CHEMICAL REVIEWS

Review

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Biological Activity of Ionic Liquids and Their Application in Pharmaceutics and Medicine

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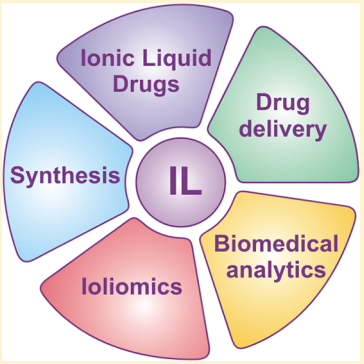
ABSTRACT: Ionic liquids are remarkable chemical compounds, which find applications in many areas of modern science. Because of their highly tunable nature and exceptional properties, ionic liquids have become essential players in the fields of synthesis and catalysis, extraction, electrochemistry, analytics, biotechnology, etc. Apart from physical and chemical features of ionic liquids, their high biological activity has been attracting significant attention from biochemists, ecologists, and medical scientists. This Review is dedicated to biological activities of ionic liquids, with a special emphasis on their potential employment in pharmaceutics and medicine. The accumulated data on the biological activity of ionic liquids, including their antimicrobial and cytotoxic properties, are discussed in view of possible applications in drug synthesis and drug delivery systems. Dedicated attention is given to a novel active pharmaceutical ingredient-ionic liquid (API-IL) concept, which suggests using traditional drugs in the form of ionic liquid species. The main aim of this Review is to attract a broad audience of chemical, biological, and medical scientists to study advantages of ionic liquid pharmaceutics. Overall, the discussed data highlight the importance of the research direction defined as "Ioliomics", studies of ions in liquids in modern chemistry, biology, and medicine.



CONTENTS

1. INTRODUCTION

The first report of Wilkes and Zaworotko on air- and moisture-stable room-temperature liquid salts in 1992[1] has initiated paramount research activity in various areas of chemistry. Further studies have shown that ionic liquids (ILs) are very efficient in chemical synthesis and catalysis,[2−24] electrochemistry,[25−32] biomass conversion,[33−41] fuel production and processing,[42,43] liquid crystal development,[44] biotransformation,[16,45] biotechnol-

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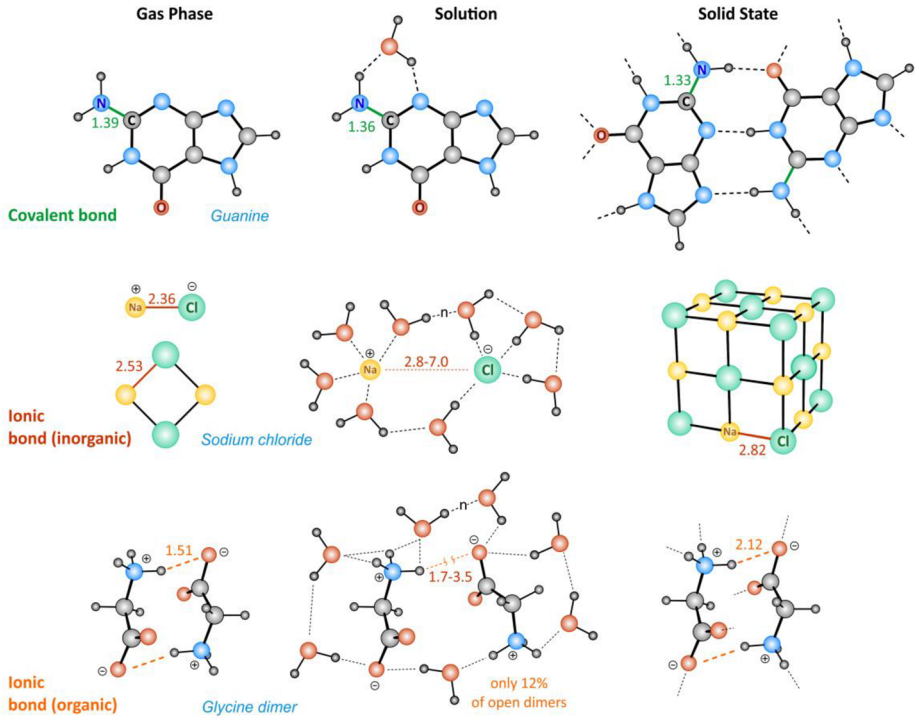

Figure 1. Differences between structures of covalent and ionic compounds in the gaseous phase, solution, and solid phase (the interatomic distances are in Å).

ogy,[20,21,24,46−50] and many other fields.[35,51−61] The scope of in-depth studies on ILs covers a wide range of topics and includes their structures and properties,[40,57,59,62−66] nano-organization and self-assembly,[53,67,68] and practical applications in advanced chemical transformations.[7−9,13,14,16,40,51,57,58,64,69−73] Improvements of separation,[35,60,74−77] electrochemical behavior,[26,29,35,40,57,64,78,79] analytics,[64,80−83] extraction,[42,84−87] purification and recovery,[88,89] energetic characteristics,[43,61,90] and biocatalytic properties[10,39,57,70,91−97] are well-established areas. Recently, the ecological impact of ILs has also been recognized as an important problem.[57,98−103] Studies on the properties and applications of ILs are discussed in a number of excellent reviews, with only some representative examples cited above.

Besides their unique properties and usage as solvents, the tunable nature of ILs has facilitated the development of novel valuable topics. ILs are already described as the basis of a quiet revolution in material science.[29] The number of articles involving ILs is impressive and is growing significantly more rapidly than that for several other actively developing research areas. It is interesting to note that the focus of many IL studies now evolves in the direction of life sciences and medicine. A thorough literature analysis of publications on ILs suggested that in the next decade bio-medical applications of ILs would become one of the major research trends.[104,105] Moreover, in a near-term perspective, efficient drugs based on ILs may be considered for approval by FDA.[106]

Studies on the biological activity of ILs and their application in pharmaceutics and medicine are newly emerging, highly important areas, which are the subject of this Review. As a necessary introduction to the topic, we briefly emphasize the fundamental origins of tunable properties of ionic interactions in liquids (section 1.1). The structure and organization of ILs in solution is the crucial point for understanding their interactions with living organisms, and it is discussed in section 1.2, followed by the description of the subject coverage and scope of this Review (section 1.3). The key areas considered in this Review include biological activity of ILs (section 2), usage of ILs as components of drugs (section 3), and applications of ILs in drug synthesis (section 4).

1.1. Tunable Nature of Ionic Compounds: Ionic versus Covalent Bonds

The tunable nature of ionic compounds, which reflects a fundamental difference between covalent and ionic binding, deserves a special note. Indeed, one of the central topics in chemistry is the nature of chemical interactions, their classification, and physically relevant, quantitative description. At the beginning of the 20th century, the concepts of covalent and ionic bonds were established; later, they were validated from the point of electronic structure of molecules.[107] The covalent bond is a binding interatomic interaction, which is realized by sharing a pair of valence electrons between the interacting atoms. Consequently, the electron pair localizes in the interatomic region and "belongs" to both covalent bond participants.[108,109] The ionic bond involves an electrostatic interaction, which is formed between atoms with significantly different electronegativity; this difference results in an almost complete (or significant) shift of the shared electron pair from the interatomic region to the more electronegative atom and therefore leads to formation of ions. Currently, the physically relevant division of interatomic interactions into covalent and ionic ones may be carried out according to the analysis of parameters of electron density in the interatomic regions of the interacting atoms.[110−112]

Significant differences in the electronic structure of covalent and ionic compounds result in substantially different behavior of the corresponding molecules, both in the solid phase and in solution. In the solid phase, ionic compounds, such as salts of alkali metals, are prone to form crystal lattices, as a rule, with close packing; in polar solvents, these compounds dissociate

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easily into ions surrounded by apparent solvate shells providing high ionic conductivity of the solution. Molecules with covalent bonds form molecular crystals and preserve molecular structure upon dissolution in liquid phase (without breakage of covalent bonds).[113]

Because of the strong interactions of ionic compounds with the solvent medium, the impact of liquid phase on chemical processes involving ions becomes essential, which, in turn, makes ionic chemistry both dramatically manifold (same ion demonstrates different chemistry depending on the media) and very tricky to study by experimental and theoretical methods (especially in the dynamic liquid phase). In particular, ions are always surrounded by solvate shells, which may have a significant influence on mechanisms and kinetics of chemical reactions.[114] Association of ions with molecules of the medium results in reorganization, arrangement, and structuring of the latter, which, in turn, influence the mobility of the ions[115] and rheological properties of the medium, the latter ones being especially important in biological systems.[102,116] The effects of structuring and self-organization are most pronounced in ionic liquids, which are effective solvents and components of modern catalytic systems.[67]

A representative example of the differences in the properties of ionic and covalent compounds is shown in Figure 1. For guanine (one of the nucleobases), insignificant changes in the covalent interatomic bond occur upon the transition between phases. The length of the covalent C−N bond in the gas phase, denoted in Figure 1 and determined by the gas-phase electron diffraction (GED) method, is 1.39 Å.[117] Microsolvation of the guanine molecule by a water molecule results in decreasing this distance only by 0.03 Å.[118] In the anhydrous crystal, guanine molecules are connected by the net of hydrogen bonds forming flat parallel sheets; as a result, the C−N distance decreases only by 0.03 Å, in comparison with the microsolvation state.[119] Therefore, for the exemplified guanine molecule, the maximum change of the covalent bond length upon the transition between the phases is less than 0.1 Å.

The ionic bond is significantly more sensitive to the influence of external factors. Thus, according to GED experiments in the gaseous phase, sodium chloride molecules exist both in the monomeric form, characterized by the Na−Cl interatomic distance of 2.36 Å, and in the dimeric form.[120] At the same time, even upon the dimerization in the gaseous phase, the Na−Cl interatomic distance increases to 2.53 Å, that is, by 0.17 Å. In the solution, sodium chloride dissociates and forms ions. The distance between the ions in solutions varies widely and reaches 7.00 Å, as established by molecular dynamic modeling.[121] In the solid state, sodium chloride forms an ionic crystal with the interionic distance of 2.82 Å.[122]

The lengths of ionic bonds in organic compounds, for example, in the dimer of the zwitterionic form of glycine, also vary widely depending on the molecular environment. In the gaseous phase, the NH−O distance is about 1.50 Å (Figure 1).[123] In the aqueous media, the distance between the zwitterions depends on the solvent concentration. In diluted solutions, the amino acid molecules are entirely separated by the solvent molecules, and even in concentrated solutions only 12% of the glycine molecules form open dimers (i.e., dimers containing monomers bonded by one hydrogen bond), while in the gaseous phase, cyclic dimers with two hydrogen bonds between the monomers are formed.[124−126] In the crystal form, the length of the hydrogen bond between the zwitterions of α-glycine is 2.12 Å, which is considerably longer than that in the gaseous phase.[127−129]

The principal role of tunable nature of ionic bonds is not limited to the simple examples described above. The crucial role in the structuring of complex natural biological molecules and self-organizing materials is established.[130−134] Controlled and predictable production of such compounds, including artificial enzymes,[135,136] nanoreactors,[137,138] and nanotubes,[139] is possible, when quantitative data on the strength of ionic interactions in the solution are available. Recently, an atomic force microscopy-based method for assessing single ionic bonds between organic substrates at the molecular level has been developed.[140] One of the most attractive ionic topics is ion-mediated conformational switches, or molecules, which change their conformation and function upon interacting with anions or cations.[141]

Ions are key participants supporting vital activity of living organisms on all levels of their organization. Thus, at the level of a single cell, catalytic metal ions, being efficient stabilizers of anionic transition states, are associated with ribozymes and protein metalloenzymes,[142,143] and are involved in the stabilization of secondary and tertiary protein structures.[144] At the level of a whole organism (mammal), extracellular ions are shown to control neuronal activity during sleep−wakefulness cycles.[145] Unsurprisingly, some severe disorders (e.g., Parkinson's and Alzheimer's diseases) arise due to abnormal functioning of ionic channels, which are positioned in the lipid bilayer of cell membranes and ensure ionic currents into and out of the cell.[146,147] Members of the family of channel kinases, ones of the most interesting ionic channel proteins, which combine the functions of an ionic channel and a protein kinase within a single polypeptide chain, are implicated in the regulation of such important processes as cell proliferation, differentiation and migration, embryonic development, and cardiac automaticity.[148−153] Studying molecular mechanisms of disturbances in the functioning of ionic channels is required for understanding causes of the associated diseases and for developing strategies of their treatment. Lately, such data have been appearing especially frequently, in particular, due to methods of molecular modeling.[147,154,155] Investigations of the mechanisms of action of ionic channels have provided the possibilities of generating ionic channel-based detectors, which are able to capture single ions, molecules, and viral particles, and of developing the method of "single-molecule" mass spectrometry.[156] Such active penetration into the "atomic" details of ionic reactions leads to uprising of new cytological areas, for example, nanophysiology.[157] The importance of ionic interactions in solutions has been highlighted in a number of recent chemical and biological problems.[44,145,158−162]

Therefore, ionic interactions possess outstanding intrinsic potential for flexible and dynamic behavior, which can be utilized to tune the properties of ionic compounds at different levels. The dynamic and tunable potential of ionic compounds can be most powerfully employed in the liquid phase.

1.2. Structure and Organization of Ionic Liquids

As discussed in the previous section, the combination of liquid phase and ionic character of bonding provides an outstanding opportunity to generate a diversity of physical and chemical properties. Indeed, this combination is most efficiently encoded in the structure of ionic liquids, and here we will briefly highlight the main aspects. Ionic liquids are molten salts, which are liquid at temperatures below 100 °C due to bulky, asymmetric cations

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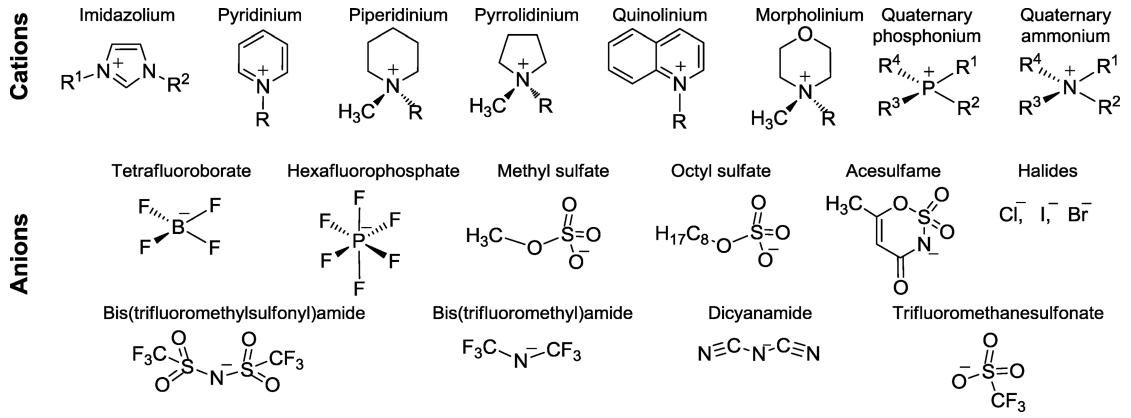

Figure 2. Examples of cations and anions commonly used in ionic liquids.

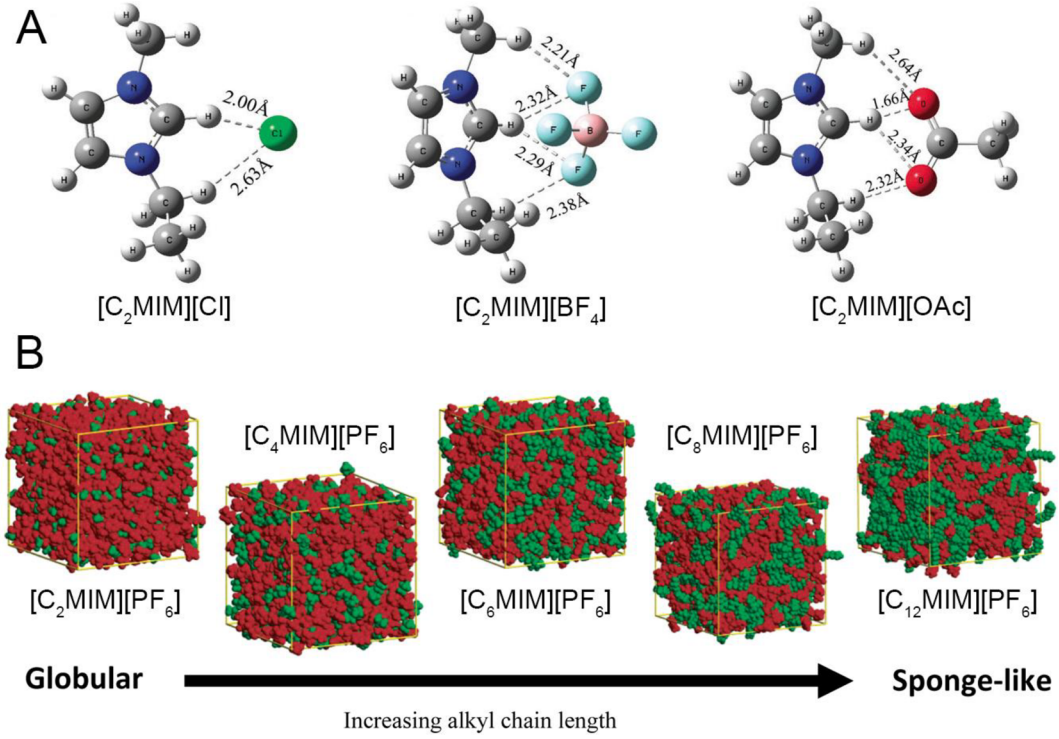

Figure 3. (A) Representative ion pairs and H-bonds in $[C_2MIM][Cl]$, $[C_2MIM][BF_4]$, and $[C_2MIM][OAc]$ (the interatomic distances are in Å). (B) Structure of $[C_nMIM][PF_6]$, where $n = 2-12$ (each box contains 700 IL ion pairs; polar domains are shown in red (anion, cation imidazolium ring), and nonpolar domains are shown in green (cation alkyl chains)). Reproduced with permission from refs 67 (Copyright 2015 American Chemical Society), 185 (Copyright 2016 Royal Society of Chemistry), and 186 (Copyright 2006 American Chemical Society).

and weakly coordinating anions that destabilize the crystal lattice.[20,53,67] The impact and wide areas of application of ILs may be explained by their extraordinary flexibility. The number of possible IL combinations is overwhelming and approaches 10^{18}, suggesting that almost any desirable properties may be combined within one IL molecule.[163] Some representative structures of cations and anions are shown in Figure 2.

Recent progress in analytical studies of ILs using NMR,[55,164−169] mass spectrometry,[170−173] thermal techniques,[174−176] theoretical modeling,[41,52,53,177−180] and other analytical approaches[181−184] has revealed an important mechanistic picture. As expected, ILs fully realize the potential of tunable interactions at the molecular level, as discussed above (Figure 1). Moreover, the molecular properties of ILs (Figure 3A) modulate higher-order nano- and microscale levels of organization (Figure 3B).

