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LETTER TO THE EDITOR

Ionic liquids in protein amyloidogenesis: a brief screenshot of the state-of-the-art

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Abstract

Ionic liquids (ILs) are a vast class of organic non-aqueous electrolytes whose interaction with biomolecules is receiving great attention for potential applications in bio-nano-technology. Recently, it has been shown that ILs can affect protein amyloidogenesis. Whereas some ILs favour the aggregation of proteins into amyloids, others inhibit their formation. Moreover, ILs can dissolve mature fibrils and restore the protein biochemical function. In this letter, we present a brief state-of-the-art summary of this emerging field that holds the promise of important developments both in basic science and in applications from bio-medicine to material science, and bio-nano-technology. The huge variety of ILs offers a vast playground for future studies and potential applications.

Introduction

Protein-protein interactions and their role in several biological functions are fascinating areas of research with potential applications in bio-nano-technology and a non-negligible impact in human wellbeing. Even though the interaction between proteins is essential for life, the aberrant increase in protein-protein interactions can lead to the formation of proteins' aggregates known as amyloids, which are playing a major role in several diseases such as Alzheimer's, diabetes type 2 and spongiform encephalopathies. Amyloids are insoluble fibres that can be found in tissues and organs. They are the result of multiple aggregation stages of specific proteins or peptides taking place under different physiological conditions such as pH, temperature and concentration (Hamley 2012). The effect of several inorganic ions, salts, and complexes on the formation and inhibition of amyloids is a widely studied area of research aimed to find solutions to resist various neurodegenerative disorders (Liu et al. 2005; Yeh et al. 2010; Ghalebani et al. 2012; Zhu et al. 2014; Branch et al. 2015; Kong et al. 2015; Yugay et al. 2016). In this respect, ionic liquids (ILs), which can be seen as the organic equivalent of inorganic salts, are the next potential good candidates to be studied.

ILs are a vast class of ionic compounds made by an organic cation and either an organic or inorganic anion; they are liquid around room temperature and have a very low vapour pressure (Welton 1999). Their high tunability and promising biocompatibility attracted the interest of the biophysical community. As a result, several studies have been carried out in the last two decades on the interaction between ILs and biomolecules, such as proteins, biomembranes, nucleic acids, and saccharides (Benedetto and Ballone 2016a, b, 2018; Benedetto 2017; Benedetto and Galla 2017). For the best of our knowledge, the first study on the ability of ILs to stabilize proteins was published in 2000 by Summers and Flowers. In their seminal work, they have shown the renaturation capability of the protic IL ethylammonium nitrate (EAN) on lysozyme (Summers and Flowers 2000). Followed by this work, several investigations on the effects of ILs on proteins have been carried out as a function of concentration, pH, cation's chain length, anion species, etc. Different proteins like lysozyme, serum albumins, myoglobin and haemoglobin, and α-chymotrypsin in presence of

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different ILs based on imidazolium, ammonium, phosphonium, and pyridinium were employed for structure, stability, dynamics, and biochemical studies. The diverse number of research works published in this domain is beyond the scope of this letter, to the interested readers, we suggest to start with some of the recent reviews on the topic (Benedetto and Ballone 2016a, b; Kumar et al. 2017; Schroeder 2017). In this letter, instead, we would like to focus on the effect of ILs on amyloids formation and inhibition, which is an emerging topic in the area of IL-protein interaction, holding the promise of important applications in bio-nano-technology.

Ionic liquids in protein amyloidogenesis: a brief screenshot of the state-of-the-art

