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EDITORIAL

Editorial of the "ionic liquids and biomolecules" special issue

Antonio Benedetto[1,2,3,4] · Hans-Joachim Galla[5]

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This special issue originates from the success of the session "Ionic liquids meet biomolecules" at the 19th international IUPAB and 11th EBSA congress held in Edinburgh in July 2017, where the speakers presented and discussed the vast and diverse aspects of ionic liquid–biosystems interactions (Benedetto and Galla 2017). The *echo* registered in our communities in the weeks around and after the meeting was indeed the reason behind this special issue entirely dedicated to the topic of "Ionic liquids and biomolecules."

In the past three decades, a new family of ionic systems, liquid around room temperature and with low-vapor pressure and other peculiar properties, has polarized the attention of an increasing number of research groups worldwide because of high tunability and "green" character. These ionic compounds are known as (room-temperature) ionic liquids (ILs) and consist of an organic cation and either an organic or inorganic anion (Welton 1999). Even though their thermal and chemical stability gave them the sexy label of "green chemicals" (Earle and Seddon 2000), several biochemical studies have shown that ionic liquids can be toxic to organisms (Bernot et al. 2005; Pretti et al. 2006; Kulacki and Lamberti 2007; Ranke et al. 2006, 2007). The initial alert generated by the toxic character of a few ionic liquids has changed, in turn, into a positive feeling for new opportunities of their use in basic research and applications; this is because *toxicity is also a measure of their affinity for biomolecules* (Benedetto and Ballone 2018). Several chemical–physical studies have been carried out especially in the last decade, with the aim to understand the microscopic mechanism behind the ionic liquid–biomolecule interaction. A vast and diverse spectrum of biological systems and ionic liquids has been considered, and it has been shown, for example, that selected ionic liquids are able to (1) diffuse into biomembranes and eventually disrupt them at high dose; (2) stabilize proteins and enzymes and their biochemical function; (3) either support or prevent the aggregation of proteins in amyloids; (4) extract, purify, and even preserve DNA; (5) dissolve polysaccharides and cellulose; and (6) kill bacteria and cancer cells while leaving eukaryotic healthy cells almost unaffected. For a recent overview of the subject, we refer the interested reader to two reviews on this subject published recently by Benedetto and Ballone (2016a, b).

As a result, the detailed knowledge of how ionic liquids interact with biomolecules and biosystems will lead to *ad hoc* tuning to target specific cellular components (Fig. 1) and may open the way for an *Ionic Liquids Era* in bio-nano-technologies.

The aim of this special issue on "Ionic liquids and biomolecules" is to present an up-to-date and comprehensive overview of this emerging and intriguing subject of research which holds the promise of breakthrough applications in several areas such as biomedicine, pharmacology, diagnostics and therapeutics, material science, food science, and, more in general, bionanotechnology.

The special issue starts with a historical overview on ionic liquids authored by Tom Welton. His historical journey starts in 1914 with the discovery of the first ionic liquid by Paul Walden (1914); it continues by highlighting several important events happened during the years and ends with the consideration that nowadays, this field is quite vast and is splitting into different and specific areas, mainly related to applications. Actually, "Ionic liquids and biomolecules" is, in our opinion, one of those new areas enriched of excitement and holding the potential for great discoveries.

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✉ Antonio Benedetto
antonio.benedetto@ucd.ie