Accumulated evidence points out that, in contrast to conventional molecular liquids, ILs can be considered as nanoheterogeneous media. The ions in the liquid phase tend to self-assemble and form long-living amphiphilic nanostructures. Such organization is uncommon, because most of molecular solvents do not demonstrate structural ordering aside from interactions between neighboring molecules. Nanoscale and microscale ordering possibly provides ILs with their unique properties, which, in conjunction with the vast variability of available ions, make ILs a substance of choice for numerous applications.[67]

Experimental studies on the microstructure and spatial characteristics of ILs are rather complicated and difficult to perform. Most data on the IL structuring at the molecular level have been obtained by theoretical methods, in particular, by

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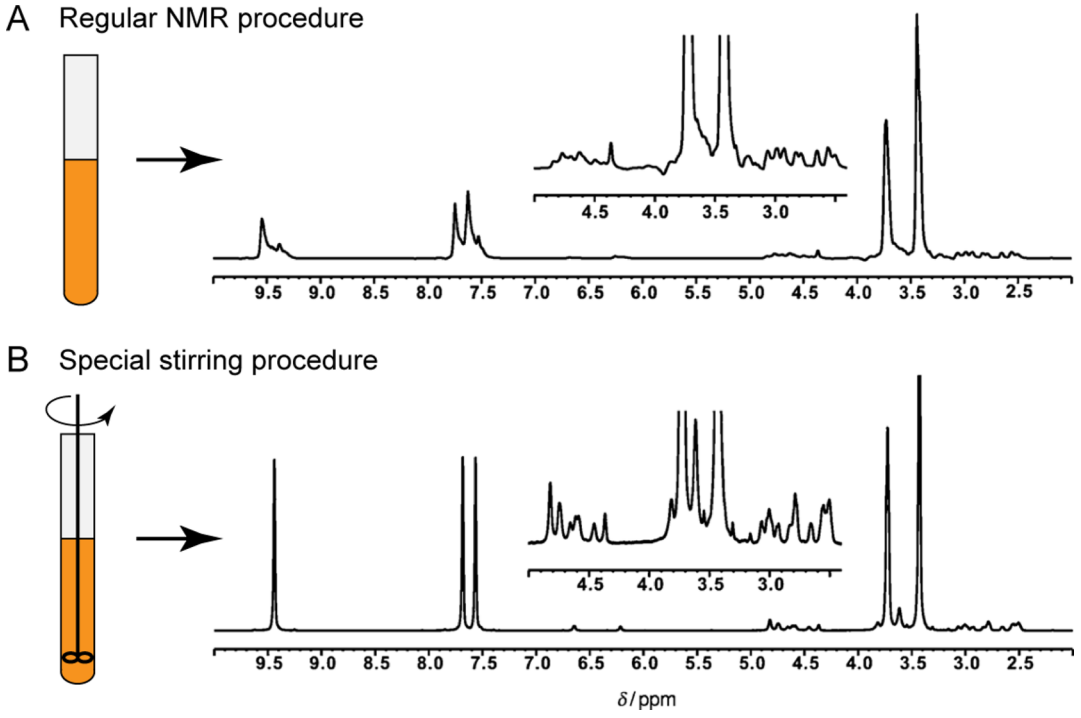

Figure 4. Spectral evidence of nanoheterogeneous nature of IL system: (A) ^{1}H NMR spectra of glucose in $[C_4MIM][Cl]$ with conventional sample preparation shows characteristic distortions, and (B) sample preparation with additional external stirring eliminates these distortions (magnified regions containing the glucose signals are shown in the insets). Spectra reproduced with permission from ref 165. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA.

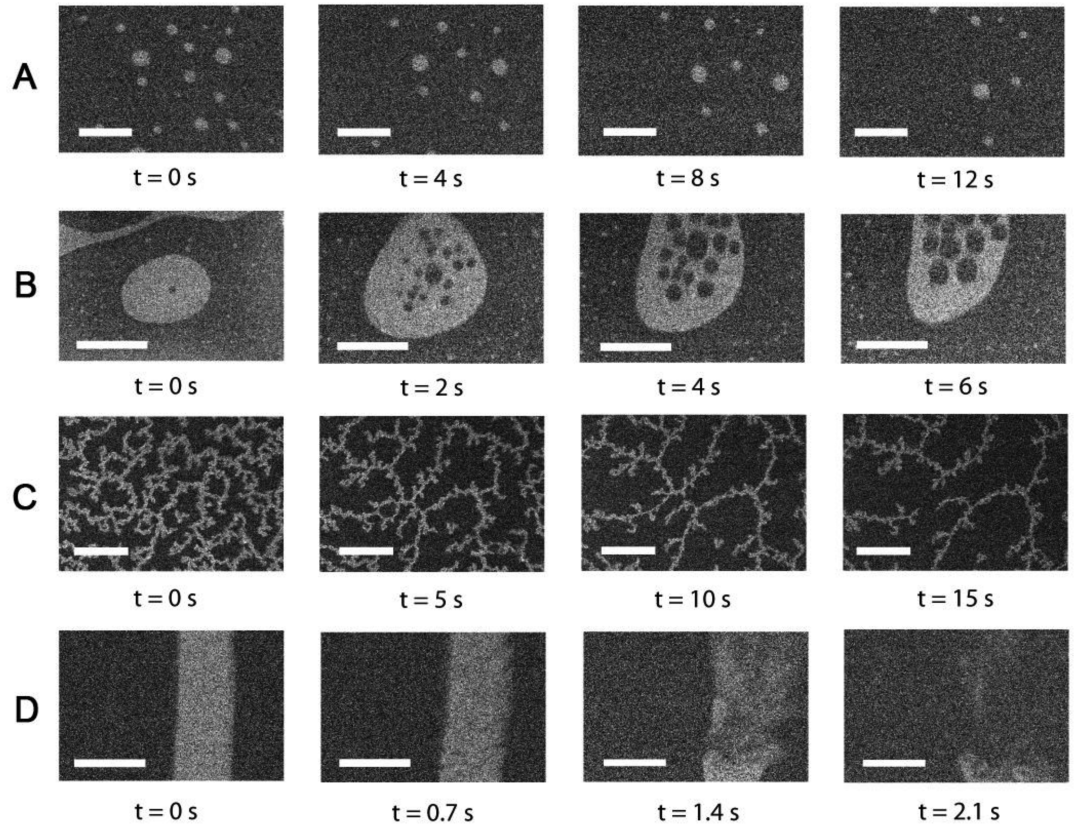

Figure 5. Self-organization and dynamics of water-containing structures in $[C_4MIM][BF_4]$ under electron-beam irradiation: (A) droplet movement; (B) formation of cavities within the droplet; (C) meshwork movement and cleavage; and (D) channel rupture (scale bars correspond to 10 μm (A,C), 20 μm for t = 0 s and 15 μm for t = 2−6 s (B), and 5 μm (D)). Reproduced with permission from ref 200. Copyright 2016 Wiley-VCH Verlag GmbH & Co. KGaA.

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Chem. Rev. 2017, 117, 7132−7189

classical and DFT molecular dynamics modeling (Figure 3B).[67,179]

The theoretically revealed nanoheterogeneous nature of ILs was confirmed by spectral studies. The heterogeneity turned out to be the main reason for difficulties in the registration of NMR spectra in some IL systems. In regular NMR studies, the sample is homogenized by self-diffusion of solvent and solute molecules in the liquid phase. However, in the case of ILs, it was not sufficient for recording high-quality NMR spectra (Figure 4A). Higher stability of the microphase structures demands a special procedure with intensive stirring directly in the NMR tube to get a required degree of homogenization (Figure 4B).[165]

Both ionic interactions and hydrogen bonds have been shown to play significant roles in the IL organization.[67,68,187,188] Some reports suggest that networks of hydrogen bonds, which stabilize ionic clusters, are, at least partly, responsible for differences between ILs and simple systems consisting of separate ions.[68] One of the main differences between "classic" organic salts and ILs is the size of the ions. Ions of inorganic salts can be considered as spherical species, whereas bulky ions of ILs possess more complicated shape, which influences the local IL structure,[189] especially the cation volume.[190] In the bulky organic ions of ILs, the charge is distributed over the large volume and is more delocalized in the space. Therefore, the charge density of IL ions is lower than that of small ions of inorganic salts. This effect reduces the strength of electrostatic repulsion between similarly charged organic ions and allows them to converge and to get additional structuring from noncovalent interactions. For example, in 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ($[HOC_2MIM][BF_4]$), the cations formed so-called anti-electrostatic hydrogen bonds, which were found by spectroscopic and theoretical methods.[191,192] In general, IL ions are capable of forming more diverse and complicated interactions, as compared to inorganic high-temperature molten salts.[187] This capability also may explain considerable differences between the IL structures in the crystalline and liquid states.[193,194]

Despite significant progress, there are still many questions concerning the IL nanostructure, and a recent review warns us against sticking to a single theory, especially considering some disagreements between different theoretical approaches.[67] For example, CPMD (Car−Parinello molecular dynamics) modeling of the pure 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4MIM][PF_6]$) showed numerous cation−anion hydrogen bonds, which were absent in the results of empirical potential molecular dynamics modeling.[195] A crucial structuring role of the hydrogen bonds between the imidazolium and chloride ions was established by CPMD modeling for 1,3-dimethylimidazolium chloride ($[C_1MIM][Cl]$); it was also shown that classical MD underestimated the influence of hydrogen bonding.[196−198]

The important feature of the IL microstructure is the existence of stable cage structures established by interionic interactions in the liquid phase. Such structures cause the cage effect confirmed by theoretical modeling[189] and experiments.[199] The cage effect manifests itself by trapping and holding substrate molecules in the cage cavity for a relatively long time. Sometimes this time is enough for facilitating a chemical reaction in the molecular cage, as in a dedicated nanoreactor.[137] The cage effect can exhibit as a catalytic effect due to an increase of molecular collision probability and due to "improvement" of the entropic factor of a chemical reaction.

Recently, the first direct experimental observation of IL microstructuring effect has been done.[200] Self-organized water compartments of various morphologies were detected in water−IL mixtures by using electron microscopy (Figure 5). The dynamic nature of the self-organized structures has been visualized by microscopy observations (Figure 5). It was also found that nanostructured domains in the solution promoted higher yields and selectivity in the biomass conversion reaction.[200] Structuring effect of water−IL interactions is known to play an important role (see, for example, refs 201−207). Small-angle neutron scattering (SANS) studies also confirmed the existence of water nanoclusters in $[C_4MIM][BF_4]$, when the water−IL molecular ratio was higher than ∼2:1, and the cluster size was shown to grow upon the increase of the water content.[208] Very recently, the effect of water on the nanostructure of alkylammonium alkanoates ($[N_{000n}][C_mCO_2]$) has been studied in details using small- (SAXS) and wide-angle (WAXS) X-ray diffraction.[209] The phenomenon concerning water structuring and the influence on molecular interactions have also been recognized in biochemical studies.[210,211]

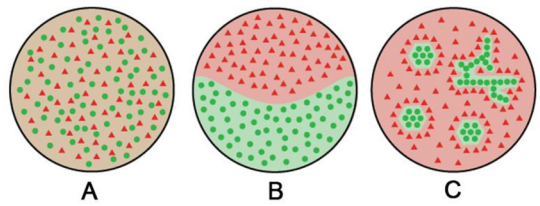

Figure 6. Different liquid-phase systems: (A) uniform mixing of components; (B) separation of phases; and (C) formation of structured system. Reproduced with permission from ref 200. Copyright 2016 Wiley-VCH Verlag GmbH & Co. KGaA.

To summarize the section, the unique nature of IL systems should be emphasized (Figure 6). Usually, liquid-phase chemistry deals with homogeneous solvent−solute systems (A) or with heterogeneous systems involving phase separation (B). In the case of ILs, both types of mixtures can exist depending on the system. However, in many cases, self-organization in ILs leads to the formation of dynamic nano- or micro-sized structures (C), which substantially change the properties of the system. This difference is crucial for the analysis of biological activity of ILs and for discussion of the material described in this Review.

1.3. Subject Coverage and Scope of This Review

A brief introduction into different generations of ILs is required to classify the studies on the biological activity. There are three generations of ILs depending on their chemical structure and properties (Figure 7). The first generation was sensitive to water and air and combined basically dialkylimidazolium and alkylpyridinium cations with metal halide anions. These ILs attracted attention mostly due to their physical properties. The second generation is air- and water-stable; the most common cations include dialkylimidazolium, alkylpyridinium, ammonium, and phosphonium, whereas halides, tetrafluoroborate, and hexafluorophosphate are among the most common anions. These ILs have attracted interest of physics and chemists alike and have found application in various chemical and physical fields. The third generation of ILs employs biodegradable and natural ions, such as choline and amino acids, or ions with known biological activities. These ILs are of interest not only for chemical topics, but also for studies in biology and ecology.[20,45,167,181,212,213]

As advantageous properties of ILs have been revealed, task-specific ionic liquids (TSILs) have begun to emerge. TSILs carry

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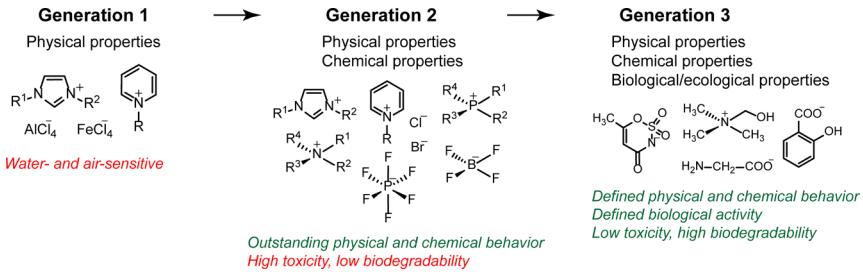

Figure 7. Evolution of ionic liquids. Figure concept reproduced with permission from ref 212. Copyright 2007 Royal Society of Chemistry.

covalently linked functionalities and are tuned for particular applications, where they perform better than traditional solvents/reagents.[45,55,214−216] Among the examples of TSILs are metal-containing ILs used in catalysis, chiral ILs employed for enantiomer sensing, magnetic ILs, etc.[55,216]

ILs of generation 2 had been thought to become a benign alternative to toxic organic solvents. Because of their nonvolatile and nonflammable nature, ILs had been supposed to be environmentally safe and "green" chemicals. However, as the data on biological activity of ILs have begun to accumulate, this belief has changed. Now it is obvious that many ILs demonstrate significant biological activity, which is of similar level or even higher, as compared to regular organic solvents and small molecules. Moreover, good water solubility assists the penetration of ILs into various ecological systems. Therefore, in the last decade, the evaluation of environmental impact of ILs has gained ground.[217] High biological activity of ILs presents disadvantages for using them as solvents or catalysts in chemical sciences. On the other hand, the biological activity of ILs has attracted special attention in pharmaceutics.[212,218] Such opportunities demand for a broad discussion and investigation of bio-related properties of ILs.

There are several books and book chapters dedicated to biological properties of ILs.[20,24,46,100−102,213,219] Dedicated reviews address biocatalytic usage,[10,39,57,70,91−97,220] toxicity and environmental effects,[56,57,217,221,222] biodegradation,[57,103] and pharmaceutical aspects[35,61,218,223−232] of ILs.

The main aim of this Review is to draw the attention of a broad audience of chemical, biological, and medical scientists to new advantages in the field of ionic liquid pharmaceutics and to discuss a novel active pharmaceutical ingredient-ionic liquid (API-IL) concept. Here, we address the advantages of using ILs in modern pharmaceutics and describe state-of-the-art in the research on their biological activity and biomedical applications. Main fields of pharmaceutical employment include usage of ILs as components of drug or drug delivery systems and as complementary participants in drug synthesis.

This Review is divided into three sections. In the first, we give a brief overview of known biological activities of ILs, environmental toxicity, antimicrobial properties, and cytotoxicity against cancer cells, and touch upon possibilities of IL biodegradation. The second section discusses direct employment of ILs as components of drug delivery systems and highlights the concept of API-ILs, together with available data on medical properties and clinical trials of ionic liquid pharmaceuticals. The third section is dedicated to IL usage in drug synthesis and also provides concise coverage on biomedical analytical applications of ILs. The overall summary of the topics considered upon preparation of this Review is shown in Figure 8.

Throughout this Review, we pay attention to mechanistic studies of ILs using experimental and theoretic approaches.

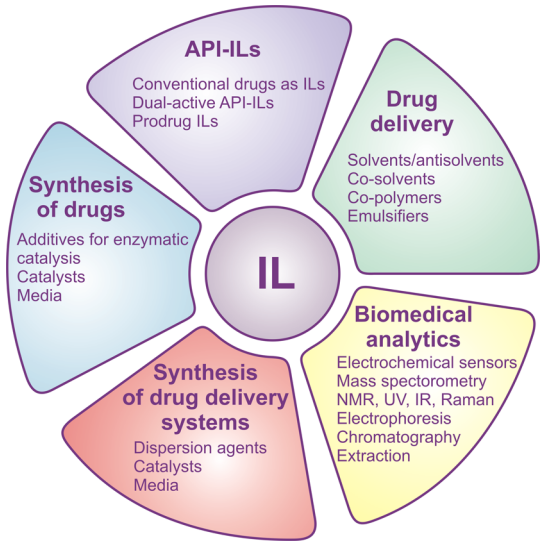

Figure 8. Graphical summary of possible pharmaceutical and medicinal applications of ionic liquids.

Understanding the nature of IL systems is important for explaining and predicting their behavior in biological and pharmaceutical systems. A graphical overview of the methods currently applied for studying biology- and medicine-related characteristics of ILs, which are discussed in this Review, is provided in Figure 9.

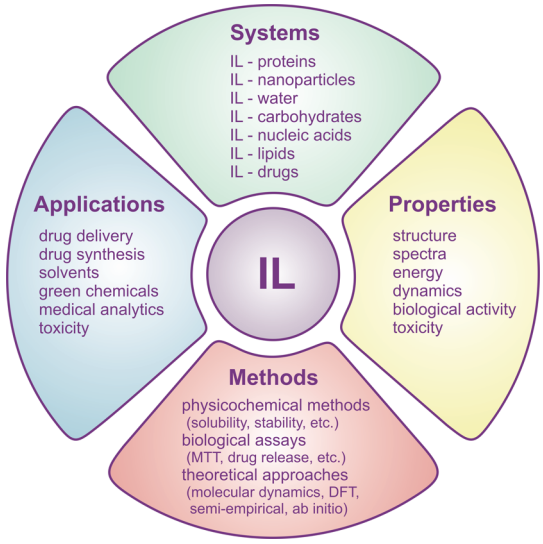

Figure 9. Systems, approaches, and methods currently applied for studying biology- and medicine-related properties of ionic liquids.