One of the major steps in protein amyloidogenesis consists in the unfolding of the protein itself. If the unfolding is forbidden or partially inhibited, proteins may maintain their biological function and they do not aggregate into amyloids. In a similar way, if amyloid aggregates can be dissolved, and proteins are properly re-folded, the biological function can then be restored. In this respect, Byrne and Angell have shown the ability of common protic ILs, like EAN, to favour the unfolding and aggregation of lysozyme into fibrils, and then promoting their dissolution to restore the protein biochemical function (Byrne et al. 2007; Byrne and Angell 2008, 2009). Following this work, Kalhor et al. (2009) have demonstrated the inhibitory and reversible effect of another protic IL, i.e., tetramethylguanidinium acetate, towards the amyloid formation of lysozyme. Transmission electron microscopy images showed that the fibrils formed in this protic IL were thinner, and optical spectroscopy data revealed that the inhibitory effect was mainly due to the functional carboxy group present in the anionic part of the IL. Takekiyo and co-workers have linked this behaviour to the nanoheterogeneity of the aqueous solutions of ILs (Takekiyo et al. 2012). In their work, they have shown also how an aprotic IL, i.e., 1-butyl-3-methylimidazolium nitrate, is able to inhibit the fibrillation of lysozyme. They had also revealed that at higher IL concentrations non-native (α-helical) structural transformations could occur in proteins (Takekiyo et al. 2013). More recently, Basu et al. (2018) have investigated the ability of another aprotic IL, i.e., 1-butyl-3-methylimidazolium bromide, in suppressing the amyloidogenesis of lysozyme (Fig. 1).

The refolding ability of EAN on lysozyme pointed out by Byrne and Angell has then been investigated by Mangialardo and co-workers by Raman spectroscopy (Mangialardo et al. 2012). The refolding pathway was studied by monitoring in the Raman spectra (i) the amide bands which show the changes in the protein secondary structure and (ii) the Tyr, Trp doublet which is a signature of the protein tertiary structure. In this study, a clear refolding ability of EAN in comparison to other ILs with higher alkyl chain length has been registered.

The effect of ILs on protein amyloidogenesis has been studied by taking also into account other proteins rather than the only model protein lysozyme. Interestingly, Takekiyo and co-workers (Takekiyo et al. 2016) have shown the high suppression effect of the protic IL EAN on the fibrillation of insulin. Their experimental results have revealed the overriding role of the interaction of ILs with the amino acid residues as a potential reason for the suppressive behaviour. This result, when compared with the one of Byrne and Angell mentioned above, highlights how the effect of ILs on proteins' amyloidogenesis strongly depends on both the protein and the IL. Pannuru and co-workers have focused on insulin as well, where they have shown the effective role of novel ammonium-based protic ILs to prevent its self-aggregation (Kumar and Venkatesu 2013). By varying anions, they have also observed that bromide and chloride provided the long-term stabilization against aggregation in comparison with various other anions (Kumar and Venkatesu 2014). The fibril inhibition ability of surface-active imidazolium-

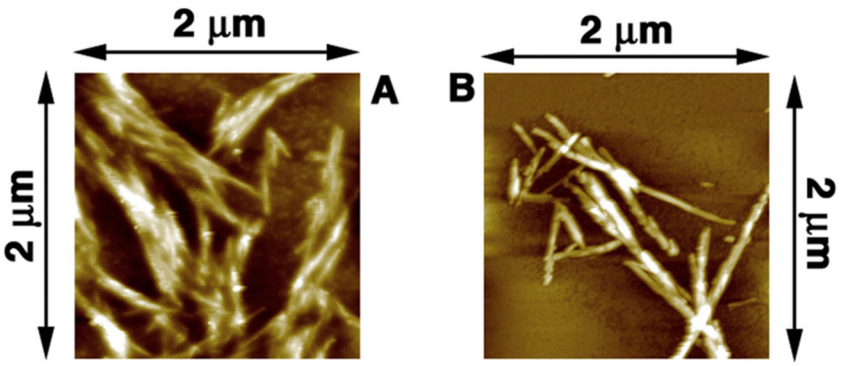

Fig. 1 Atomic force microscopy image of lysozyme fibrils (**a**) in the absence and (**b**) in the presence of the 1-butyl-3-methylimidazolium bromide IL after 8 h of incubation taken from (Basu et al. 2018). The images show the ability of this IL to attenuate the fibrillogenesis of lysozyme, something that may be useful in developing new therapeutical strategies against amyloids. Figure reproduced with permission from the publisher