1 School of Physics, University College Dublin, Dublin 4, Ireland

2 Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland

3 School of Chemistry, University College Dublin, Dublin 4, Ireland

4 Laboratory for Neutron Scattering, Paul Scherrer Institut, Villigen, Switzerland

5 Institute of Biochemistry, University of Münster, Wilhelm-Klemm-Str. 2, 48149 Münster, Germany

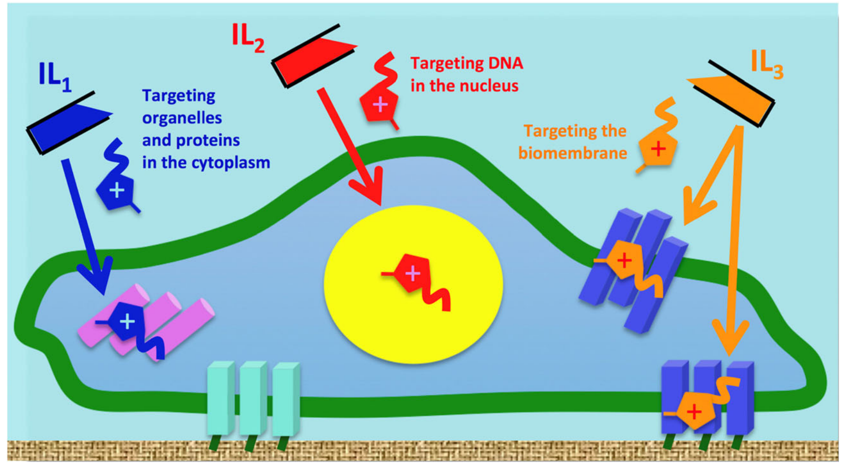

Fig. 1 *Living cell under attack by ionic liquids* (*ILs*). Ionic liquids can be synthesized to target specific biomolecules as (i) lipids and proteins of the cell biomembranes, (ii) proteins and organelles in the cytoplasm, and (iii) DNA in the nucleus. A deep knowledge of IL–biomolecule interactions can then lead to unprecedented applications in bionanotechnology

The bulk of this special issue is organized in three distinct sections focused, respectively, on biomembranes, proteins and nucleic acids, and applications.

The first section starts with the review by Ghosh and co-workers dedicated to the interaction between ionic liquids and phospholipid monolayers, followed by two reviews focused on phospholipid bilayers. The first by Sharma and Mukhopadhyay shows how the microscopic structural and dynamic properties can be explored with neutron and X-ray scattering. The second review by Drücker and co-workers focuses on a new type of *lipid-mimic* imidazolium-based ionic liquids having two hydrocarbon tails rather than one as in the most common versions. Together with the earlier review by Benedetto (2017), these two reviews can properly introduce the reader to this fascinating subject. Then, in a short contribution, Rakers and Glorius present a *tutorial* on the synthesis of this two-tail lipid-mimic imidazolium-based ionic liquids. This first section ends with the letter by Benedetto and co-workers on the effects of ionic liquids on the mechanoelasticity of model biomembranes that shows the way for the next potential applications in this area.

The second section starts with the review by Bhattacharyya and co-workers focused on the microscopic aspects of the interactions between ionic liquids and proteins, and nicely highlights how the combined use of experimental techniques together with computer simulation approaches is a key ingredient for a more complete characterization of the interactions. The contribution by Sajeevan and Roy focuses on a very specific case study, i.e., how ionic liquids influence the disulfide bond isoform equilibrium in a model conotoxin. The section then moves back to more general point of view with the next four reviews. In the first, Reslan and Kayser present a general overview of the subject, pointing to the potential impact for the formulations of stable biopharmaceuticals, something also highlighted in the very informative review by Ananikov and co-workers earlier last year (Egorova et al. 2017). Saha and Mukherjee introduce the major role played by water. They highlight the interactions in this ternary systems, i.e., biomolecules, ionic liquids, and water, that make the balance between the different forces very delicate and show how drastic changes can be induced by just small variations in the system composition. Since, at least for the moment, it is almost impossible to determine all the ionic liquids—proteins and ionic liquids—amino acids combinations experimentally, an important role in this area of research is played by *predictions*. Either theory-based or computer-based approaches are well suited to elucidate the effect of a specific ionic liquid on a specific biosystem. This is the subject of the two reviews that follow in this section. Oprzeska-Zingrebe and Smiatek present, based on statistical thermodynamics theories, an efficient framework able to classify the structure modification effect of ionic liquids on biomolecules, highlighting both the enthalpic and entropic origin of such modifications. Then, Zeindlhofer and Schröder report on current computational approaches to study the interaction between ionic liquids and biomolecules, focusing also on small molecule drugs. However, what about solvated proteins in a mixture of two or more ionic liquids? In their exciting review, Kumar and Venkatesu drive the reader to the innovative aspects of protein stability in ionic liquid mixtures. This section finally ends with a short review by Pillai and Benedetto on the diverse effects of ionic liquids on the amyloidogenesis of proteins, followed by a more extensive but focused review by Takekiyo and Yoshimura devoted to their ability in suppressing the amyloidogenesis and in dissolving mature fibrils.