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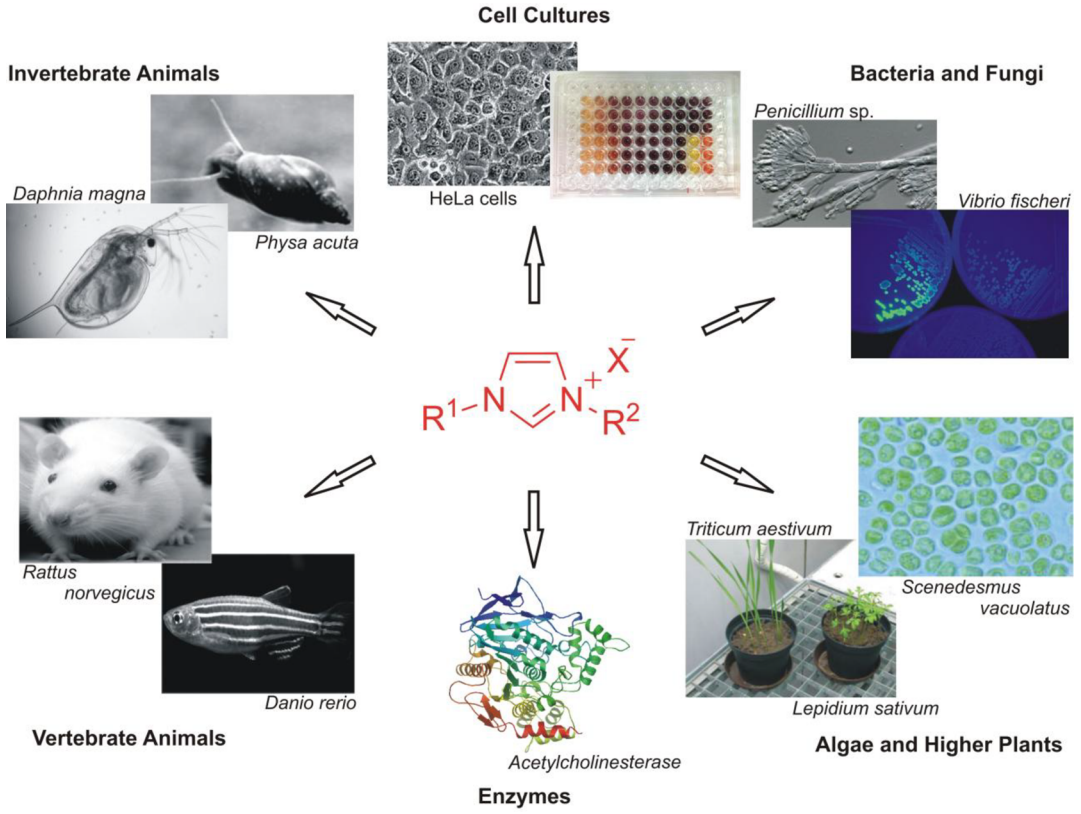

Figure 10. Ionic liquids are active toward all levels of life. Reproduced with permission from ref 217. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.

2. REVEALING BIOLOGICAL ACTIVITY OF IONIC LIQUIDS

2.1. Organism-Dependent Biological Activity of Ionic Liquids

Nowadays, it is clearly established that ILs have an impact on different levels of life, from single proteins to higher multicellular organisms (Figure 10).[233−235] In this section, we point out the major key points of biological activity of ILs.

First, an apparently high bioavailability of ILs should be taken into account. Although the particular mechanism of biological activity of ILs may vary from one organism to another, water is crucial for all living systems. Therefore, solubility and interactions with water are one of the factors determining environmental/biological activity of ILs. In the study on ILs with various cations containing butyl or isobutyl side chains and the bis(trifluoromethylsulfonyl)amide anion ($[NTf_2]^-$), the water solubility of ILs decreased as follows, imidazolium ILs > pyrrolidinium ILs > pyridinium ILs > piperidinium ILs, and was suggested to depend on the water cavitation potential, which was influenced by the size of the IL cation and, to some degree, by the IL aromaticity.[236] A theoretical study on imidazolium ILs with small inorganic anions suggested that both the cation and the chloride ($[Cl]^-$), bromide ($[Br]^-$), and tetrafluoroborate ($[BF_4]^-$) anions interacted strongly with water molecules, whereas the hydrophobic hexafluorophosphate ($[PF_6]^-$) anion formed no stable interactions with water. According to this study, the ion pairs also interacted with water, but these interactions were significantly weaker.[237] In the case of aqueous 1-ethyl-3-methylimidazolium acetate ($[C_2MIM][OAc]$), the main interactions were hydrogen bonds between water molecules and the anion.[238] $[C_4MIM][OAc]$ demonstrated weakening of cation−anion interactions due to interactions between the anion and water in water solutions.[239]

Biological activity of ILs was shown to depend on their hydration state, and a threshold hydration number was established. About seven water molecules per ion pair were suggested to be the boundary at which biological effects of IL−water mixtures changed dramatically, independent of the ion nature. The first six molecules of water supposedly formed strong interactions with the ion pair.[240] Interestingly, when the ratio of water molecules to IL molecules did not exceed one to three, the solution retained the polar ionic network.[236] Upon subsequent dilution, water molecules surrounded the IL network causing its stretching and, finally, disruption.[241]

Corroborating the above-mentioned dependence of biological activity of ILs on the presence of water (for possible structural factors, see also section 1.2), simulations of interactions between water solutions of ILs and phospholipid bilayers suggest that the behavior of the IL anion is governed by its interactions with water molecules. Thus, small hydrophilic anions, such as $[Cl]^-$, stayed in the solution, whereas more hydrophobic, bulkier $[PF_6]^-$ formed a film at the lipid/water boundary. In the case of the hydrophobic $[NTf_2]^-$, the anion followed the imidazolium cation into the lipid bilayer and was located in the interjacent region between the hydrocarbon tails and polar heads of the phospholipid (Figure 11).[242] The chloride anion reduced the cation insertion, as compared to lactate.[243]

The analysis of the general profile of biological activity of ILs shows that it is strongly dependent on the organism.[217,221,222] Thus, in the case of the common IL $[C_4MIM][NTf_2]$, the experimental values of EC_{50} (the effective concentration resulting in 50% reduction of processes) vary as follows: 500 and 1170 μM for the cell cultures HeLa and IPC-81, respectively;

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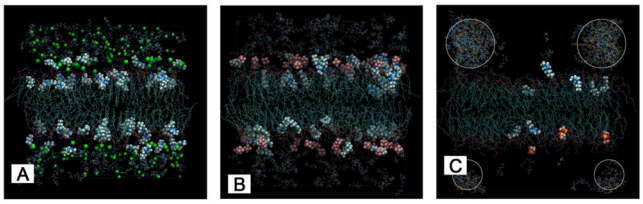

Figure 11. $[C_4MIM][Cl]$ (A), $[C_4MIM][PF_6]$ (B), and $[C_4MIM][NTf_2]$ (C) in the phospholipid bilayer. Figures reproduced with permission from ref 242. Copyright 2012 American Chemical Society.

30 μmol kg^{-1} dry weight soil for reproduction inhibition of the springtail *Folsomia candida*; 50 μM for reproduction inhibition of the alga *Scenedesmus vacuolatus*; and 380 μM for growth inhibition of the freshwater plant *Lemna minor*. The 24-hour minimum inhibitory concentrations (MIC) of the IL for various fungi and Gram-positive and Gram-negative bacteria exceed 500 μM.[217] Similar trends are observed for other ILs, such as $[C_4MIM][Br]$ (48-h EC_{50} 2692 and 2750 μM for the IPC-81 and HeLa cells, respectively; 48-h LC_{50} 70 μM for the crustacean *Daphnia magna*; 96-h LC_{50} 5887 and 1045 μM for the zebra mussel *Dreissena polymorpha* and freshwater snail *Physa acuta*, respectively; 96-h EC_{50} (growth inhibition) 102 and 110 μM for the green algae *Scenedesmus obliquus* and *Chlorella vulgaris*, respectively; 4-d LC_{50} 9800 μM for the marine macroalga *Ulva lactuca*; and 15 min EC_{50} (luminescence inhibition) 3359 μM for the Gram-negative marine bacterium *Vibrio fischeri*), $[(C_4)_4N][Br]$ (48-h EC_{50} 178 μM for the IPC-81 cells; 96-h LC_{50} 1800 μM for *Physa acuta*; and 15 min EC_{50} (luminescence inhibition) 1862 μM for *Vibrio fischeri*), and $[C_1C_4Pyr][NTf_2]$ (48-h EC_{50} 1000 μM for the IPC-81 cells; 48-h LC_{50} 88 μM for *Daphnia magna*; 72-h EC_{50} (growth inhibition) >237 μM for *Scenedesmus capricornutum*; EC_{50} (growth inhibition) 955 μM for *Lemna minor*; and 30 min EC_{50} (luminescence inhibition) 350 μM for *Vibrio fischeri*).[217]

In the subsequent sections 2.2–2.5, we discuss particular aspects of biological activity of ILs important for the topic of this Review. Note that these sections provide data on common ILs, which are most often used in chemical research and industry. ILs with tailored biological activity are discussed later in section 3.

2.2. Ionic Liquids as Antibacterial and Antifungal Agents

Antimicrobial activity of ionic liquids has quickly attracted the attention of researchers. When it became obvious that numerous types of ILs inhibited growth of various bacterial and fungal species, the medical and industrial potentials of ILs have manifested.

Imidazolium, pyridinium, pyrrolidinium, piperidinium, ammonium, and other ILs were shown to inhibit growth of pathogenic and nonpathogenic bacteria and fungi.[217,244−257] These results have presented both advantages and disadvantages. Thus, high activity toward microorganisms may seriously hinder the application of ILs in biotechnology; however, it may be used as a valuable property in medicine (Figure 12).

From the biotechnological point of view, toxicity of new IL solvents may become a serious problem, and evaluation and selection of appropriate ILs for various biotechnological processes have been actively investigated lately.[258−261] Imidazolium ILs were shown to be toxic toward the probiotic bacterium *Propionibacterium freudenreichii* subsp. *freudenreichii* applied in the dairy industry,[262] whereas pyridinium ILs inhibited *Clostridium* sp. involved in biosorption of uranium.[263] Residual 1-ethyl-3-methylimidazolium acetate ($[C_2MIM][OAc]$) in

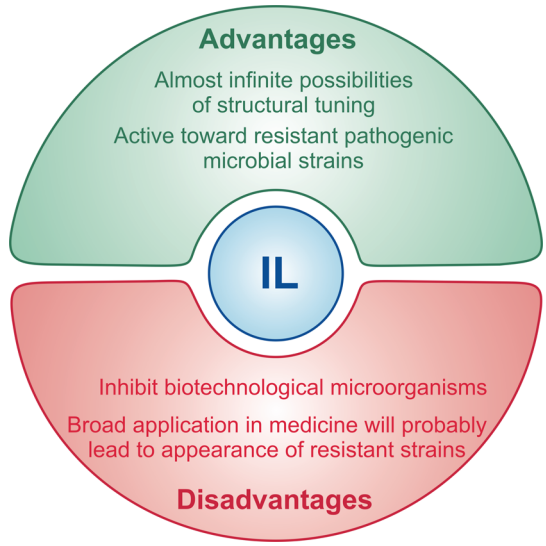

Figure 12. Graphic summary of current advantages and disadvantages of using ionic liquids as antimicrobial agents.

hydrolysates of pretreated lignocellulose biomass inhibited growth and ethanol production of the model yeast *Saccharomyces cerevisiae*.[264] Addition of either 1-ethyl-3-methylimidazolium acetate or 1-ethyl-3-methylimidazolium methylphosphonate in small quantities (≤5%) led to a metabolic switch from respiration to fermentation (ethanol production);[265] in higher concentrations, both ILs inhibited the yeast growth.[265,266]

The lignocellulolytic bacterium *Enterobacter lignolyticus* was tolerant to high concentrations of $[C_2MIM][Cl]$, possibly due to changes in the cell membrane composition, down-regulation of membrane porins, and up-regulation of drug efflux pumps.[267,268] Correspondingly, a method for tolerance enhancement via heterologous expression of efflux pumps in bacteria was proposed,[269] and a technique for enrichment of IL-tolerant microorganisms in microbial communities was suggested.[270] Interestingly, a single mutation in a transcriptional regulator made *Escherichia coli* tolerant to $[C_2MIM][OAc]$.[271] $[C_4MIM][PF_6]$ and $[C_4MIM][NTf_2]$ were considered compatible with whole-cell biotechnological applications.[272] *Penicillium* sp., the specimen of which could produce valuable bioactive substances, demonstrated very high tolerance to IL treatment; in some cases, even 50 mM of IL did not inhibit the growth of the fungi.[273] *Aspergillus* isolates were tolerant to $[C_2MIM][OAc]$.[274] Morpholinium ILs demonstrated low toxicity toward bacteria and fungi.[275] Thus, a search for IL-tolerant valuable microbial communities is ongoing.[276]

From the medical point of view, ever-evolving resistance of microorganisms to the existing drugs is an urgent issue, and a whole new class of possible antimicrobial agents is a very timely finding. Targeted attempts to develop antimicrobial ILs for medical purposes have been made. Thus, comparison of activity of ampicillin-carrying ILs with that of sodium ampicillin clearly showed possible advantages of using ILs as antimicrobial agents.[277] More examples of ILs with targeted antimicrobial activity are discussed in section 3.4.

ILs have demonstrated impressive inhibitory results even in the case of resistant and biofilm-forming microorganisms. Low concentrations of $[C_{16}MIM][Cl]$ strongly inhibited growth of multidrug-resistant *Candida tropicalis*,[278] whereas 1-alkyl-3-methylimidazolium chlorides, bromides, and iodide were active toward both planktonic and biofilm bacteria and fungi.[279−281] 1-

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Alkyl-3-methylimidazolium fumarates possessed high antimicrobial potential and were suggested to be used for medical purposes.[282] Ammonium ILs with azolate anions were found to be powerful antibacterial and antifungal substances;[283] hydroxylammonium ILs were highly active against such human pathogens as *Staphylococcus aureus*, *Salmonella typhi*, and *Vibrio cholera*,[284] whereas diphosphohium ILs displayed a broad spectrum of antimicrobial activity against ocular pathogens.[285] Of note, triphenylamine phosphonium ILs, which self-assembled into nanostructures, showed potent activity against Gram-positive bacteria, including *S. aureus*.[286]

However, possible negative effects associated with broad application of ILs in medicine should not be overlooked. While increased IL tolerance is a benefit in biotechnologically relevant microorganisms, in pathogenic bacteria and fungi it may become a significant difficulty. It seems that, similarly to conventional antimicrobial agents, ILs also may provoke the appearance of resistant strains. Thus, $[C_4MIM][PF_6]$ was shown to induce the expression of antibiotic resistance genes and to activate horizontal gene transfer in freshwater bacteria.[287] Of note, cholinium chloride ([Cho][Cl]) and $[C_2MIM][Cl]$ significantly influenced the expression of genes involved in primary and secondary metabolism in *Aspergillus nidulans*; the authors suggested the treatment with ILs to be employed for boosting the diversity of natural active compounds produced by the fungus.[288]

As we discuss in section 2.5, high antimicrobial activity of many ILs may be possibly explained by interactions between IL and the cell membrane.[49,259,289,290] Thus, alkyltributylphosphonium chlorides with long alkyl chains provoked substantial damage in conidia of *A. nidulans*.[291] For imidazolium ILs with short alkyl chains, the toxicity was found to depend on the chaotropicity of the anion.[292]

Antimicrobial properties of ILs were suggested to be employed in the development of new IL fungicides,[293] and in the protection of natural fabric,[294] paper,[295] and metal surfaces[296,297] against microbial growth. Similarly, graft polymers of poly(ionic liquids) were proposed to be used in antibacterial coatings.[298,299] Alkoxymethyl(2-decanoyloxyethyl)dimethylammonium bis(trifluoromethylsulfonyl)amides and 1-methyl-3-octyloxymethylimidazolium tetrafluoroborate performed good in preservation and fixation of tissues.[245,300,301] Attempts to create imidazolium-based poly-IL membranes with improved antibacterial activity have been made.[302]

2.3. Ionic Liquids as Anticancer Agents

Cytotoxicity of a substance is a form of its biological activity, and numerous studies on cytotoxicity of ionic liquids toward various cells have been reported. Both normal and cancerous cells of invertebrate and vertebrate species were investigated, including insects (S2, *Drosophila melanogaster* cell culture),[303] fish (CCO, channel catfish ovary cell line),[304−306] mouse (3T3, fibroblasts;[307,308] EMT6, mammary cell line;[309] J774, macrophages;[310] MC3T3-E1, osteoblasts[311]), rat (C_6, glial cells;[257,312] IPC-81, promyelotic leukemia;[234,275,312−317] PC12, pheochromocytoma[318−320]), Chinese hamster (V79, lung fibroblasts),[321] and human (3215 LS, fibroblasts;[322] A549, lung carcinoma;[323−325] A431, squamous carcinoma;[326] CaCo-2, colon carcinoma;[308,322,327−332] HaCaT, immortalized keratinocytes;[333] HCT-116, colon carcinoma;[323,324,326,334] HEK, embryonic kidney;[257,335] HeLa, cervical cancer;[304,336−339] HepG2, hepatocyte carcinoma;[332,334,340] HT-29, colon carcinoma;[323,324,326,328] MCF-7, breast cancer;[323,324,326,334,341−344] T98G, brain cancer;[335] U937, histiocytic lymphoma;[345] and other[323,324,326]).

There are several methods for assessing cytotoxicity of a chemical, and the MTT assay is among the most popular. It is based on detecting the activity of mitochondrial enzymes, which reduce the tetrazolium dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) or the related MTS, XTT, and WST dyes.[346] Preliminary studies on the mechanism of IL cytotoxicity have also been carried out. By using fluorescence microscopy and dedicated apoptosis assays, ILs were shown to induce oxidative stress, DNA damage, and apoptosis in the cells.[307,308,319,320,326,338,340]

The cytotoxicity of ILs depends on their structure and varies widely, from micromolar to millimolar ranges. Thus, cholinium ILs in general demonstrated lower cytotoxicity than ILs with other common cations, such as imidazolium and pyridinium. Several attempts to create a prediction model for assessing IL cytotoxicity in silico have been made;[329,347−351] however, at the moment, there is no possibility to distinguish the cytotoxicity of ILs only by their structure, because it also strongly depends on the external factors, such as the cell type.[217]

When the cytotoxic activity of ILs has become evident, studies on possible application of ILs as anticancer agents have begun. Once again, the high tunability of ILs has become the major driving force of research: an idea of creating therapeutic agents with tailored anticancer activity and reduced toxicity toward the human organism seems very attractive.[323,324] Nevertheless, despite active investigations in the area, our knowledge on the possibility of using ILs as anticancer agents remains incomplete (Figure 13).

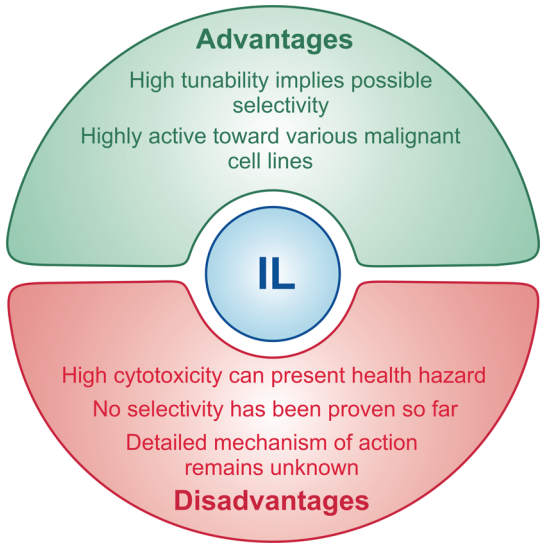

Figure 13. Graphic summary of current advantages and disadvantages of using ionic liquids as anticancer agents.