Table 1 List of several studies on the effect of ILs on protein amyloidogenesis

Proteins	Ionic liquids	Techniques	References
Lysozyme	Ethylammonium nitrate	DSC, UV-vis, and fluorescence	Summers and Flowers 2000
Lysozyme	Ethylammonium nitrate	DSC	Byrne et al. 2007
Lysozyme	Ammonium-based protic ionic liquids	DSC, NMR	Byrne and Angell 2008
Lysozyme	Ethylammonium nitrate, triethylammonium mesylate, and triethylammonium triflate	SEM, CD, and fluorescence	Byrne and Angell 2009
Lysozyme	Tetramethylguanidinium cation	TEM, CD, UV-vis, and fluorescence	Kalhor et al. 2009
Lysozyme	1-butyl-3-methylimidazolium bromide	AFM, CD, UV-vis, and fluorescence	Basu et al. 2018
Lysozyme	2-methoxy ethyl ammonium nitrate, ethyl ammonium nitrate, propyl ammonium nitrate, and butyl ammonium nitrate	Raman spectroscopy	Mangialardo et al. 2012
Lysozyme	1-butyl-3-methylimidazolium nitrate	CD, SAXS, FTIR, and Raman spectroscopy	Takekiyo et al. 2012
β-Lactoglobulin	1-butyl-3-methylimidazolium nitrate, ethyl ammonium nitrate	FTIR, CD	Takekiyo et al. 2013
Several proteins	1-butyl-3-methylimidazolium thiocyanate	FTIR, CD, and Raman spectroscopy	Takekiyo et al. 2015
Insulin	Ammonium-based protic ionic liquids	UV-vis, fluorescene, CD, and DLS	Kumar and Venkatesu 2013
Insulin	1-butyl-3-methylimidazolium cation	UV-vis, fluorescene, CD, and DLS	Kumar and Venkatesu 2014
Bovine serum albumin, human serum albumin	1-methyl-3-octylimidazolium chloride, 1-dodecyl-3-methyllimidazolium chloride, and 1-hexadecyl-3-methyllimidazolium chloride	SEM, fluorescence, FCS, AFM, and surface tension	Kundu et al. 2017
Myoglobin	1-ethyl-3-methylimidazolium phenylalanine	QCM, UV-vis, fluorescence, SEM, and CD	Sankaranarayanan et al. 2012
Insulin	1-butyl-3-methylimidazolium thiocyanate; ethyl ammonium nitrate; and propyl ammonium nitrate	FTIR	Takekiyo et al. 2016
α-Synuclein and α-tandem	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	Chromatography, TEM, CD, fluorescence	Bae et al. 2010
α-Synuclein	Imidazolium-based ionic liquids	Fluorescence	Hwang et al. 2009
α-Lactalbumin, Ca2 binding protein	1-butyl-3-methylimidazolium cation	Flow cytometry, TEM, and fluorescence	Bae et al. 2011
Aβ(16–22)	Ethylammonium mesylate; diethylammonium mesylate; and triethylammonium mesylate	TEM, CD, and fluorescence	Debeljuh et al. 2012
Aβ (16–22)	Triethylammonium lactate; triethylammonium trifluoroacetate; triethylammonium mesylate; triethylammonium dihydrogen sulfate; triethylammonium hydrogen sulfate; and triethylammonium triflate	TEM, CD, and fluorescence	Debeljuh et al. 2011a
Aβ(1–40)	Triethylammonium methanesulfonate	CD, TEM	Debeljuh et al. 2011b
β-Lactoglobulin	Triethylammonium acetate; triethylammonium trifluoroacetate; triethylammonium mesylate; and trimethylammonium sulfate	TEM, CD, and fluorescence	Byrne et al. 2013
Bovine liver catalase	Dodecyltrimethylammonium bromide, Tetradecyltrimethylammonium bromide	TEM, CD, fluorescence, UV-vis, isothermal titration calorimetry, DLS, and RLS	Khan et al. 2017
Enzymes	1-butyl-3-methylimidazolium tetrafluoroborate	TEM, SEM	Kim et al. 2012
Recombinant protein (E. coli)	Cholinium dihydrogen phosphate	CD, and fluorescence	Fujita et al. 2016
Several proteins	1-alkyl-3-methylimidazolium nitrate	FTIR, UV	Takekiyo et al. 2014
β-Casein	1-octyl-3-methylimidazolium bromide, 1-butyl-3-methylimidazolium bromide	UV-vis, fluorescence, microcalorimetry, DLS, TEM, and conductivity measurement	Liu et al. 2014
Bovine serum albumin	1-dodecyl-3-methylimidazolium chloride; amide functionalized 1-dodecyl-3-methylimidazolium chloride;	Isothermal titration calorimetry, DLS, CD, fluorescence, SEM, confocal LSM, and FTIR	Singh and Kang 2015

