMR spectra reported, a technique that is typically used for that purpose. This leads to erroneous assignments of absorption peaks in glucosamine. Four of these bands are located in the 4.20–5.00 ppm region for lactone-substituted aminosugars, due to similar chemical environments (ester groups), and regardless of lactone used. However, due to the inherent CL-to-GluN proton ratio the signals of the sugar ring are very weak and are located at different discrete chemical shifts, contrary to assumptions of Li et al. For the past three years, we tested a series of these polymers based on glucosmine and N-acetylglucosamine used as initiators for caprolactone polymerization prepared at different reaction conditions. Sugar ring protons are consistently present at the chemical shifts described above. Below for example, we present the HSQC NMR spectrum of one of our glucosamine-caprolactone samples labeled as GluN-CL 1:12, and prepared under the same conditions (4 h at 40 °C).



4. Experiments carried out in our laboratory indicate that the strong peak at 3.10 ppm (ascribed incorrectly as proton 2′ of glucosamine by Y. Li and others) is the signal from the methyl group of residual methanesufonic acid attached at the end of the PCL chain (these results were confirmed by elemental analysis, clearly indicating presence up to 1% of sulfur atoms). Failure to interpret their data properly leads to lack of conclusions in their paper on the issue of cytotoxicity of CS-g-PCL polymers. Considering the low degradability of PCL, this can be only attributed to rapid hydrolysis of mesylate esters, and a concomitant release of methanesulfonic acid. A decrease in pH due to L-lactic acid release was a major cause of cytotoxicity for our CHIT-g-LLA materials with short oligomeric poly-L-lactide chains. Similar results would be expected for CHIT-g-CL. However, the cytotoxicity data presented by Li et al. indicates that purification of CHIT-g-CL via dialysis is an ineffective approach. These materials are insoluble in water, and mesylate esters canot be cleaved efficiently under these conditions.

5. After detailed inspection of Fig. 3, we can safely conclude that the FTIR spectrum of the CS-g-PCL(1:12) sample is interpreted incorrectly. This represents, in our professional opinion, an attempt to manipulate experimental data. The bands attributed to chitosan, are clearly less intense bands of oligomeric polycaprolactone chains. It is obvious that the two bands in spectrum (c) marked as 1664 and 1616 cm^{-1} and attributed to amide I and amino groups, respectively, are in fact bands of PCL, not chitosan as suggested by authors. These bands overlap with the respective bands of pure PCL presented in spectrum b (as demonstrated in the figure below). In our opinion, it is hard to find reasonable justification as to why these bands were marked as 1616 and 1664 cm^{-1} in spectrum c. This, so it seems, was done regardless of their true location to simply justify the incorrect chemistry model assumed. Please, make special note that the band marked as 1616 cm^{-1} is in fact located at 1664 cm^{-1}, and band marked as 1664 cm^{-1} is also shifted by roughly 50 cm^{-1} towards higher wavenumbers. The figure below was reproduced without any modifications from guidelines in the manuscript by Li and coworkers, and vertical lines were drawn to illustrate the errors described above. Clearly, the two bands that are characteristic of chitosan are not present in spectrum c but were nevertheless marked as such, regardless of their true origin.

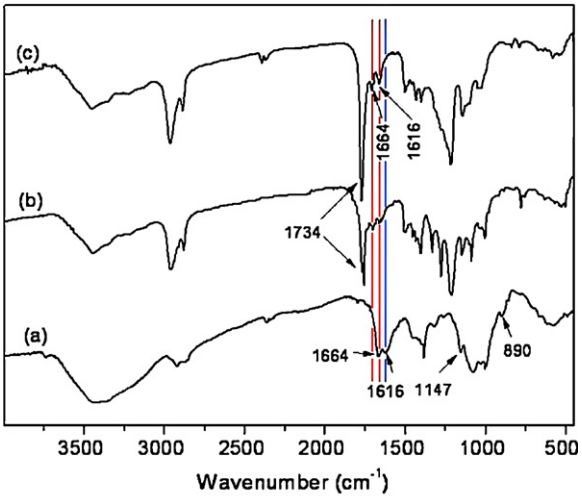


Fig. 3. FT-IR spectra of (a) CS; (b) PCL and (c) CS-g-PCL(1:12).

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