A screening of imidazolium, phosphonium, and ammonium ILs in 60 human tumor cell lines was conducted in search of potential anticancer substances with high cytostatic and low cytotoxic activity.[323,324,326] Guanidinium ILs with long alkyl chains showed high cytotoxicity toward several tumor cell lines.[352] While searching for environmentally safe ILs, it was demonstrated that introduction of natural amino acids into ILs with the tetrafluoroborate anion led to an unexpected increase of their cytotoxicity, possibly due to the enhancement of transport of the toxic anion into the cells.[308] Still, almost no attempts to

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Chem. Rev. 2017, 117, 7132−7189

compare the cytotoxic effect of ILs on tumor and normal cells have been made so far.

Triethylammonium sulfate, triethylammonium phosphate, 1-methylimidazolium chloride, and 1-butyl-3-methylimidazolium chloride were less toxic toward nonmalignant HEK (human embryonic kidney) cells than toward T98G brain cancer cells.[335] However, no significant difference was found for cytotoxicity exhibited by imidazolium-based ILs toward normal human fibroblasts and CaCo-2 (colorectal adenocarcinoma) cells,[322] which indicated that the IL effect was nonselective.

Accumulated data on mechanisms of IL cytotoxicity suggest that ILs disturb lipid bilayers of the cell membrane, and hydrophobicity and lipophilicity of the cation correlate with the cytotoxic action.[307,314,315,318,345,353,354] Treatment with 1-alkylquinolinium ILs caused cell membrane disruption in the 3T3 cells.[307] Imidazolium ILs induced mitochondrial failure, oxidative stress, and apoptosis both in malignant and in normal cells.[308,319,320,326,338,340] In the mouse mammary carcinoma cells EMT6, treatment with 1-octyl-3-methylimidazolium chloride ($[C_8MIM][Cl]$) induced expression of cytochrome P450 genes, products of which were involved in metabolism of drugs and other exogenous substances.[309] In HeLa cells, imidazolium ILs induced the multixenobiotic/multidrug resistance (MXR/MDR) system.[339]

Apparently, the mechanism of action is the current stumbling block of studies on anticancer properties of ILs. It will be impossible to design novel ILs with targeted antitumor activity until we know the details of transformations and actions displayed by ILs inside both the malignant and the normal cells.

2.4. Biodegradation of Ionic Liquids

Wide application of ionic liquids in chemistry, biochemistry, and industry inevitably results in their contact with the environment. From the point of view of ecological safety, chemical compounds should be easily degradable and should decompose into harmless substances that do not accumulate in the environment.[355,356] Biodegradability of ILs is a hot research topic,[103,357,358] and in this section we sum the current knowledge on natural possibilities to decompose ILs.

Biodegradation is realized by bacterial or fungal enzymes and leads to destruction of a chemical structure with corresponding loss of its properties. There are several categories of biodegradability of a substance: primary (the ability to lose a particular structural feature); inherent (the ability to undergo biodegradation); ready (the ability to biodegrade a given % during a given time period, suggesting the possibility of ultimate complete biodegradation); ultimate (the ability to breakdown completely); and mineralization (the ability to decompose into plant-accessible molecules).[103,357] Substances are classified as "readily biodegradable", if they have demonstrated the ability to biodegrade ultimately and completely; those that have not passed ready biodegradation tests, but nevertheless have demonstrated clear evidence of partial biodegradation, are classified as "inherently biodegradable".[358] The Organization of Economic Co-Operation and Development (OECD) proposes standard assays for assessment of the substance biodegradability, which include aerobic and anaerobic conversion in soil, aquatic sediment systems, and surface water.[359] Ready biodegradation tests employ strict conditions and are not very realistic regarding a typical environment, whereas inherent biodegradation tests use less constrained conditions and therefore correspond better to the real environment.[358]

There are several general factors that facilitate or hamper biodegradability of a compound. Thus, the presence of long unsubstituted alkyl chains, oxygen atoms (hydroxyl, aldehyde, or carboxylic groups), sites for enzymatic hydrolysis (ester or amide bonds), and aromatic rings promote biodegradability, whereas branched alkyl chains, quaternary carbon or tertiary nitrogen atoms, halides, and heterocycles hinder biodegradation.[103,360]

Existing data suggest that ILs with long alkyl side chains are more readily biodegradable but possess higher antimicrobial activity.[103,361,362] For example, the 1-octyl-3-methylimidazolium cation was readily biodegradable by microbial community of a sewage treatment plant (Jeonju, Korea). The biodegradation process started with oxidation at one of three points in the alkyl chain, and the resulting oxidized compounds could initiate three different degradation pathways.[363] 1-Ethyl-3-methylimidazolium and 1-butyl-3-methylimidazolium ILs showed negligible biodegradability[272,364−368] and were suggested to be subjected to electrochemical treatment prior to biodegradation.[369] Peralkylated and dicationic imidazolium ILs also were not readily biodegradable.[317,368,370]

The introduction of target groups for enzymatic hydrolysis, such as esters, especially with long alkyl chains, substantially enhanced the biodegradability of imidazolium ILs,[364,366,371] whereas the introduction of oxygen groups reduced their antibacterial activity.[371] The presence of long alkyl chains in the anion, for example, in alkylsulfates, also correlated with better biodegradability, whereas halogen-containing anions, such as chlorides, bromides, tetrafluoroborates, and hexafluorophosphates, as well as fluoroorganic and cyano-based anions, could not act as carbon source and therefore did not undergo biodegradation.[103,365,366,369,372−374]

3-Methyl-1-propoxycarbonylimidazolium, 2,3-dimethyl-1-propoxycarbonylimidazolium, 3-methyl-1-pentoxycarbonylimidazolium, and 2,3-dimethyl-1-pentoxycarbonylimidazolium octyl sulfates were readily biodegradable;[366] the same was observed for imidazolium ILs containing alkyl side chains with butoxy or propoxy termini and the octyl sulfate anion, whereas ILs with methoxy or ethoxy termini showed lower biodegradability.[375] 1-Butyl-3-methylpyridinium, 1-hexyl-3-methylpyridinium, and 1-octyl-3-methylpyridinium bromides could be fully mineralized by microbial community, but only 1-octyl-3-methylpyridinium bromide was readily biodegradable.[367,376]

A study on biodegradability of 27 ILs with imidazolium, pyridinium, pyrrolidinium, piperidinium, and morpholinium cations demonstrated that each IL class included readily biodegradable members. Good biodegradability was usually associated with the presence of a long unbranched alkyl side chain or hydroxyl-bearing side chain.[377] According to a recent review, several dozens of readily biodegradable ILs have been synthesized to date, and almost 50% of them contain cholinium as cation and an organic acid as anion.[103] Amino acid-based ILs with the lauryl sulfate anion also demonstrated high biodegradability.[378] Conventional imidazolium ILs,[272,364−368,377,379−382] as well as most tetraalkylammonium,[313,382,383] morpholinium,[251,275,377] piperidinium,[377] and pyrrolidinium ILs,[103,357,383] are mostly resistant to biodegradation. Examples of highly and poorly biodegradable ILs are shown in Figure 14.

It also should be noted that the choice of a microorganism can significantly impact the biodegradation. Thus, by using the bacteria *Sphingomonas paucimobilis*, the ILs, which were previously shown to be resistant to degradation, were biodegraded successfully.[384]

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Chem. Rev. 2017, 117, 7132−7189

Cationic head group	Side chain (R)	Anion	Biodegradation potential
Imidazolium	$-C_2H_5$	Cl^-	Not readily
	$-C_3H_7$	PF_6^-	Not readily
	$-C_4H_9$	Cl^-	Not readily
	$-C_8H_{17}$	Cl^-	Inherently
	$-CH_2C(=O)OCH_2CH_3$	Br^-	Inherently
	$-CH_2CH_2OH$	I^-	Not readily
	$-CH_2OCH_2CH_3$	Cl^-	Not readily
Pyridinium	$-C_2H_5$	Cl^-	Not readily
	$-C_3H_7$	Br^-	Not readily
	$-C_4H_9$	Br^-	Not readily
	$-CH_2CH_2OH$	Cl^-	Inherently
	$-CH_2CH_2OH$	I^-	Inherently and ultimately
Pyrrolidinium	$-C_4H_9$	Br^-	Inherently and ultimately
	$-C_8H_{17}$	Cl^-	Readily
	$-CH_2CH_2OH$	I^-	Not readily
	$-CH_2C(=O)OCH_2CH_3$	Br^-	Inherently and ultimately
Morpholinium	$-C_4H_9$	Br^-	Not readily
	$-CH_2CH_2OH$	I^-	Not readily
	$-CH_2CH_2CH_2OH$	Cl^-	Inherently
	$-CH_2OCH_2CH_3$	Cl^-	Not readily

Figure 14. Biodegradation potential of exemplary ionic liquids using the original OECD classification of biodegradability (note that it can depend on the evaluation method). "Readily biodegradable" are substances that have passed a ready biodegradation test and have demonstrated the ability to biodegrade a given % during a given time period; "inherently biodegradable" are substances that have demonstrated the ability to biodegrade in an inherent biodegradation test; and those for which such biodegradation is complete are called "inherently and ultimately biodegradable"; "not readily biodegradable" are substances that have not passed a ready biodegradation test and have shown no evidence of inherent biodegradability. Figure concept and data reproduced with permission from ref 377. Copyright 2014 Royal Society of Chemistry.

Several methods of chemically induced degradation of nonbiodegradable ILs have been suggested. These approaches employ electrochemical degradation[369,385,386] or advanced oxidation processes, such as UV/H_2O_2 oxidation,[387] ultrasonic treatment,[388−390] ozonation,[391] and the Fenton oxidation.[390,392,393] In many cases, such pretreatment allows significantly decreasing ecotoxicity and increasing biodegradability of various structural classes of ILs.[103]

As is evident from this section, a considerable part of the existing ionic liquids is nonbiodegradable. Therefore, the issue of their interaction with the environment is of high importance, and we discuss it in the next section.

2.5. Toxicity and Environmental Effects

The number of possible cationic−anionic combinations is virtually unlimited, and, unsurprisingly, a natural IL was discovered. This IL forms when solenopsins from the venom of the ant *Solenopsis invicta* mix with formic acid from the venom of its competitor, the ant *Nylanderia fulva*. Thus, *N. fulva* detoxifies the opponent's venom by means of IL synthesis.[394] Still, not every IL is safer than its precursors, and by now ILs have been shown to influence all levels of life (Figure 15).[233−235] Several recent reviews discuss the subject of IL ecotoxicology in detail;[217,222,395] here, we will mention only the major issues.

There is no uniformity in toxic activities exhibited by ILs. Some of them demonstrate relatively low toxicity, whereas others

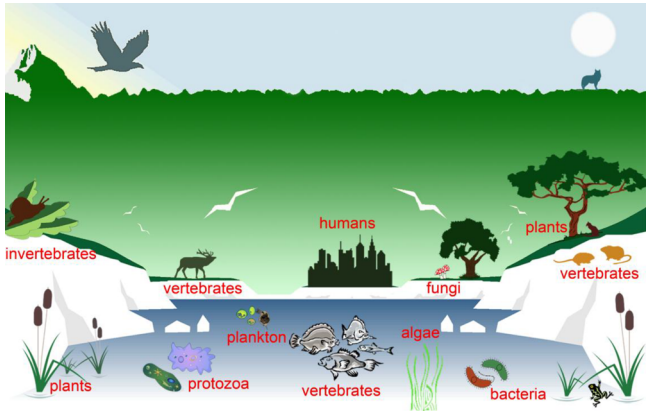

Figure 15. Ecosystems vulnerable to contamination by ionic liquids. Reproduced with permission from ref 217. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.

impose significant inhibitory effects in various biological systems. Presumably, higher water solubility should correlate with higher environmental danger due to ease of penetration of a water-soluble chemical into various ecosystems. This suggestion is corroborated by the evident interrelation between the biological effect of IL and its interactions with water molecules (see sections 2.1 and 4.1). Many studies have been aimed at finding relationships that link the IL structure to its toxicity. Although no general correlations have been discovered so far, several trends have been revealed. Thus, according to the accumulated data, the IL toxicity depends on (1) the length of alkyl side chain in the cation; (2) the presence and nature of functional groups in the cation; (3) the anion and cation nature; and (4) interactions between anion and cation. It is also clear that the nature of the biological object should be taken into account.[217]

From the environmental point of view, research on multicellular organisms and whole ecosystems provides the best estimation of the ecological impact of a substance. Thus, the influence of ILs has been investigated in plants,[235,321,396−410] fish,[411−420] rodents,[421−427] mollusca,[428−430] worms,[431−438] and crustaceans.[235,317,318,439−443] The small planktonic crustacean *Daphnia magna*, one of the favorite objects of ecologists, proved to be rather sensitive to imidazolium and phosphonium ILs.[317,318,439−442] Imidazolium ILs provoked developmental damage,[421,425] whereas ammonium ILs induced acute and subacute toxicity[423,426,427] in mice and rats. Imidazolium ILs caused oxidative stress and growth inhibition in aquatic algae[399,401−404,444] and terrestrial plants.[396,397,400,405,407] Similar results in plants were obtained for ammonium ILs.[406,408] Even cholinium ILs, which were supposed to be relatively safe due to the natural origin of the cation, exhibited toxicity toward *Daphnia magna* and the common duckweed *Lemna minor*.[445]

Because multicellular organisms are rather problematic and time-consuming objects, which usually do not allow conducting high-throughput screening, many toxicological studies have been carried out on bacteria, fungi, and cell cultures. High antimicrobial, antifungal, and cytotoxic activity of many ILs (see sections 2.2 and 2.3, respectively) may be explained by interactions between alkyl side chains of the IL cation and the membrane of the cell. Long alkyl chains may destabilize the membrane by penetrating into the lipid bilayer and inducing structural damage.[255,283−285,307,314,315,318,345,353,446,447] According to molecular simulations, imidazolium cations formed hydrophobic contacts with the phosphatidylcholine lipid bilayer,

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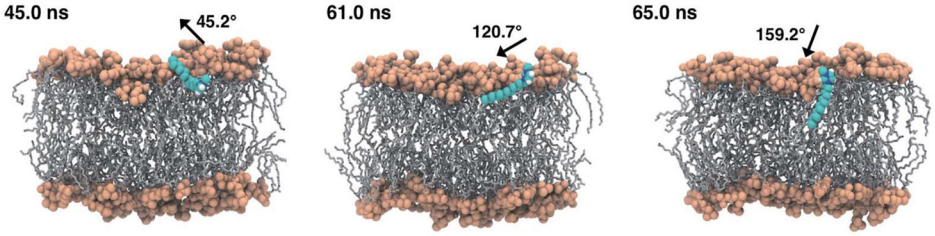

Figure 16. Penetration of the cation of $[C_{12}MIM][Cl]$ into the lipid bilayer. Reproduced with permission from ref 446. Copyright 2014 Royal Society of Chemistry.

entered into it, and subsequently caused roughening of its surface (Figure 16). After partial insertion of the imidazolium ring into the bilayer, the IL cation flipped to bring the whole alkyl chain into the hydrophobic area. Regardless of the alkyl side chain length (n = 4, 8, 12), the imidazolium ring and alkyl chain demonstrated strong interactions with the lipid head and tail group, correspondingly; however, the cations with longer alkyl chains penetrated deeper into the bilayer. In contrast to the cation, the hydrophobicity of the anion did not correlate with the structural transformations of the lipid bilayer.[446] Upon reaching the saturation limit for the insertion of the IL cations, the membrane began to arch, therefore maximizing the area of contact between the lipid and IL. Such bending supposedly caused subsequent morphological defects.[448] Asymmetric insertion of the IL cations into the lipid bilayer caused morphological transformations.[449] The presence of oxygen in the side chain hindered the cation insertion,[243] which agreed with lower toxicity of such ILs.[217,318,345]

Empirical molecular dynamics simulations of a neutral cholesterol lipid bilayer in the water solution of $[C_4MIM][Cl]$ and $[C_4MIM][NTf_2]$ demonstrated that both ILs adsorbed selectively at the water−cholesterol interface, and the ions penetrated partially into the bilayer. $[C_4MIM][Cl]$ is highly soluble in water, and the $[C_4MIM]^+$ cations adsorbed at the cholesterol−water interface, whereas the butyl side chains entered the bilayer. $[C_4MIM][Tf_2N]$, which possessed lower water solubility, formed a thick IL film at the water−cholesterol interface. The hydrophobic $[NTf_2]^-$ anions easily penetrated into the cholesterol bilayer, which resulted in limited inclusion of the cation imidazolium rings and reduced penetration of the butyl side chains into the cholesterol. It should be noted that upon the contact with the cholesterol bilayer, NaCl and LiCl solutions demonstrated very restrained interactions between the ions and the organic part of the system; that is, the affinity of the bulky organic ions of ILs to the bilayer was governed by dispersion interactions and hydrophobic/hydrophilic effects.[450]

Incorporation of imidazolium ILs into lipid bilayers had an impact on activities of membrane proteins. By decreasing the membrane deformation energy, ILs increased the lifetime of transmembrane channels; positive charges, which accumulated on the membrane surface in the presence of ILs, hindered the cation flux.[451,452] According to another study, $[C_4MIM][Cl]$ significantly decelerated the translocation of DNA and antibiotics through protein and graphene nanopores.[453,454]

These theoretical results were supported by experimental data obtained on model lipid membranes,[49,318,345,353,455−457] cell cultures,[307] fungi,[291] worms,[434] and the single-cell green alga *Chlamydomonas reinhardtii*, where ILs manifested their toxicity via cell membrane swelling with subsequent disruption; longer alkyl side chains penetrated into the membrane more easily and therefore displayed more pronounced cytotoxicity.[448]

The toxicity of ILs also may depend on interactions with more specific targets. For example, 1-alkyl-3-methylimidazolium bromide/hydroxide ILs with different alkyl side chains demonstrated the $\pi-\pi$ stacking interaction with phenyl rings of the β-tubulin receptor. According to molecular docking studies, the alkyl side chain of the imidazolium core influenced the binding of ILs to the receptor and therefore the vermicidal activity of these ILs. Thus, longer side chains correlated with higher vermicidal activity.[434] In cells expressing human organic cation transporter 2 (hOCT2), $[C_1C_4Pyr][Cl]$ was shown to inhibit hOCT2-mediated transport processes.[424]

Although this evidence betrays the hopes of ILs to be ecologically safe reagents, they also suggest both nonspecific and specific mechanisms of IL biological action, which can potentially be used in the development of IL-based biochemical and pharmaceutical agents (see section 3.4).

3. IONIC LIQUIDS AS COMPONENTS OF DRUG FORMULATIONS

3.1. Problems of Conventional Drugs: Low Solubility, Limited Bioavailability, and Polymorphism

The efficiency of a drug depends strongly on its bioavailability, which, in the case of the human organism, relates directly to drug permeability and solubility. Because physiological accessibility of a drug often implies its dissolution in the body liquids, lower solubility results in lower dissolution and absorption rates. Therefore, higher doses are required for reaching a therapeutic effect.[458−460] Limited water solubility and low dissolution rate are among the major problems of modern drug development, especially for drugs that are delivered into the organism orally, which is one of the most common and easy administration routes. It should be noted that dissolution and solubility are different properties of a drug: the solubility reflects the ability of a compound to dissolve in a given solvent, whereas dissolution is a process per se and is characterized by rate.