Table 1 (continued)

Proteins	Ionic liquids	Techniques	References
	ester functionalized 1-dodecyl-3-methylimidazolium chloride		
Recombinant plasminogen activator	N-ethyl-N-methylimidazolium cation	UV-vis, DSC	Buchfink et al. 2010
Heparin	1-alkyl-3-methylimidazolium chloride	DLS, CD, FTIR, and Raman spectroscopy	Rawat and Bohidar 2015
Ribonuclease A	Choline dihydrogenphosphate, 1-ethyl-3-methylimidazolium dicyanamide	CD, DSC	Constatinescu et al. 2010
Collagen	1-butyl-3-methylimidazolium chloride; 1-ethyl-3-methylimidazolium chloride; and 1,3-dimethylimidazolium chloride	SEM, CD, UV-vis, thermoporometry, DSC, FTIR, and optical microscopy	Mehta et al. 2014
Collagen	Tributyl methyl phosphoniummethyl sulfate, Tributyl ethyl phosphonium diethylphosphate	Viscometry, UV-vis, fluorescence, CD, FTIR, optical microscopy, MD simulation, and dielectric spectroscopy	Tarannum et al. 2016
Collagen	1-butyl-3-methylimidazolium chloride	Optical microscopy, FTIR, XRD, and SEM	Meng et al. 2012
Collagen	Bischoline sulfate, 1-butyl-3-methylimidazolium dimethyl phosphate	Optical microscopy, CD, DSC, NMR, and impedance	Tarannum et al. 2018

based ILs on serum albumin proteins has been investigated by Nilmoni and co-workers (Kundu et al. 2017). Their experimental results have revealed the disruption of fibrils by these surface-active ILs due to the hydrophobicity related with the long alkyl chain length of the cation. The effect of ILs on model amyloid fibres has been investigated as well. It has been shown that the amyloid fibrillations in Aβ16–22 and Aβ1–40 peptides is inhibited in triethylammonium mesylate and triethylammonium methane sulfonate, respectively (Debeljuh et al. 2011a, b).

Also, the ability of hydrated ILs in re-folding proteins has been proved. For instance, Dhathathreyan and co-workers have observed that reversible and irreversible structural transitions take place in myoglobin while solvated in water solution of amino acid ILs at different concentrations (Sankaranarayanan et al. 2012). At low hydration level of phenylalanine IL, the protein transforms to complete β-sheet from its helical conformation; rehydration reverses the β-sheet to an α-helix. Moreover, Fujita et al. (2016) have shown that hydrated

