



PennState

Department of Chemistry
Department of Biochemistry &
Molecular Biology
Eberly College of Science

The Pennsylvania State University
242 Chemistry Building
University Park, PA 16802-6300

Philip C. Bevilacqua

Voice: (814) 863-3812
Lab: (814) 863-1962
Fax: (814) 865-2927
e-mail: pcb5@psu.edu
sites.psu.edu/bevilacqua

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JACS Cover Letter Guidelines -

A cover letter must accompany every manuscript submission. During the submission process, you may type it or paste it into the submission system, or you may attach it as a file.

The letter must provide the corresponding author's name, postal and e-mail addresses, and telephone and fax numbers. All Editorial correspondence concerning receipt, status, review, revision, and publication of a manuscript will be sent only to one person who has been designated as the corresponding author during the evaluation period. The corresponding author is responsible for communicating the manuscript status to all coauthors of the paper and for obtaining the coauthors' assent to any substantial changes of content or interpretation made during revision. The cover letter may suggest the name of an appropriate *JACS* Associate Editor. However, manuscript assignment to an Associate Editor is ultimately at the discretion of the Editor. Authors must suggest a minimum of **six to eight** persons competent to review their manuscript. The selection of appropriate reviewers is the prerogative of the Associate Editor handling the manuscript.

The cover letter should provide explicit assurance that the manuscript is not under consideration for publication and has not been published elsewhere. Please note any use of a preprint server in the cover letter and include a link to the preprint, and as appropriate, state how the manuscript has been adjusted/updated between deposition and submission.

To Whom it may concern,

Here we are submitting our contribution “*The Metabolome Weakens RNA Helix Stability and Increases RNA Chemical Stability*” as an original research paper to “*JACS*.” The development of experimental techniques that study RNA in the cell has demonstrated a gap between RNA folding and function *in vivo* and the thermodynamic and mechanistic insight provided by simple systems *in vitro*. Thus, *in-vivo*-like systems that simulate elements of the complex cellular environment provide valuable understanding *in vitro*. Currently, the development of *in-vivo*-like conditions to study RNA has focused on highly simplified systems, usually non-biological crowders, such as polyethylene glycol, or a couple of biologically relevant small molecules. Our manuscript describes development of Eco80, an artificial cytoplasm that contains 80% of *E. coli* metabolites, as an *in vivo*-like system for studying RNA *in vitro*. We demonstrate that Eco80 metabolites buffer the free Mg^{2+} concentration, destabilize RNA helices, protect RNA from degradation, and support RNA catalysis. We believe that this study provides a new approach to simulating the cellular environment *in vitro* by providing a complex but manageable environment for studying RNA, making it one of the most impactful studies to come out of our lab recently. Eco80 is likely the most biologically relevant artificial cytoplasm currently in development. Moreover, Eco80 is an environment for characterization of a wide range of systems, including RNA, proteins, and membranes. Thus, we expect this work to have broad appeal, and it is thus appropriate for *JACS*.

Commented [SJP1]: I believe that you told me to say this

We recommend Mathew Disney as an associate editor and Gary Pielak, Danny Incarnato, Martin Gruebele, Dan Herschlag, Jean-Denis Beaudoin, and Silvie Rouskin, as reviewers.

Commented [SJP2]: We discussed Pielak, Gruebele, and Herschlag. The other reviewers were suggested based on their positive engagement with our Biochemistry perspective on twitter

This manuscript is not under consideration for publication and has not been published elsewhere.

Thank you very much for handling our manuscript.

Yours Sincerely,



Philip C. Bevilacqua
Distinguished Professor of Chemistry and of Biochemistry & Molecular Biology