Pharmaceutical substances are often obtained in a crystal form, which leads to another complication: polymorphism. Thus, one crystalline chemical can exist as several polymorphs or pseudopolymorphs with different properties, for example, mechanical characteristics, stability, melting point, solubility, and bioavailability. Moreover, pharmaceutical polymorphs can undergo unpredictable interchanges, and their formation is difficult to control.[458,461,462]

There are numerous approaches for improving drug formulations, and the methodology is being updated regularly. The existing methods may be divided into those that imply chemical modification of a drug and those that do not. The first ones suggest the formation of drug salts and derivatives, for example, prodrugs, whereas the second ones include crystal engineering techniques for controlled crystallization, comminu-

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tion for decreasing the particle size of a drug, preparation of hydrates and solvates, cocrystallization, micellization or dispersion, and employment of alternative solvents and cosolvents (Figure 17).[231,459,460,463−467]

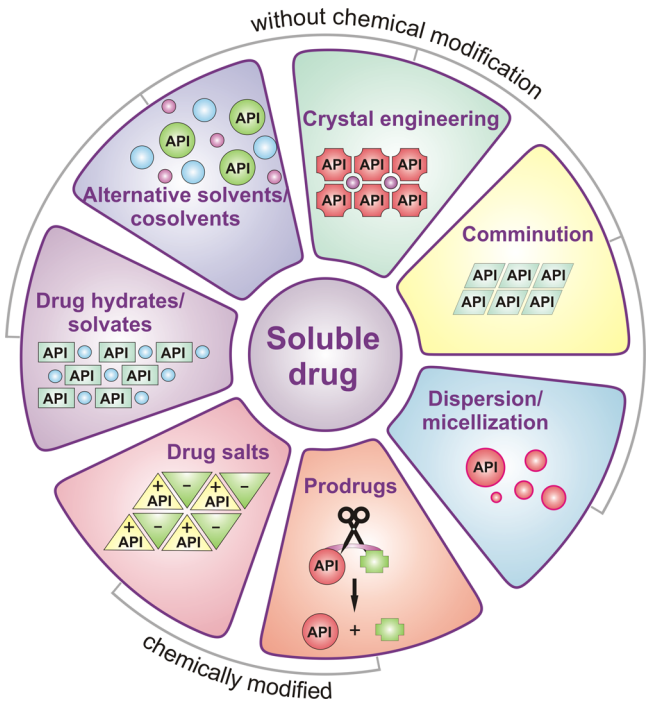

Figure 17. Main approaches to improve drug solubility: crystal engineering, comminution, preparation of hydrates and solvates, dispersion/micellization, and usage of alternative solvents/cosolvents do not imply chemical modifications of the drug structure, whereas formation of drug salts and prodrugs does.

Among the most popular strategies, decreasing the particle size of a drug is a very common approach for increasing its solubility and dissolution rate due to expansion of the surface area, which contacts with the solvent. The existing methods allow one to obtain nanoscale particles and nanocrystals.[460,468]

Another common approach is disturbing or disrupting the crystal lattice by using salts and cocrystals. If a drug is an ionizable substance, turning it into a salt is usually the easiest way to significantly increase its solubility and dissolution rate, although it should be remembered that soluble salts are often unstable and are subject to fast hydrolysis.[469] The choice of a counterion may strongly influence the solubility and dissolution rate of a compound; thus, the solubility and dissolution rate of hydrochloride salts may drop in the stomach because of the presence of endogenous chloride ions (common-ion effect). Therefore, in some cases, basic drugs may demonstrate higher dissolution rates than salts at gastric pH.[465]

If a drug cannot be ionized, cocrystals may be used. There is no conventional definition of a cocrystal, but it can be described as crystalline matter, which includes at least two constituents. One of disadvantages of the cocrystal strategy is that upon dissolution the released free drug may form a supersaturated solution and may precipitate.[464] Amorphous solid dispersions, which contain polymer carriers for stabilizing an amorphous drug, are also used for improving solubility and bioavailability of pharmaceutical agents; moreover, this strategy alleviates the problem of polymorphism.[466] However, amorphous preparations are prone to spontaneous crystallization.[470]

Another way to increase the solubility of a drug is using solubilizing attachments, charged, or polar groups, which are added to the drug molecule so that its active part stays intact. The most popular solubilizing groups are amines, including cyclic ones, which can also be used for salt formation. If charged moieties are undesirable, amides or hydroxyl groups may be employed.[471]

One of the latest and most promising strategies for improving solubility and bioavailability of medications is prodrugs. A prodrug is a chemically modified drug, from which the active substance is released in the organism. A good prodrug possesses negligible activity, but high water solubility and stability; it permeates through cell membranes efficiently, does not undergo hydrolysis during absorption, and releases the active part readily at the place of action. The prodrug strategy allows enhancing lipophilicity, solubility, stability and period of action of a parental pharmaceutical molecule, as well as relieving its toxicity and promoting its target delivery. There are two main categories of prodrugs: carrier-linked prodrugs and bioprecursors. The former consists of a drug part and a carrier, optionally linked via a spacer; the latter are inactive substances without carrier, which transform into an active substance in the organism.[472] In most cases, simple chemical or enzymatic changes are needed to turn a prodrug into an active drug. Depending on the functionality present in the parent drug molecule, various prodrug structures can be employed: esters, amides, oximes, and substances with disulfide bridges.[472−475] Among the most interesting potentials of prodrugs is their employment in target delivery. A drug molecule may be conjugated with a specific antibody, peptide, or agonist.[476] Prodrugs may selectively target cell membrane transporters in intestinal enterocytes and specific organs.[474,477] The parent drug may be released by specific enzymes active only in specific organs/tissues.[477] Several prodrug approaches have been suggested for "difficult cases", such as surmounting the blood brain barrier and targeting tumors.[476,478,479] Recently, a promising strategy on employing quarternary ammonium-based bioreversible linkages for connecting tertiary or heteroaryl amines, which are often present in therapeutic agents, to carrier proteins has been proposed as an instrument for target drug delivery. This strategy has also allowed significantly decreasing hydrophobicity of drugs upon conjugating with the linker, which can be proteolytically or reductively cleaved upon entering the target cell.[480]

Limitations of traditional drugs have led to the development of sophisticated encapsulation strategies for efficient delivery and prolonged release of active pharmaceutical ingredients at the destination. These strategies suggest using polymeric nanoparticles and micelles, lipid nanoparticles, liposomes, and nanotubes as colloid delivery carriers.[481−483] The drug may be covalently linked to the nanoparticle or physically incorporated inside it, whereas amphiphilic drugs and prodrugs may self-assemble into nanoparticles without additional emulsifiers. The surface of a nanoparticle may bear specific targeting molecules, for example, antibodies or cell-penetrating peptides.[478,484−486]

The cost of a drug is directly related to its ability to form polymorphs and to dissolve in the aqueous media. Nevertheless, despite obvious problems with solid drug formulations, the vast majority of medicinal substances are solids, whereas liquid formulations are very rare and are based on eutectic mixtures.[223] Approximately one-half of modern drugs are salts.[487] The development of pharmaceutically active "liquid salts" presents a good opportunity to alleviate polymorphism and solubility issues.

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3.2. Benefits of Ionic Liquids in Drug Development

Considering numerous unique properties of ionic liquids, it is not surprising that they have drawn the attention of biomedical research not only as convenient catalytic media for drug synthesis, but also as potential components of drug formulations. To date, several notable reviews have emphasized the advantages of using ionic liquids in medicine chemistry.[61,218,223,224,228−230]

Initial optimistic expectations for ILs to be "green", environmentally friendly chemicals have been replaced by understanding that ILs possess high toxic potential, which may influence the environment significantly.[217] However, high biological activity of ILs may be seen not only as disadvantage, but also as opportunity. Several years ago, ionic liquid salts of active pharmaceutical ingredients were proposed to become an alternative to common crystalline salts.[106,218,223,225]

What exactly makes ILs an interesting and beneficial object of study for medical reasons? As we have discussed in the previous sections, ILs are chemicals with an astounding fine-tuning potential: the number of possible IL combinations is about 10^{18}, and this is not the limit.[163] Thus, one may create an IL with practically any properties, including good water solubility, improved absorption, desired dissolution rate, and even targeting ability. Application of active pharmaceutical ingredients (API) in an ionic liquid form (API-ILs) also would solve the problem of polymorphism.[223,228,230] Still, not every conventional drug can be turned into an ionic liquid salt, and new approaches for relieving the solubility and delivery issues are constantly demanded. Thus, apart from API-ILs, other possible applications of ILs in drug research and development include their employment as adjuvant agents for solubility enhancement and drug delivery.

In the following sections, we describe the recent progress in the application of ionic liquids in medicine formulations and delivery.

3.3. Ionic Liquids as Adjuvant Components in Drug Delivery

Striking solvent abilities of ionic liquids are widely known and are being exploited in extraction[81,85,87,166,488−490] and dissolution of biomolecules.[36,37,95,491−494] ILs can enhance water solubility of hydrophobic compounds, possibly due to formation of aggregates between ILs and biomolecules.[495] Experimental data and molecular dynamics simulations suggest that upon dissolution in water, the continuous polar network, which is found in most pure ILs, disrupts into smaller domains; therefore, water solutions of ILs resemble a water matrix with incorporated ionic filaments (see also section 1.2). The anions in these filaments form hydrogen bonds with the water molecules, which stabilize the IL filamentous structure in the water solution. Addition of the model biomolecule vanillin to the system does not lead to the disappearance of the IL filaments, whereas vanillin molecules form cation−vanillin clusters via dispersion forces and other specific interactions, such as hydrogen bonds and $\pi-\pi$ interactions, and mix with water more readily (Figure 18).[495] Other studies support the correlation between excellent solubilizing properties of ILs and their ability to form numerous interactions with the solute.[496−498] Thus, cholesterol underwent self-assembly and formed ordered mesoscopic structures in the nanostructured tetrabutylphosphonium carboxylate ILs; this strategy led to the enhancement of solubility of several model drug molecules.[499]

In the case of drugs, the solvent must not only dissolve the active pharmaceutical ingredient (API), but also prevent its precipitation and aggregation. Solubility of various API in various

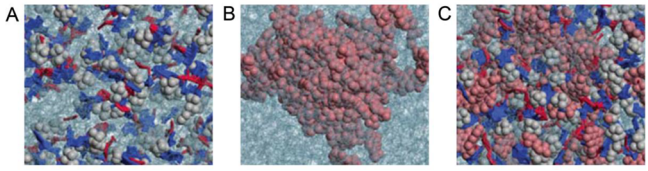

Figure 18. Simulation snapshots: (A) $[C_4MIM][N(CN)_2]$ + water; (B) vanillin + water; and (C) $[C_4MIM][N(CN)_2]$ + vanillin+ water. Figures reproduced with permission from ref 495. Copyright 2015 Royal Society of Chemistry.

ionic liquids is a popular research subject, and employment of ILs for external[500] and internal[501] drug delivery has been patented.

In general, ionic liquids may be used as (1) cosolvents, (2) emulsifiers, (3) copolymers, and (4) solvents or antisolvents for design of crystalline substances. Several dissolution, micellization, electrochemical, and spectroscopic studies on the behavior of drugs in the presence of IL solutions have been carried out.[498,502,503] Attempts to decipher the dependence of the API solubility on the IL structure have been made, but have produced ambiguous results. It is clear that both IL anion and cation influence the solubility of a given API. In general, hydrophilic drugs show better solubility in hydrophilic ILs, whereas hydrophobic drugs prefer hydrophobic solvents. The length of alkyl chains in the imidazolium cation correlates with the solubility of drug molecules.[504−507] However, the influence of the anion is complicated.[504] Below we state the data on solubility of various API in various ILs, which have been accumulated so far. Examples of available studies on application of ILs as solubility enhancing and emulsifying agents are provided in Table 1. According to the table, ILs are applicable to broad classes of pharmaceutical substances, including antioxidants, anesthetics, anticancer drugs, antiviral and antimicrobial agents, anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and others. Most studies are dedicated to imidazolium-based ILs; there are also several examples of using ammonium and phosphonium ILs.

N-Acetyl-L-cysteine and 4-hydroxycoumarin were readily soluble in hydrophilic ILs with short alkyl side chains in the cation, such as $[C_2MIM][OTf]$, whereas coumarin, 4′-isobutylacetophenone, thymoquinone, and ibuprofen demonstrated high solubility in the hydrophobic ILs $[C_{10}MIM][NTf_2]$, $[(C_6)_3C_{14}P][Cl]$, and $[(C_6)_3C_{14}P][NTf_2]$.[505,508,509] Water-soluble acetaminophen and caffeine showed high solubility in $[C_4MIM][BF_4]$, $[C_8MIM][BF_4]$, and $[C_4MIM][PF_6]$, but not in $[C_8MIM][PF_6]$;[504] the presence of $[C_6MIM][Br]$ or $[C_4MIM][Br]$ led to even higher water solubility of acetaminophen.[510,511] Poorly water-soluble albendazole was soluble in $[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, and $[C_8MIM][PF_6]$, whereas danazol dissolved in $[C_4MIM][PF_6]$, $[C_8MIM][PF_6]$, and $[C_8MIM][BF_4]$; addition of a water-miscible IL to a water-immiscible one improved the water miscibility of the system.[504,512] The IL consisting of choline and tryptophan enhanced solubility of glibenclamide.[497] Solubility of isoniazid and pyrazine-2-carboxamide was higher in imidazolium ILs with the trifluoromethanesulfonate anion than in those with the bis(trifluoromethylsulfonyl)amide one, and $[C_{10}MIM][OTf]$ was the best solvent. An increase in the alkyl chain length in the cation led to a decrease in the solubility.[506,507] $[(C_{10})_2(C_1)_2N][NO_3]$ also proved to be a good solvent for isoniazid and, to a lesser degree, for pyrazine-2-carboxamide.[513]

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Chem. Rev. 2017, 117, 7132−7189

Table 1. ILs as Solubility Enhancers and Emulsifiers in Drug Delivery

drug system	activity	IL	ref
N-acetyl-L-cysteine	antioxidant	$[C_2MIM][OTf]$, $[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][NTf_2]$	505,508,509
acetaminophen	analgesic	$[C_4MIM][BF_4]$, $[C_8MIM][BF_4]$, $[C_4MIM][PF_6]$, $[C_4MIM][Br]$, $[C_6MIM][Br]$	504,510,511
acyclovir	antiviral drug	$[C_1MIM][DMP]$	529−531
albendazole	antiparasitic agent	$[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, $[C_8MIM][PF_6]$	504,512
amphotericin B	antifungal agent	$[C_2MIM][OAc]$, $[C_nNH_3][OAc]$ (n = 4, 6, 8), [m-PEG_{350}-NH_3][OAc]	514
coumarin	anticoagulant	$[C_{10}MIM][NTf_2]$, $[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][NTf_2]$	505,508,509
4-hydroxycoumarin	anticoagulant	$[C_2MIM][OTf]$	505,508,509
curcumin	antioxidant, anti-inflammatory, antitumor agent	$[C_4MIM][BF_4]$	527
danazol	steroid drug	$[C_6C_6OCOPy][NTf_2]$, $[C_6C_6OCOPy][N(CN)_2]$, $[C_4MIM][PF_6]$, $[C_8MIM][PF_6]$, $[C_4MIM][BF_4]$	504,515
dantrolene sodium	muscle relaxant	$[C_1MIM][DMP]$	530
dehydroepiandrosterone	steroid hormone	$[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, $[C_8MIM][PF_6]$	330
dexametasone	steroid drug	$[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, $[C_8MIM][PF_6]$	330,577
diclofenac	NSAID	$[C_6MIM][Br]$, $[C_{12}MIM][Br]$, $[C_{14}MIM][Br]$	500,578
diltiazem	calcium channel blocker	DABCO-based ILs, $[C_{10}C_1Mor][Br]$	523
doxorubicin	antitumor agent	poly(ionic liquid-*co*-*N*-isopropylacrylamide)	544
etodolac	NSAID	$[C_4MIM][PF_6]$	533
5-fluorouracil	antitumor agent	$[C_4MIM][Br]$, $[C_4MIM][PF_6]$	532,533
glibenclamide	antidiabetic drug	[Cho][Trp]	497
gramicidin	antibiotic (pentadecapeptide)	1,4-bis(3-dodecylimidazolium-1-yl) butane bromide	572
ibuprofen	NSAID	$[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][NTf_2]$, $[C_2MIM][NTf_2]$	508,509,560
ibuprofen	NSAID	$[C_{12}MIM][Cl]$, formation of $[C_{12}MIM][Ibu]$ was observed	496
ibuprofen	NSAID	$[C_4MIM][Ibu]$-containing ionogels	545
4′-isobutylacetophenone	precursor in ibuprofen synthesis	$[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][NTf_2]$	508,509
isoniazid	antituberculosis agent	$[C_{10}MIM][OTf]$, $[(C_{10})_2(C_1)_2N][NO_3]$	506,513
itraconazole	antifungal drug	$[C_6C_6OCOPy][NTf_2]$, $[C_6C_6OCOPy][N(CN)_2]$, [m-PEG_{350}-NH_3][OAc], [m-PEG_{350}-NH_3][C_nCOO] (n = 3, 5, 7, 9)	514,515
lidocaine hydrochloride	local anesthetic	$[C_{12}MIM][Cl]$, $[C_{14}MIM][Cl]$	520
methotrexate	anticancer, anti-autoimmune disease agent	$[C_1MIM][DMP]$	530
nimesulide	NSAID	$[C_2MIM][BF_4]$, $[C_2MIM][OTf]$, $[C_2MIM][Ms]$	536
penicillin V	antibiotic	$[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, $[C_8MIM][PF_6]$	330
progesterone	steroid hormone	$[C_4MIM][PF_6]$, $[C_6MIM][PF_6]$, $[C_8MIM][PF_6]$	330
pyrazine-2-carboxamide	antituberculosis agent	$[(C_{10})_2(C_1)_2N][NO_3]$, $[C_{10}MIM][OTf]$	507,513
rutaecarpine	plant alkaloid	$[C_{12}MIM][Br]$	537
thymoquinone	antibiotic, antitumor agent	$[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][NTf_2]$	508,509

One of the most promising applications of ILs as pharmaceutical solvents is the development of dedicated ILs for dissolving "hard-case" API with poor water solubility. This concept has been proved empirically by using targeted structural tuning. Thus, ILs with tunable lipophilicity in one ion (alkylamine cation or fatty acid−based anion) and tunable hydrophilicity in the other (polyethylene glycol-based cation) were suggested to be used as solubility-enhancing agents and drug delivery systems (Figure 19).[514]