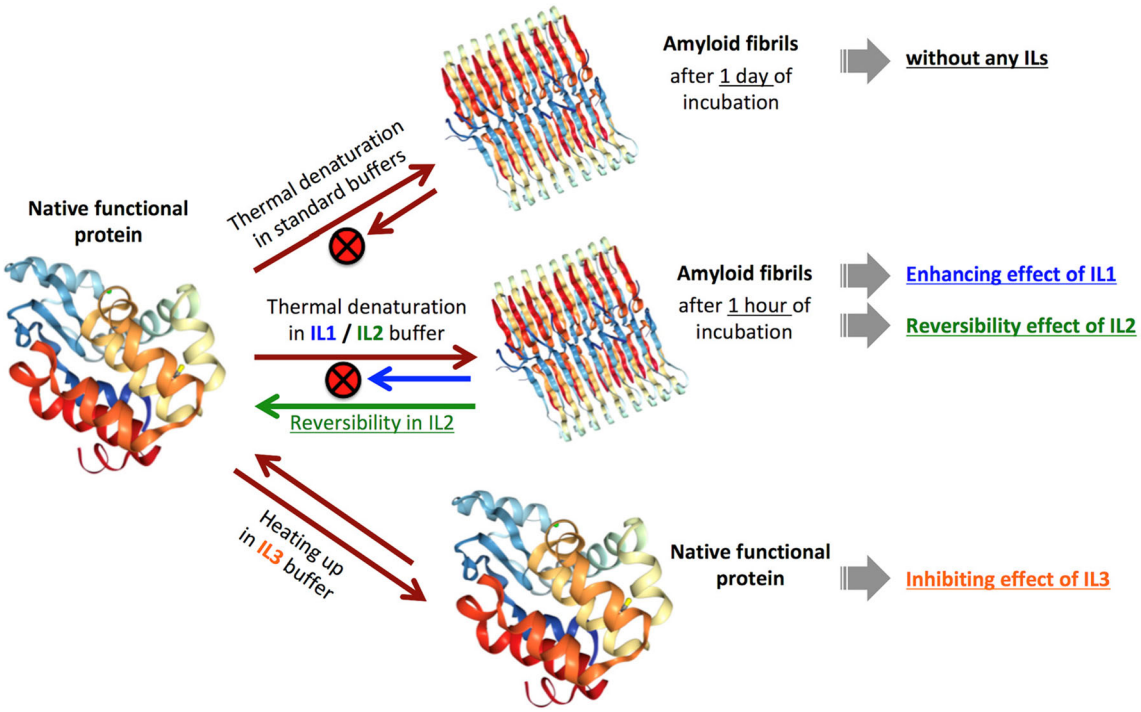

Fig. 2 A screenshot of ionic liquids in protein amyloidogenesis

cholinium dihydrogen phosphate is able to dissolve and re-fold the aggregated recombinant cellulase protein from *Escherichia coli* bacteria.

ILs have also the ability to favour protein amyloidogenesis, rather than only to inhibit it. Several studies, for instance, have shown the role of imidazolium-based ILs in favouring amyloidogenesis (Hwang et al. 2009; Bae et al. 2010, 2011; Debeljuh et al. 2011a). Byrne and co-workers (Debeljuh et al. 2012), moreover, have compared the efficiency of different amine-based ILs on the conversion of Aβ16–22 peptides from monomers to amyloid fibrils; they concluded that the primary amine IL is having higher conversion efficiency than others due to the higher degree of proton transfer. They have also observed that the protic ammonium IL triethylammonium mesylate maintains the native β-barrel structure of the β-lactoglobulin protein at low concentration (20 wt%) even after heating, but at a higher concentration (40 wt%), it induces the formation of amyloids (Byrne et al. 2013). In a recent work, Khan et al. (2017) have demonstrated the role of ammonium-based ILs in favouring the amyloidogenesis of bovine liver catalase.

Table 1 summarizes the above-mentioned data and other studies on the effect of ILs on protein amyloidogenesis.

Conclusions and future outlook

ILs are a vast class of organic salts, which shows high affinity with proteins and, more in general, biomolecules and biosystems. In this letter, we had the opportunity to enjoy and discover their quite broad effect on protein amyloidogenesis (Fig. 2). Whereas some ILs are able to inhibit the amyloidogenesis and to dissolve the mature fibrils back to the native protein structures restoring also their biochemical function, other ILs are acting in the opposite direction by favouring the aggregation of proteins into amyloids. Moreover, other ILs are able to make the amyloidogenesis reversible by first favouring the unfolding of proteins and their aggregation into fibrils, and then promoting the fibrils' dissolution and the refolding of the proteins. Another key ingredient is the presence of water, since it has been shown that in some cases the effect of ILs on protein amyloidogenesis changes by changing the amount of water surrounding the protein. Interestingly, in some cases, ILs that behave in one way with one specific protein show a totally opposite effect on a different protein. This points out the extremely important role of the specificity of the chemical-physical interactions, something that on the one hand makes hard to a priori predict the behaviour of a given IL on a specific protein, but on the other hand represents a vast playground for applications in bio-medicine, pharmacology, diagnostic, therapeutics, material science, food science, and, more in general, bio-nano-technology. In this respect, the huge variety of ILs including, in particular, ILs based on amino acids (Benedetto et al. 2014) and surface-active ILs, together with their tuneable character offer an almost unlimited scenario of combinations and opportunities.

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Compliance with ethical standards

Conflicts of interest Visakh VS Pillai declares that he has no conflict of interest. Antonio Benedetto declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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