The third and last section contains a collection of eight representative contributions dedicated to applications. The first two reviews focus on "just" ionic liquids. Sarkar and co-workers introduce the reader to the ability of ionic liquids to form aggregates by self-assembly, something that, for example, ionic liquids share with lipids. This review perfectly combines with the *lipid-mimic* ionic liquids introduced earlier by Drücker and co-workers in the section dedicated to biomembranes. In the second review, Gontrani focuses on amino acid ionic liquids, whose nature makes them intrinsically biocompatible. A few applications of this new family of bioionic liquids are presented. Two reviews on the use of ionic liquids in biocatalysis follow. The one by Egorova and Ananikov mainly focuses on whole-cell biocatalysis, and how the toxicity of water solutions of ionic liquids can be used to develop efficient applications in practical organic transformations. Kragl and co-workers present recent developments in the field of multiphasic ionic liquid-based reaction concepts, highlighting the bright future of such approaches at both, laboratory and industrial scales. Then, in a short review, Singh shows the ability of ionic liquids to inhibit and denature cellulases giving links to lignocellulosic industry employing ionic liquids for bioconversion. A specific application for bioextraction is presented by Freire and co-workers. They show how aqueous solutions of surface-active ionic liquids can be effectively used for the extraction and recovery of cynaropicrin from the leaves of *Cynara cardunculus* L., concluding that they display a better performance compared with a wide range of conventional surfactants and molecular organic solvents. Finally, a letter and a review close this last section and, in turn, this special issue. In the letter by Tsuda et al., a new protocol to image with transmission electron microscopy biosamples treated with ionic liquids is introduced, and its advantage in comparison to standard protocol highlighted. In the review by Tateishi-Karimata and Sugimoto, biological and nanotechnological applications based on the interaction between ionic liquids and nucleic acids are presented. They also highlight the ability of ionic liquids, in particular magnetic ionic liquids, to extract and purify nucleic acids. Actually, in our opinion, magnetic ionic liquids give an *extra dimension* to the already quite rich panorama of ionic liquids in biophysics, something that can led to a specific and new area of intense research (Benedetto and Ballone 2018).

In summary, this special issue comprises a total of 23 contributions in the emerging and broad area of ionic liquids and biomolecules, authored by colleagues spread all around the globe, i.e., Australia, Europe, India, Japan, Russia, and the USA. The bulk of these contributions is represented by review papers, but few selected original research contributions have been also included.

In concluding this Editorial, we would like to make the following remarks about the future. Screening the effects of this vast class of organic and ionic compounds on biomolecules and biosystems is certainly a major step the scientific community needs to address to boost research and application in this exciting field of study. Computational methods, as also reported in this special issue, have been proposed that overcome the limits of experimental screening; however, we believe that automatic and semi-automatic experimental screening approaches need to be developed in the near future. This should provide a reasonable number of cases to be investigated in depth with standard biochemical and physicochemical methods, focusing, for example, on the microscopic characterization of the relevant interactions.

We are convinced that this special issue will inspire a series of new investigations and discoveries in this emerging and exciting field of research. We hope also that this special issue stimulates the gathering of the researchers of this area, and the creation, or at least the feeling, of a dedicated and strong and diverse research community of "Ionic liquids and Biomolecules."

During the writing of this special issue, Ken Seddon passed away. He was indeed one of the major representatives of the ionic liquid community. An obituary written by his colleague and friend Tom Welton immediately follows Welton's historical overview.

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