Fine-tuning of the IL structure was employed for optimization of solubility of danazol and itraconazole. These poorly water-soluble drugs effectively dissolved in $[C_6C_6OCOPy][NTf_2]$ and $[C_6C_6OCOPy][N(CN)_2]$. The solubility of itraconazole was shown to be 100 times higher in $[C_6C_6OCOPy][NTf_2]$ and 500 times higher in $[C_6C_6OCOPy][N(CN)_2]$, as compared to soybean oil.[515]

The IL-based vesicles, micelles, and microemulsions attract significant attention as potential carriers of poorly soluble drugs.[516−519] This strategy has been studied thoroughly, and IL-containing formulations have shown promising potential in topical drug delivery. Thus, lidocaine hydrochloride was shown to adsorb on the surface of the aggregates formed by the surface-active ionic liquids $[C_{12}MIM][Cl]$ and $[C_{14}MIM][Cl]$; the drug also modulated the aggregation behavior of the ILs, which assisted efficient drug delivery.[520] The model formulation containing the IL formed by octanoic or isostearic acid and diisopropanolamine or triisopropanolamine demonstrated improved skin permeability together with prolonged release of a model drug, and caused no skin damage.[521] Oil-in-water and water-in-oil emulsions with $[C_6MIM][Cl]$ or $[C_4MIM][PF_6]$ possessed antimicrobial activity and enhanced the skin penetration of a model substance in vitro.[333] IL-containing solid-in-oil nanodispersions demonstrated enhanced skin penetration and were suggested to be used for transcutaneous vaccination with hydrophilic macromolecules.[522] An addition of 1% w/w of DABCO-based or morpholinium ILs enhanced the transdermal transport of the calcium channel blocker diltiazem.[523] Cholinium geranate was shown to be an effective permeation enhancer with antimicrobial activity and low toxicity toward epithelial cells.[524] Cholinium IL-containing microemulsions demonstrated long-term stability at room temperature.[525] Another possible application of cholinium-based ILs is extraction and partitioning of drugs, which has been demonstrated by the examples of phenacetin, ibuprofen, lidocaine, and indomethacin.[526]

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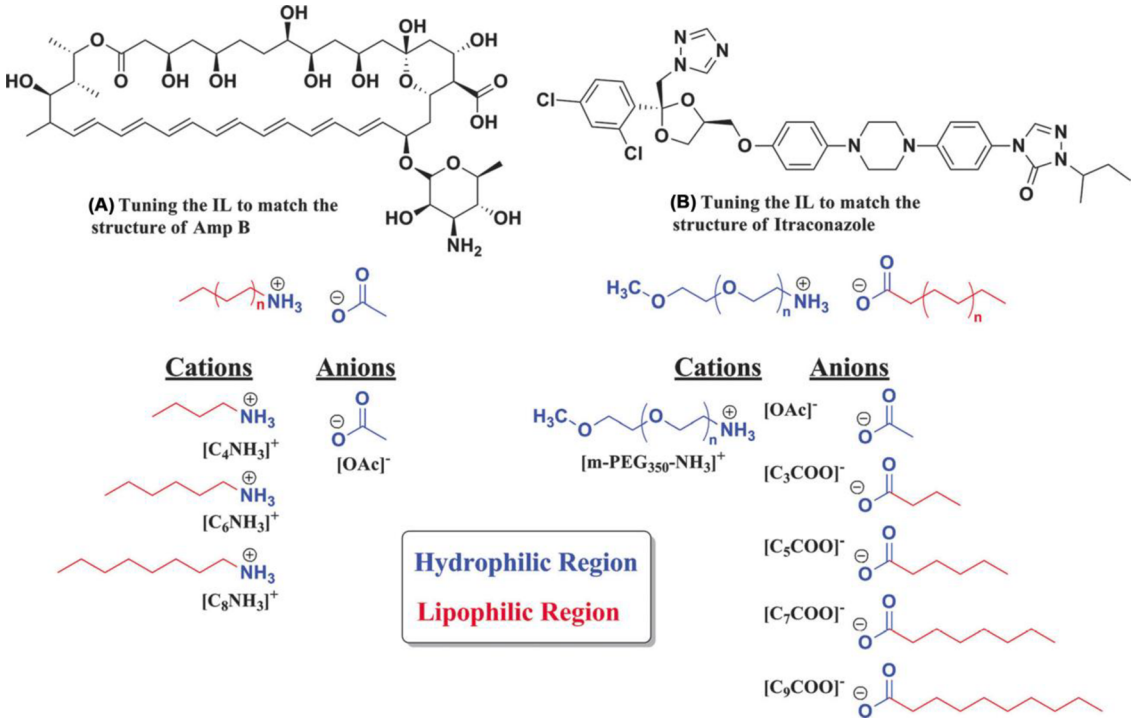

Figure 19. Ionic liquids as tunable solvents for (A) amphotericin B (cation hydrophobicity tuning) or (B) itraconazole (anion hydrophobicity tuning). Reproduced with permission from ref 514. Copyright 2013 Royal Society of Chemistry.

The hydrophilic IL $[C_4MIM][BF_4]$ affected micellization of various surfactant solutions of curcumin,[527] whereas $[C_4MIM][C_8SO_4]$ stabilized curcumin, presumably via hydrogen bonds and strong hydrophobic interactions.[528] Water-immiscible ILs demonstrated prolonged release of model drugs from IL microemulsions.[330] A similar approach was employed for transdermal delivery of acyclovir and methotrexate.[529−531] An ionic liquid-in-oil microemulsion containing $[C_4MIM][Br]$ or $[C_4MIM][PF_6]$ was developed for transdermal delivery of 5-fluorouracil or etodolac, respectively. The obtained formulations were used for in vivo treatment of skin cancer, arthritis, and inflammation in rodents, and produced promising results.[532,533] The detailed role of IL ($[C_8MIM][Cl]$) and an IL-type imidazolium gemini surfactant in micellization was studied for the antidepressant amitriptyline hydrochloride.[534,535]

$[C_2MIM][BF_4]$, $[C_2MIM][OTf]$, and $[C_2MIM][Ms]$ were shown to influence the interaction of nimesulide with human serum albumin (HSA); despite the increased lipophilicity of the system, nimesulide was able to bind to HSA efficiently.[536] Addition of $[C_{12}MIM][Br]$ to a colloidal solution of rutaecarpine led to dissociation of the aggregates and changed their morphology.[537] Similarly, $[C_4MIM][BF_4]$ modulated aggregation properties of the biological surfactant sodium deoxycholate.[538] Interestingly, in a study on micellization and intermolecular interactions between $[C_{12}MIM][Cl]$ and ibuprofen, the formation of $[C_{12}MIM][Ibu]$ complexes was observed.[496]

Liquid-in-oil microemulsions containing double-chain surface-active ILs were described. $[C_1C_3Pyr][NTf_2]$ or $[C_6MIM][NTf_2]$ was used as polar core, whereas 1-butyl-3-methylimidazolium 1,4-bis(2-ethylhexyl) sulfosuccinate or *N*,*N*-dimethylethanolammonium 1,4-bis(2-ethylhexyl) sulfosuccinate was used as surfactant. These microemulsions demonstrated high thermostability, and the size of aggregates could be regulated by selection of appropriate polar constituents.[539,540]

Similarly to polyion complex micelles formed by interactions between ionic copolymers and macromolecules of opposite charge, which are studied as potential drug carriers capable of targeted release of their load,[541−543] polymeric ILs also find potential application in drug delivery. Nanoparticles from poly(ionic liquid-*co*-*N*-isopropylacrylamide) with deoxycholic acid were assembled via electrostatic interactions; by using doxorubicin as model drug, drug release and cytotoxic activity of the system were demonstrated.[544] An IL-based hybrid material (ionogel) containing $[C_4MIM][Ibu]$ was suggested to be used as a novel drug delivery system.[545,546] Other reported applications of gelled ILs include a self-polymerasing IL gel prepared from choline formate and 2-hydroxyethyl methacrylate; from this gel, curcumin-loaded nanoparticles were obtained.[547,548] The synthesis of a polyethylenimine-based ionic liquid colloid for possible environmental and medical applications was described.[549] A pH-sensitive ionogel from choline polyacrylate (polymeric IL) was efficiently employed for prolonged delivery of 5-fluorouracil.[550] A temperature-sensitive *N*-isopropyl acrylamide-based copolymer doped with 1-butyl-3-vinylimidazolium bromide demonstrated high potential for drug entrapping and release, and low cytotoxicty.[551]

Hexafluorophosphate and chloride salts of 1-(4-vinylbenzyl)-3-methylimidazolium and 1-(4-vinylbenzyl)-4-(dimethylamino)-pyridinium were used as monomers for synthesis of positively charged polymers, into which the anionic drug naproxen was loaded. Presumably, such complexes may pass acidic and neutral environment to be released in the intestine.[552,553] Similarly, positively charged silica nanoparticles modified by pH-sensitive ILs were suggested to be employed for targeted delivery of naproxen[554] and methotrexate.[555,556] Positively charged silica nanoparticles modified with 4-acetyl-*N*-butylpyridinium hexafluorophosphate or 4-acetyl-*N*-propenylpyridinium hexafluorophosphate targeted mitochondria and inhibited proliferation of tumor cells in vitro.[557,558] Gold

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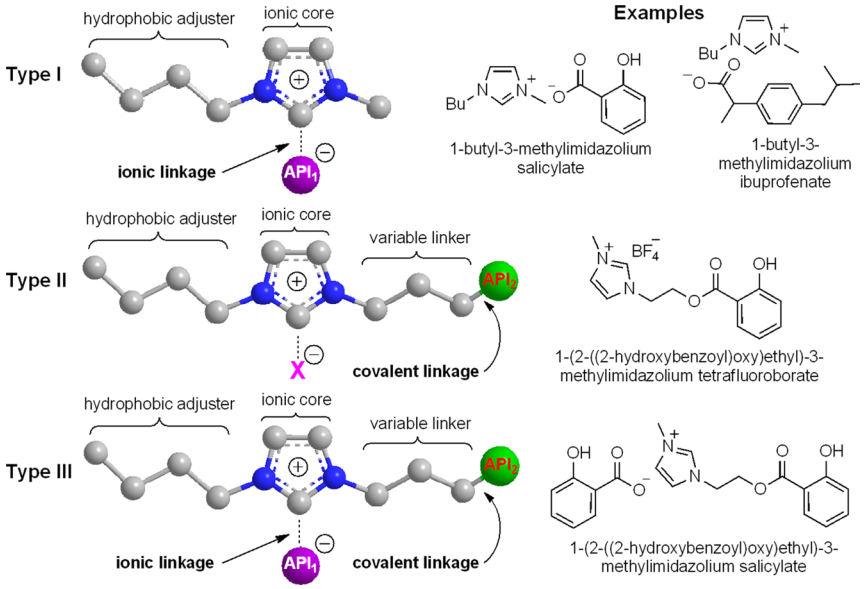

Figure 20. API-ILs containing ionic API as anion (Type I), covalently linked API in the cation (Type II), or combining both options (Type III); note that in the case of Type II, covalent binding to the anion is also possible (omitted for clarity). Figure reproduced with permission from ref 322. Copyright 2015 American Chemical Society.

nanoparticles grown on single-walled carbon nanotubes coated with 1-allyl-3-(3-mercaptopropyl)imidazolium chloride possessed low cytotoxicity and were able to enter lysosomes and to kill tumor cells by heat emission after laser irradiation.[559]

Another promising application of ILs in drug development is adjuvant components in crystallization, and Table 1 shows examples of such usage. Potential employment of ILs for cooling crystallization was suggested by investigating solubility of 12 API, including ibuprofen, acetylsalicylic acid, cyclosporine, and itraconazole, in $[C_2MIM][NTf_2]$. Ten of the API proved to be soluble in the IL at their melting point, whereas ibuprofen formed an immiscible phase. Products of cooling crystallization of acetaminophen in $[C_2MIM][NTf_2]$ were of substantial purity.[560] Adjusting solubility of acetaminophen via manipulating hydrogen-bonding interactions between the drug and IL was proposed to be employed for drug crystallization.[561] ILs were applied for design of drug polymorphs via drowning-out crystallization: usage of $[AEIM][BF_4]$ led to the formation of new polymorphs of adefovir dipivoxil and thermostabilized the drug in the IL−water mixture.[562] $[AEIM][BF_4]$ was also used as antisolvent for studying polymorphic transformations of clopidogrel bisulfate.[563] In another study, $[AEIM][BF_4]$ and $[C_4C_1MIM][BF_4]$ were employed as solvent and antisolvent, respectively, in antisolvent crystallization of adefovir dipivoxil. The authors demonstrated that different combinations of ILs produced different polymorphs.[564] When $[AEIM][BF_4]$ and $[C_4C_1MIM][BF_4]$ were used in the solvent-mediated phase transformation method, a metastable polymorph of adefovir dipivoxil was transformed into a stable one.[565] 1-Ethyl-3-methylimidazolium methyl phosphonate was employed for preparation of ultrafine particles of rifampicin, which showed good solubility in the IL. Addition of the rifampicin solution in the IL to an aqueous antisolvent produced amorphous submicrometer particles of the drug.[566]

In the end of the section, we would like to mention several interesting examples of indirect application of ILs in drug delivery. Thus, IL was employed as coating/drug carrier in the paclitaxel-coated balloon catheter, a probable alternative for treatment of coronary and peripheral artery disease. Cetylpyridinium salicylate was used as matrix for drug transfer enhancement. This IL was suggested to meet all of the demands required for good performance of the balloon catheter: it formed a thin, smooth layer on the surface, provided efficient drug incorporation into the coating, and possessed high but postponed solubility in water.[567−569]

Another interesting example is imidazolium poly(ionic liquid) membranes with the L-tryptophan anion; these membranes demonstrated high antimicrobial activity and induced no crucial hemolysis or cytotoxicity toward human cells.[570]

Polydopamine nanoparticles loaded with $[C_4MIM][PF_6]$ and doxorubicin were used as a successful chemotherapeutic and microwave thermal therapeutic agent for treatment of tumors in mice. Of note, the formulation induced no significant tissue toxicity. In this case, IL was employed as microwave sensitizer.[571]

The IL-type gemini surfactant 1,4-bis(3-dodecylimidazolium-1-yl) butane bromide was shown to interact with gramicidin vesicles, therefore triggering a significant change in the conformation of the latter and suggesting a possibility of modulation of drug properties via interactions with such ionic surfactants.[572]

Finally, noncovalent complexes of cholinium-based amino acid ILs with hemocyanin from *Rapana thomasiana* demonstrated significantly improved selective activity toward tumor cells in vitro. The presence of IL caused rearrangements in the secondary structure of the protein.[573] According to several reports, ILs impacted the structure of various amyloid peptides via interaction with specific amino acid residues; both promoting and inhibiting effects were observed.[574−576]

3.4. Active Pharmaceutical Ingredient-Ionic Liquids (API-ILs)

3.4.1. Solubility and Physicochemical Behavior. As discussed in section 3.1, turning a drug into a salt is a common way to increase its solubility;[469] therefore, because ionic liquids are liquid salts, turning a drug into an ionic liquid is an obvious method to improve its bioavailability and to relieve the problem of polymorphs. Moreover, it has been suggested that using active pharmaceutical ingredients in an ionic liquid form would allow

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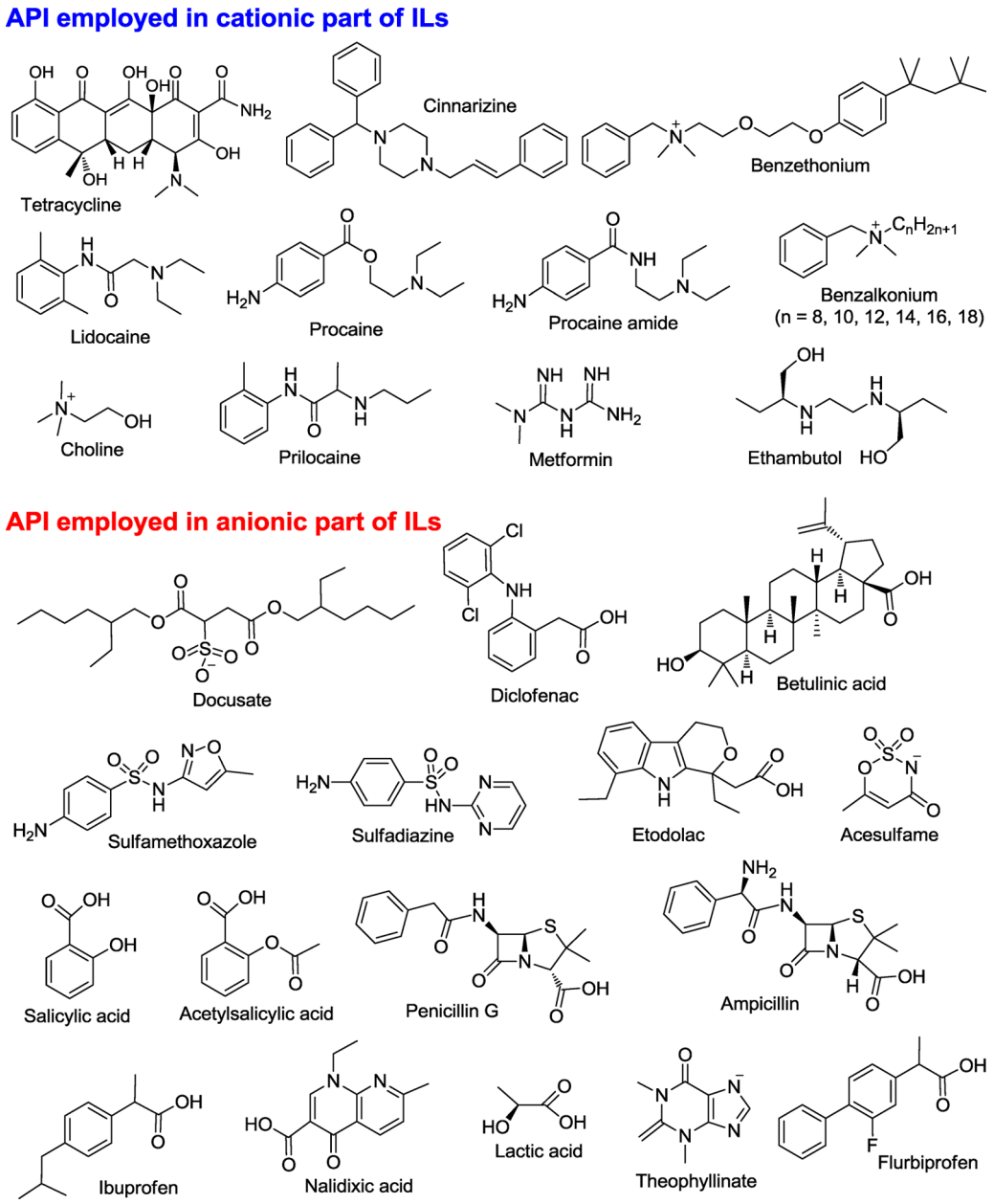

Figure 21. Examples of active pharmaceutical ingredients used in anions and cations of API-ILs (see Table 2 for details).

fine-tuning their physicochemical or biological properties, such as lipophilicity or toxicity.[106,218,223,225,228] Self-assembled API-IL vesicles were proposed to be an efficient drug delivery system, where IL acted both as carrier and as drug.[579] For neutral API, obtaining prodrugs via functionalization with ionizable groups was offered.[580] API-ILs were called "the third evolution" of ionic liquids.[212]

There are three ways to introduce API into IL systems (Figure 20): (1) Type I, via ionic binding (using API as anion or cation); (2) Type II, via covalent linkage; and (3) Type III, by using both ways to produce API-ILs with dual activities, where similar or different APIs may be combined in one IL.[228,322] At the moment, the vast majority of the available API-ILs belongs to Type I, that is, contains readily ionizable API moieties, which can be used as IL anions or cations (Figure 21).

In 1998, the first ILs derived from a bioactive substance (miconazole) were reported.[581] Since then, many ILs bearing active pharmaceutical ingredients in the cation or anion have been obtained (Figure 21). The preparation of various API-IL compositions with lidocaine, docusate, ibuprofen, procaine, and other drugs, including dual-active API-ILs, was patented.[582] An essential summary for the API-ILs investigated so far is presented in Table 2. The most studied physicochemical properties of API-ILs are thermal behavior and solubility in various media, including water, as well as surface activity and aggregation behavior.

As it has been anticipated, API-ILs are characterized by significantly lower temperatures of glass transition and liquid−liquid transition, in comparison with the corresponding parent drugs. Thus, ranitidinium docusate, a combination of a histamine H_2 receptor antagonist (ranitidine) and a laxative (docusate), is liquid at T > 29 °C (T_g −12 °C), whereas T_g values of lidocainium docusate and didecyldimethylammonium ibuprofen are −29 and −63 (−73) °C, respectively.[212,583] T_g of ranitidinium ibuprofenate and ranitidinium sulfacetamide was −12 and 25 °C, respectively; no melting point was found for

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Table 2. Current Data on API-ILs and Their Properties[a]

API-IL	studied physicochemical properties	studied biomedical properties	ref
[**Tet**][**Doc**]	thermal stability; water solubility; octanol−water and liposome−water partition coefficients	not studied	603
[$(C_1)_4$N][Nal]	basic characterization	antibacterial activity	623
[$(C_1)_3C_4$N][Nal]	basic characterization	antibacterial activity	623
[$(C_1)_3C_8$N][Nal]	basic characterization	antibacterial activity	623
[$(C_1)_3C_{10}$N][Nal]	basic characterization	antibacterial activity	623
[$(C_1)_3C_{12}$N][Nal]	basic characterization	antibacterial activity	623
***[$(C_1)_3C_{16}$N]*: [Nal], valproate**	thermal stability; thermal properties; surfactant properties, viscosity; conductivity; solubility in various solvents and simulated biological fluid	antibacterial activity	601,623
***[Cho]*: [Nal], pyrazinate, niflumate, picolinate, 4-amino-salicylate, [Ibu], [Amp], ketoprofenate, naproxenate, sulfasalazine, betulinic acid - glycine, betulinate, [Sal], [Sac], [Acesulf]**	solubility in various solvents and simulated biological fluids; thermal behavior; partition properties	in vitro cytotoxicity; antibacterial activity; HSA binding; metabolic stability; exposure kinetics; cell layer permeability; HIV-1 protease inhibition activity	583,585,589,596,599,604,624−626,640−642
[2-(methacryloyloxy)ethyl]trimethylammonium salicylate	copolymers with methyl methacrylate were synthesized, and their size distribution, morphology, and thermal properties were studied	not studied	611
***[$(C_{10})_2(C_1)_2N$]*: [Ibu], [Acesulf], [Sulf], trans-cinnamate, Colawet MA-80, Fast Green FCF, piperacillin, penicillin G, [Sal], 2-[(2,6-dichlorophenyl)amino]benzeneacetate, *N*-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-glutamate, (*S*)-6-methoxy-α-methyl-2-naphthaleneacetate, [Bz], mandelate, 2-acetoxybenzoate, nicotiate, [Doc], [Lac], L-prolinate**	thermal behavior; thermal properties	antibacterial activity; antifungal activity; feeding deterrent activity; acute oral toxicity in rats; skin irritation in rabbits	212,247,295,582,583,614,615
[$(C_{11})_2(C_1)_2N$]: [Sac], [Acesulf]	thermal properties	not studied	582
[$(C_4)_3C_1$N][Nal]	basic characterization	antibacterial activity	623
[$(C_8)_3C_1$N][Nal]	basic characterization	antibacterial activity	623
[$(C_2)_4N$]: [Amp], [Sal]	thermal properties; solubility in various solvents; partition properties	not studied	589,604,624,625,643
[$(HOC_2)_3$NH][Sal]	crystal structure	antifungal activity	616
(2-hydroxyethyl)dimethylundecyloxymethylammonium, (2-acetoxyethyl)beptyloxymethyldimethylammonium, (2-acetoxyethyl)dodecyloxymethyldimethylammonium, (2-hydroxyethyl)cyclododecyloxymethyldimethylammonium benzoates	thermal properties	not studied	582
[tuammoniumheptane]: [Sal], [Bz], [Bz-Bz], [Bz-Sal], gentisate	thermal properties; ionic conductivity; viscosity	membrane transport	608,609
cocodi(2-hydroxyethyl)methylammonium, oleyldi(2-hydroxyethyl)methylammonium, polyoxyethylene (15) (hydrogenated tallow)methylammonium, oleyltrimethylammonium, cocotrimethylammonium, dicocotrimethylammonium, di(hydrogenated tallow alkyl) dimethylammonium, allylbenzyldimethylammonium, alkylbenzyldimethylammonium, dibenzyldimethylammonium, cyclohexyldecyldimethylammonium, cyclohexyldodecyldimethylammonium theophyllinates	thermal properties; surface activity	feeding deterrent activity; antifungal activity; antibacterial activity	617,627
[Im][Sal]	basic characterization	in vitro cytotoxicity; toxicity toward *Artemia salina*	622
[C_1MIM][Nal]	basic characterization	antibacterial activity	623
[C_2MIM]: [Sal], [Amp], [Nal]	thermal properties; solubility in various solvents; partition properties; surfactant properties	ecotoxicity study (carboxylesterase assay, *Vibrio fischeri* assay); antibacterial activity; in vitro cytotoxicity; HSA binding	322,589,604,618,623−625,633

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Table 2. continued

API-IL	studied physicochemical properties	studied biomedical properties	ref
[HOC_2MIM]: [Amp], [Ibu]	thermal properties; solubility in various solvents; partition properties; conductivity	antibacterial activity; in vitro cytotoxicity	589,598,604,624,625
[C_2OC_2MIM][Sal]	basic characterization	in vitro cytotoxicity; toxicity toward *Artemia salina*	622
[HOC_3MIM][Sal]	basic characterization	in vitro cytotoxicity; toxicity toward *Artemia salina*	622
[$SalOC_2MIM$]: [BF_4], [Cl], [Sal]	thermal properties; water solubility	in vitro cytotoxicity	322
[$SalOC_3MIM$][Cl]	thermal properties; water solubility	in vitro cytotoxicity	322
[C_4MIM]: [Sal], chloramphenicol, sulfadiazine, sulfamethoxazol, fosfomycin, [Dic], [Ibu], [Nal], [Sac], [Acesulf]	DFT studies; water solubility; thermal properties; viscosity; hydrolytic stability; corrosion test; friction and wear test; surface activity; conductivity; aggregation behavior; gelation; degradation	in vitro cytotoxicity; antibacterial activity; release kinetics; in vitro release from polylactic membranes; toxicity toward *Artemia salina*	322,545,590,592−594,606,622,623,642,644−649
[HOC_2OC_2MIM][Sal]	basic characterization	in vitro cytotoxicity; toxicity toward *Artemia salina*	622
[C_5MIM][Nal]	basic characterization	antibacterial activity	623
[C_6MIM]: [Sal], [Ibu]	water solubility; thermal properties; viscosity; hydrolytic stability; corrosion test; friction and wear test; surface activity; conductivity; aggregation behavior	in vitro cytotoxicity	322,592−594,623
[C_8MIM]: sulfadiazine, sulfamethoxazol, fosfomycin, [ASal], [Ibu], [Nal]	thermal properties; viscosity; hydrolytic stability; corrosion test; friction and wear test; surface activity; electrical conductivity; aggregation behavior; self-encapsulation into mesoporous silica materials	antibacterial activity	590,592−594,623,650
[$C_{16}MIM$]: [Amp], sulfadiazine, sulfamethoxazol, fosfomycin	water solubility; thermal properties	antibacterial activity	277,590
[$C_{16}C_1MIM$][Amp]	water solubility; thermal properties	antibacterial activity	277
methimazole (1-methyl-2-(prop-2-en-1-ylsulfanyl)-1*H*-imidazol-3-ium) bromide	crystal structure	not studied	651
[C_2Py][Doc]	studies on incorporation into medical-grade PVC	antimicrobial activity	607
***[$C_{16}Py$]:* [Sal], [ASal], [Amp], [Sac], [Acesulf], [Sulf], sulfathiazole, Colawet MA-80, Fast Green FCF, piperacillin, penicillin G, valproate**	thermal properties; solubility in various solvents; partition properties; crystal structure; surfactant properties	ecotoxicity study (carboxylesterase assay, *Vibrio fischeri* assay); antibacterial activity; in vitro cytotoxicity; HSA binding	247,277,296,567−569,582,587,589,604,618,624,625,628,633
[C_8OC_1HOPy]: [Sac], [Acesulf]	thermal properties; crystal structure	not studied	247
[C_4C_2Pyr][Nal]	basic characterization	antibacterial activity	623
[HOC_2Pyr]: [Bz], [Bz-Bz], [Sal], [Bz-Sal], gentisate	thermal properties; ionic conductivity; viscosity	transmembrane transport	609
N-(2′,3′-epoxypropyl)-*N*-methyl-2-oxopyrrolidinium salicylate	density; speed of sound	not studied	652
[C_2C_1Pip][Nal]	basic characterization	antibacterial activity	623
[$C_{10}C_1Pip$][Theophyl]	thermal properties; surface activity	feeding deterrent activity; antifungal activity; antibacterial activity	617
[$C_{12}C_1Pip$]: [Theophyl], [ASal]	thermal properties; surface activity; aggregation behavior; viscosity	feeding deterrent activity; antifungal activity; antibacterial activity; release of acetylsalicylate	595,617
[C_2C_1Mor][Nal]	basic characterization	antibacterial activity	623
[$C_1(C_4)_3P$][Nal]	basic characterization	antibacterial activity	623

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Chem. Rev. 2017, 117, 7132−7189

Table 2. continued

API-IL	studied physicochemical properties	studied biomedical properties	ref
$[C_1(C_8)_3P][Nal]$	basic characterization	antibacterial activity	623
$[(C_4)_4P]$: [Dic], [Ibu], [ASal], [Sal] (+oligomeric ions), *N*-[7-isopropyl-6-(2-methyl-2*H*-pyrazol-3-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-methanesulfonamide, ketoprofenate, naproxenate, sulfadiazinate, sulfamethoxazole, tolbutamide	dissolution kinetics; saturation concentration; thermal properties	in vitro release from mesoporous support; release profiles; transmembrane transport; in vitro permeability through cell monolayer	586,588,597,605,610
$[HOC_2(C_4)_3P][Doc]$	studies on incorporation into medical-grade PVC	antimicrobial activity	607
[$(C_6)_3C_{14}P$]: [Sal], [Doc], [NTf_2], [Amp]	thermal properties; solubility in various solvents; partition properties	ecotoxicity study (carboxylesterase assay, *Vibrio fischeri* assay); antibacterial activity; in vitro cytotoxicity	589,604,624,625,633
hexetidinium: **[Sal], [ASal]**	thermal properties	not studied	587
tramadolium: **[Sal], [ASal]**	thermal properties; crystal structure	not studied	587
[Lid]: **[Ibu], [Sal] (+oligomeric ions), [ASal], [Doc], [Dic], [Sac], [Acesulf], [Flurb], [Fluf],** [HCl], [Lac], **[Etodolac]**	thermal properties, and behavior; water solubility; degree of ionicity; conductivity; simulated interactions in solution; molecular dynamics	in vitro release from mesoporous support and polylactic membranes; antinociception activity; neuritic outgrowth inhibition; local anesthesia; transmembrane transport; *phase III clinical trials ([Lid][Etodolac])*	212,582,583,587,600,605,606,610,619,629,634,636,653−655
[Pril]: **[Sal], [Doc], [Dic], [Sac], [Acesulf], [Flurb], [Fluf]**	degree of ionicity	not studied	634
[Bupiv]: **[Sal], [Doc], [Dic], [Sac], [Acesulf], [Flurb], [Fluf]**	degree of ionicity	not studied	634
[Proc]: **[Sal], [ASal],** [OAc], [HCl]	thermal properties; crystal structure; study on IL hydrates; structural dynamics in the glassy state	not studied	587,613,656
[ProcA]: **[Sal], [ASal], HCl-($ZnCl_2$)$_2$,** [HCl]	thermal properties; conductivity	not studied	587,620,657
[Metf]: **[Sal], [Doc], [Dic], [Sac], [Acesulf], [Flurb], [Fluf]**	degree of ionicity	not studied	634
ethambutol dibenzoate	first example of polymorphism in API-IL	not studied	612
ethambutol: **adipate, HCl-($ZnCl_2$)$_2$, hydrochloride nalidixate,** [Lac]	thermal properties	antimicrobial activity	296,620,658
acetaminophen prodrugs paired with the docusate anion	thermal properties; hydrolysis study	not studied	580
[Benzeth]: **[Doc],** [NTf_2], **[Sal], [ASal], [Sac], HCl-($ZnCl_2$)$_2$**	thermal properties	ecotoxicity study (carboxylesterase assay, *Vibrio fischeri* assay); antibacterial activity	587,620,633,635
[Benzalk]: **[Sal], [ASal], [Ibu], [Sulf], Colawet MA-80, [Sac], [Acesulf], [Theophyl], betulinic acid−glycine, betulinate, *trans*-cinnamate, Fast Green FCF, piperacillin, penicillin G, [Bz], sulfathiazole, [Doc], thimerosal,** [Lac], L-prolinate, **mandelate,** [NO_3]	thermal properties; surfactant properties; partition properties	ecotoxicity study (carboxylesterase assay, *Vibrio fischeri* assay); antibacterial activity; antifungal activity; feeding deterrent activity; HSA binding; in vitro cytotoxicity; HIV-1 protease inhibition activity	218,247,295,582,587,599,614,615,617,618,626,633
miconazole derivatives paired with [PF_6]	first bioactive ILs	not studied	581
propanthelinium: **[Acesulf],** *p*-toluenesulfonate	thermal properties	not studied	635
ranitidinium: **[Doc], HCl-($ZnCl_2$)$_2$, [Ibu], [Sulf]**	thermal properties; water solubility	antimicrobial activity; antioxidant activity; cytotoxicity	212,582,584,620
phenoxybenzamine-HCl-($ZnCl_2$)$_2$	thermal properties	not studied	620
homatropine-HCl-($ZnCl_2$)$_2$	thermal properties	not studied	620
nicardipine-HCl-($ZnCl_2$)$_2$	thermal properties	not studied	620
imipramine-HCl-($ZnCl_2$)$_2$	thermal properties	not studied	620
Rhodamine-6G: tetraphenylborate, bis(perfluoroethylsulfonyl)imide	colloidal stability data	cytotoxicity toward tumor cells	621
cinnarizine: [$C_{10}SO_4$], [$C_{12}SO_4$], [$C_{18}SO_4$], 7-ethyl-2-methyl-4-undecylsulfate, oleate, stearate, [NTf_2]	thermal properties; solubility; dispersion	plasma concentration	591

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Chem. Rev. 2017, 117, 7132−7189

Table 2. continued

API-IL	studied physicochemical properties	studied biomedical properties	ref
halofantrine: $[C_{10}SO_4]$, $[C_{12}SO_4]$, oleate, $[NTf_2]$	thermal properties; solubility; dispersion	not studied	591
itraconazole: $[C_{12}SO_4]$, 7-ethyl-2-methyl-4-undecylsulfate, **[Doc]**	thermal properties; solubility; dispersion	plasma concentration	591
[bromohexinium][Ibu]	basic characterization	transmembrane transport	608
[ephedrinium][Ibu]	thermal properties	transmembrane transport	610
verapamil hydrochloride	thermal behavior; conductivity; entropic models	not studied	659,660
[carvediol][H_2PO_4]	structural dynamics in the glassy state	not studied	656
[amitriptyline][$C_{12}SO_4$]	surface activity; aggregation behavior	hemolytic toxicity; drug release	579
[mepenzolate][Doc]	thermal properties	not studied	582
domiphen mandelate	basic characterization	antibacterial activity; antifungal activity	615
proline ethylester ibuprofenate	basic characterization	skin permeation	631
ketokonazole: citrate, tartrate	thermal properties; viscosity; solubility;	not studied	602
diphenhydraminium: **[Ibu]**, **[Doc]**	thermal properties; water solubility; ionicity	antimicrobial activity; antioxidant activity; cytotoxicity	584
glycinium, ethylglycinium: [Doc]	thermal properties; water solubility; ionicity	antimicrobial activity; antioxidant activity; cytotoxicity	584

[a]For convenience, API-ILs are classified by cations, and dual-active API-ILs are shown in bold.

these API-ILs. Similarly, diphenhydraminium docusate, glycinium docusate, and ethylglycinium docusate possessed no melting point, and their T_g values were below 0 °C.[584] T_m of cholinium nalidixate is −4.7 °C (205 °C for nalidixate).[585] Tetrabutylphosphonium ibuprofenate, tetrabutylphosphonium ketoprofenate, and tetrabutylphosphonium naproxenate are liquid at room temperature.[586] A wide panel of salicylate- or acetylsalycilate-containing dual-active API-ILs with tetrabutylphosphonium, cetylpyridinium, benzalkonium, benzethonium, lidocainium, procainium, and other counterions demonstrated relatively low T_g and T_m, together with acceptable thermostability.[587] Lidocainium salicylate and tetrabutylphosphonium salicylate were used for the preparation of oligomeric ILs with various thermal properties.[588] Ampicillin-bearing ILs with ammonium, pyridinium and imidazolium as cations, as well as 1-alkyl-3-methylimidazolium ILs bearing sulfadiazine, sulfamethoxazol, acetylsalicylate, and other API as anion, possessed low T_g.[589,590] The same was observed for API-ILs combining cinnarizine, halofantrine, and itraconazole with decylsulfate, dodecylsulfate, oleate, and other anions.[591] 1-Alkyl-3-methylimidazolium ibuprofenates showed high thermal and hydrolytic stability, together with good tribological properties, and were proposed to be used as lubricants.[592] Surfactant properties of these ILs suggested the possibility to modulate their aggregation via changing the alkyl side chain length.[593,594] 1-Butyl-3-methylimidazolium ibuprofenate was employed for the preparation of ionogels, which were shown to be a promising drug delivery system.[545] Similarly, studies on aggregation behavior of 1-dodecyl-1-methylpiperidinium acetylsalicylate and anion release from gels formed by this IL suggested its possible pharmaceutical application. Interestingly, small $[C_{12}C_1Pip]$-[ASal] aggregates transformed into gel-like wide micellar networks upon addition of sodium salicylate.[595]

The prodrug-IL concept was tested on a series of acetaminophen-based prodrugs with the docusate anion. The obtained prodrug-ILs demonstrated low T_g and underwent fast hydrolysis in simulated body fluids.[580]

Another anticipated advantage of API-ILs is improved solubility, in comparison with parent API. Thus, in the case of cholinium nalidixate, water solubility was almost 5000 times higher than that of the parent drug, whereas in the case of cholinium niflumate it was 56 000 times higher.[585] Cholinium sulfasalazin demonstrated 4000-fold improved saline solubility and increased exposure, in comparison with the parent sulfalazine.[596] Tetrabutylphosphonium API-ILs showed improved dissolution rates, as compared to the parent drugs diclofenac, ibuprofen, naproxen, and others.[586,597] 1-(2-Hydroxyethyl)-3-methylimidazolium ibuprofenate showed very high water solubility (150 000 times higher than the pure ibuprofen),[598] whereas 1-alkyl-3-methylimidazolium salicylates were significantly more water-soluble than the pure salicylic acid.[322] Water solubility of ionic derivatives of betulinic acid was improved up to 100 times, in comparison with the parent drug.[599] Both lidocaine and etodolac in the form of lidocainium etodolac showed higher water solubility than either drug alone.[600] Trimethylhexadecylammonium valproate demonstrated enhanced solubility in the simulated gastric fluid.[601] Ketokonazole citrate and tartrate showed improved solubility in the phosphate buffer, in comparison with the pure ketoconazole (antifungal drug) or its physical mixtures with citric or tartaric acid.[602]

The solubility of API-IL can be modulated by varying the counterion hydrophilicity/hydrophobicity. Thus, tetracycline

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docusate demonstrated significantly lower water solubility than tetracycline hydrochloride or sodium docusate, but showed preferential partitioning toward a lipophilic phase.[603] Ampicillin-bearing ILs were miscible with various solvents, depending on the cation.[589,604] API-ILs combining cinnarizine, halofantrine, and itraconazole with decylsulfate, dodecylsulfate, oleate, and other anions demonstrated improved solubility in lipid-based emulsions.[591]

Tetrabutylphosphonium ibuprofenate and lidocainium ibuprofenate were stable when immobilized on mesoporous silica, and were readily released from the support.[605] Lidocainium ibuprofenate also acted as plasticizer in poly(L-lactic acid) membranes.[606] 1-Ethylpyridinium docusate and tri-*n*-butyl(2-hydroxyethyl)phosphonium docusate were employed as both plasticizers and antimicrobial agents for medical-grade polyvinyl chlorides.[607]

Several API-ILs demonstrated rapid transport through a model membrane, possibly in the form of hydrogen-bonded clusters (see also section 1.2).[608] The authors suggested that lower ionicity may be an advantage for API-ILs and may facilitate their trans-membrane transfer.[609] This suggestion was confirmed by the study of simultaneous transport of lidocaine and ibuprofen through the membrane, where the formation of a hydrogen-bonded complex of the two API occurred in the solution.[610]

Aggregate structures formed by ILs with surface-active API were studied by the example of 1-alkyl-3-methylimidazolium ibuprofenate. In the case of the cations with short alkyl chains, the micelles contained mainly the ibuprofenate anion; upon increasing the alkyl chain length, the amount of imidazolium cations in the micelles increased until aggregates with stoichiometric composition were formed; these aggregates interacted with each other giving globular conglomerates.[593,594] Similarly to common ILs, API-ILs were suggested to be used for preparation of polymers with the ability to exchange biologically active ions ([2-(methacryloyloxy)ethyl]trimethylammonium salicylate was used as a building block of such a copolymer).[611]

API-ILs look to be a very promising pharmaceutical strategy; nevertheless, some drawbacks of the API-ILs concept should also be mentioned. The API-IL strategy cannot be considered the ultimate solution of the polymorphism problem, because polymorphs of API-ILs have been described. Ethambutol dibenzoate was found to form three polymorphs, which demonstrated close T_m (93−96 °C), but different thermal stability.[612] High hygroscopicity of many ILs also may be a problem. Thus, procainium acetate formed a dihydrate, which underwent irreversible crystallization.[613] Crystallization and glass transition of 1-(2-hydroxyethyl)-3-methylimidazolium ibuprofenate showed high sensitivity to the water content.[598] These findings highlight the importance of studying the formation of polymorphs and hydrates even in the case of API-ILs.

3.4.2. Biomedical Activity. Despite numerous reports on the preparation and physicochemical properties of API-ILs, their biomedical activity is significantly less studied, and the available data have been obtained mostly using in vitro models (see Table 2). In this section, we describe the current status of the knowledge on biomedical properties of API-ILs. Most studies available so far are dedicated to either physicochemical or biological properties of API-ILs, and only about two dozen works address both aspects (see, e.g., refs 212,247,277,322,545,579,584,585,591,595−597,599,600,606,607,609,610,614−621). Usually these studies concern surface properties and the enhancement of solubility of API-ILs, with respect to their biological activity or ability to penetrate biological membranes.

Increased water solubility suggests that API-ILs should demonstrate higher bioavailability than poorly soluble parent drugs. However, effective doses of many conventional solid drugs are very low, and their main issue is rather polymorphism, which is difficult to control. Moreover, the impact of incorporating API into IL is not always obvious. Therefore, an ideal API-IL should be liquid, so not to form polymorphs, and should retain the level of activity exhibited by the parent drug.

The influence of the drug transition from the solid to ionic liquid form was studied for several APIs. Thus, the introduction of salicylic acid into an imidazolium-type IL via an ionic or covalent linkage did not disturb the cytotoxic activity of the API: API-ILs of all three types (see Figure 20) exhibited cytotoxicity similar to that of the pure drug.[322] As expected, oxygenation of the alkyl side chain of the imidazolium cation led to significant reduction of toxicity exhibited by salicylate-containing ILs toward cell cultures and the brine shrimp *Artemia salina*.[622]

Usage of cholinium as counterion did not perturb the cytotoxicity of nalidixic, niflumic, and pyrazinoic acids.[585] When studying ILs with the nalidixate anion, no improvement of antimicrobial activity against *Salmonella* was observed; however, according to this study, ILs with different cations showed different modes of toxic action.[623] Imidazolium- and cetylpyridinium-based ILs bearing ampicillin demonstrated significantly lower water solubility than sodium ampicillin, but their antibacterial activity was improved.[277,624] Moreover, these API-ILs also showed pronounced inhibitory activity toward tumor cell lines, but not normal fibroblasts, in vitro.[625] Ionic derivatives of betulinic acid, a plant compound possessing antitumor properties, demonstrated enhanced water solubility, together with enhanced inhibition of HIV-1 protease and cytotoxicity against various tumor cell lines.[599,626] 1-Alkyl-3-methylimidazolium ILs bearing sulfadiazine, sulfamethoxazol, acetylsalicylate, and other API as anion, as well as the chlorometallate-based IL benzethonium-Cl-$(ZnCl_2)_2$, possessed antibacterial and antibiofilm activity.[590,620] Surface-active theophyllinate-containing ILs showed a promising fungicidal and bactericidal potential.[617,627] Triethanolammonium salicylate inhibited growth of the fungus *Rhizopus oryzae*.[616] Ranitidinium ibuprofenate and diphenhydraminium ibuprofenate demonstrated activity against various *Candida* species, and the union of ethylglycine and docusate, which did not possess antibacterial activity in their pure forms, produced ethylglycinium docusate, which demonstrated activity against penicillin- and methicillin-resistant *Staphylococcus aureus*.[584]

Using rhodamin 6G-based IL-like compounds, a cooperative effect of both ions on antitumor activity was demonstrated.[621] Employment of cetylpyridinium salicylate, which itself possessed antibacterial activity, as dispersing agent for silver nanoparticles allowed one to produce nanoformulations with a broader antibacterial effect.[628]

Unsurprisingly, biological activity of API-ILs turned out to depend on the ion structure. Thus, the cation nature influenced antibacterial activity of dual-active API-ILs combining an antibacterial agent (didecyldimethylammonium, benzalkonium, cetylpyridinium, or 3-hydroxy-1-octyloxymethylpyridinium) with an artificial sweetener (acesulfame or saccharinate).[247] Several dual-active API-ILs were tested against bacterial species involved in biofouling. Ethambutol hydrochloride nalidixate and cetrimonium nalidixate demonstrated excellent antibacterial properties; however, when ethambutol was combined with the

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Chem. Rev. 2017, 117, 7132−7189

lactate anion, the resulting IL showed weak antibacterial activity, possibly because the bacteria utilized lactate as source of carbon.[296] On the other hand, didecyldimethylammonium and benzalkonium D,L- and L-lactates were recognized as effective antimicrobial agents.[614]

Lidocainium docusate provided a longer and more pronounced analgesic effect than lidocainium hydrochloride,[212] possibly due to association of the ions in the aqueous media, which led to a synergistic impact on the activity;[629] lidocainium ibuprofen was also efficiently applied for dermal anesthesia in rats.[619] Lidocainium etodolac demonstrated higher skin permeation than etodolac alone, due to improved lipophilicity/hydrophobicity of the drug.[600] Tetrabutylphosphonium *N*-[7-isopropyl-6-(2-methyl-2*H*-pyrazol-3-yl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-methanesulfonamide penetrated a cell monolayer more efficiently than the free drug (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist).[597] For API-ILs combining cinnarizine, halofantrine, and itraconazole with decylsulfate, dodecylsulfate, oleate, and other anions, enhanced drug absorption was observed in rats.[591] An external preparation containing fatty acid-based ILs for enhanced transdermal penetration has been patented.[630] Implying biocompatible nature of amino acids, proline ethylester was suggested to be used as counterion to ibuprofenate; the resulting IL, proline ethylester-ibuprofenate, showed significantly improved transdermal permeation, as compared to a saturated ibuprofen solution.[631]

According to an interesting example of antimicrobial peptides conjugated with one or multiple instances of imidazolium cations, the presence of these cations produced synergestic effects, which correlated with the cation number.[632]

In addition to biomedical properties of API-ILs, their environmental impact also should not be forgotten. Bioassays based on inhibition of human carboxylesterase 2 and *Vibrio fischeri* were suggested to assess the ecotoxicity of selected API-ILs bearing 1-ethyl-3-methylimidazolium, benzethonium, benzalkonium, cetylpyridinium, or trihexyltetradecylphosphonium as cation and salicylate, docusate, or bis(trifluoromethylsulfonyl)amide as anion. According to this study, 1-ethyl-3-methylimidazolium salicylate may be considered practically harmless, benzalkonium salicylate and cetylpyridinium salicylate were slightly toxic, whereas benzethonium salicylate and benzethonium docusate demonstrated moderate aquatoxicity.[633] Didecyldimethylammonium saccharinate and didecyldimethylammonium acesulfame exhibited significant oral toxicity and skin irritation.[247]

3.4.3. Combining Dual Activities within One Molecule. The idea of combining two (or more) activities within one drug molecule seems very tempting.[228] The role of the API-IL counterion should not necessarily be limited by preclusion of crystallization; it can also possess its own biomedical activity, thus providing API-IL with dual function or giving some new synergistic active combination not achievable with two separate APIs. We should note that it is not always easy to distinguish API-ILs with one activity from those with two or even more; nevertheless, we tentatively show most apparent examples of dual-active API-ILs in bold in Table 2. Undoubtedly, the targeted combining of ions, which possess several desired activities, within one IL has been attracting more attention lately.[296,582,587,618,620,634,635] Here, we discuss several interesting examples.

The synthesis and behavior of dual-active API-ILs have been reported.[582,587] Antibacterial cations, such as didecyldimethylammonium, benzalkonium, and others, were united with the "sweet" anions saccharinate and acesulfame. Some of these dual-active API-ILs demonstrated improved antimicrobial activity. $[(C_{10})_2(C_1)_2N][Sac]$ and $[(C_{10})_2(C_1)_2N][Acesulf]$ also exhibited good deterrent activity against insects, but caused oral toxicity and skin irritation.[247]

Several attempts to combine the antibiotic ampicillin with the antiseptic cetylpyridinium have been made. The resulting API-IL $[C_{16}Py][Amp]$ demonstrated significantly higher activity against several Gram-positive and Gram-negative bacterial strains, as compared to the parent [Na][Amp] or $[C_{16}Py][Cl]$.[277,624] Among the API-ILs tested, $[C_{16}Py][Amp]$ possessed the highest potential for reversion of resistance of ampicillin-resistant clinical strains.[624] Interestingly, $[C_{16}Py][Amp]$ also inhibited growth of some tumor cell lines more efficiently than [Na][Amp].[625]

In search for agents against microbial corrosion, the antituberculous drug ethambutol and the antiseptic cetrimonium were combined with the antibiotic nalidixic acid. The resulting ethambutol hydrochloride nalidixate and cetrimonium nalidixate demonstrated enhanced antibacterial activity against bacteria found in marine biofilms on steel constructions.[296]

Lewis-acid ILs containing metal chlorides are an interesting example of an attractive pharmaceutical formulation. When the antiseptic benzethonium was combined with $ZnCl_2$, which also possessed antimicrobial properties, the resulting IL benzethohium-Cl-$(ZnCl_2)_2$ demonstrated improved antibacterial activity, in comparison with benzethonium chloride.[620]

The combination of the antibiotic tetracycline with the laxative docusate produced an API-IL, which showed rather poor water solubility, in comparison with tetracycline hydrochloride and sodium docusate. However, [Tet][Doc] demonstrated a higher partition coefficient in liposomes, possibly due to more intense interactions with the phosphatydilcholine bilayer, suggesting better pharmacokinetics.[603] When docusate was used as counteranion for lidocaine, lidocainium docusate possessed higher bioavailability;[212] this effect may be explained by improved membrane permeability due to formation of ionic associates near the cell membrane.[629] Similarly, lidocaine and ibuprofen were shown to pass the membrane together, as a hydrogen-bonded complex,[610] and were effectively applied as local anesthetic.[619]

Etodolac is a nonsteroidal anti-inflammatory drug commonly used for relieving pain and inflammation caused by rheumatoid arthritis and osteoarthritis. To improve its transdermal penetration, etodolac was combined with the local anesthetic lidocaine. The resulting API-IL lidocainium etodolac demonstrated significantly higher saturation solubility in water than etodolac alone; solubility of lidocaine in the IL form was also improved, in comparison with the parent drug. As part of API-IL, etodolac was transferred through the skin more efficiently; however, the opposite was observed for lidocaine.[600] Of note, lidocainium etodolac has recently entered clinical trials, which are described in the following section.

3.4.4. Clinical Application. It seems that at the moment, lidocainium etodolac[600,636] is the only API-IL that has reached clinical trials. In 2013, the results of the phase I trial of the MRX-7EAT (Etoreat) Etodolac-Lidocaine Topical Patch were published by IL Pharma Inc. (MEDRx).[637] Usage of etodolac in an IL form was found to increase its skin absorption, whereas adverse effects were mild to moderate. The phase II/III trials on efficacy and safety of MRX-7EAT in the pain treatment have been conducted.[638] Several trials on using MRX-7EAT in the treatment of ankle sprains (NCT01198834), low back pain

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Table 3. Application of ILs in the Synthesis of Drugs and Their Intermediates

compound	activity	IL	role of IL	ref
(*R*,*S*)-ibuprofen	NSAID[a]	$[C_4MIM][PF_6]$, $[C_8C_1Py][BF_4]$	media for enzymatic enantioselective esterification or hydrolytic resolution	666,667,714,715
iodoquinol	antiprotozoal drug	$[C_4C_1Py][ICl_2]$	iodinating reagent	668
clioquinol	antifungal drug	$[C_4C_1Py][ICl_2]$	iodinating reagent	668
pravadoline	NSAID	$[C_4MIM][PF_6]$	media	665
(*R*)-modafinil	wakefulness-promoting agent	$[C_2MIM][Br]$	media for enzymatic enantioselective esterification	716
stavudine	anti-HIV[a] drug	$[C_1OC_2MIM][Ms]$, $[C_1OC_2MIM][TFa]$, $[C_4MIM][TFa]$	media	670
brivudine	anti-HSV[a] drug	$[C_1OC_2MIM][Ms]$, $[C_1OC_2MIM][TFa]$, $[C_4MIM][TFa]$	media	670
trifluridine	anti-HSV drug	$[C_1OC_2MIM][Ms]$, $[C_1OC_2MIM][TFa]$, $[C_4MIM][TFa]$	media	670
(*S*)-naproxen	NSAID	$[C_4MIM][BF_4]$	media	664
tioconazole	antifungal drug	[AlkMIM][Br]	catalyst	717
hydrocortisone	steroid hormone	$[C_1MIM][BF_4]$, $[C_2MIM][BF_4]$, $[C_4MIM][PF_6]$, $[(C_1)_4N][BF_4]$, $[(C_4)_4N][Br]$	catalyst	718
hydrazinyl phthalazines	antimalarial agents	$[C_1C_1MIM][C_1SO_4]$	dehydrating agent	687
ciclesonide	anti-asthmatic, anti-allergenic drug	acidic ILs	catalyst, media	719
α-tocopherol succinate	vitamin E ester	$[C_5MIM][NO_3]$	catalyst, media	720
modafinil and its derivatives	stimulant for treatment of sleep disorders	$[C_4MIM][PF_6]$	media	721
isoxazolines	precursor of antimicrobial agents	$[C_4MIM][BF_4]$	media	722
1-[(*E*)-3-methyl-4-benzenesulfonyl-3-methylbut-2-enyl]-2,3,4,5-tetramethoxy-6-methylbenzene	coenzyme Q_{10} intermediate	$[C_2Py][BF_4][MCl_m]$ (MCl_m = $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_2$, $SnCl_4$, CuCl)	catalyst	723
(*S*)-3-chloro-1-phenyl-1-propanol	precursor of antidepressant drugs	$[C_4MIM][NTf_2]$	IL phase, whole-cell catalysis	724
(*R*)-phenylacetylcarbinol	precursor of (1*R*,2*S*)ephedrine and (1*S*,2*S*)pseudoephedrine	$[C_4MIM][PF_6]$	IL phase, whole-cell catalysis	725
3-phenylglycidol	precursor of various drugs, e.g., tomoxetine and reboxetine	$[C_4MIM][NTf_2]$	media	726
(*R*,*S*)-1-chloro-3-(3,4-difluorophenoxy)-2-propanol	intermediate in the synthesis of (*S*)-lubeluzole	$[C_4MIM][PF_6]$, $[C_4MIM][BF_4]$	media for enzymatic enantioselective esterification	727
thiazolidine derivatives, including rhodanine ones	antimicrobial agents, intermediates for preparation of antidiabetic drugs, other activities	$[(C_1)_2(C_1)_2G][Lac]$, $[(C_1)_2(C_1)_2G][OAc]$, $[(C_1)_2(C_1)_2G][TFa]$, $[(C_1)_2(C_1)_2G][Pro]$, $[(C_1)_2(C_1)_2G][IBut]$, $[HDBU][HSO_4]$, $[C_4MIM][PF_6]$, $[(C_2)_3NH][HSO_4]$	catalyst, media	685,686,712,713,728
11α-hydroxy-16α,17-epoxyprogesterone	intermediate in the synthesis of steroidal drugs	$[C_4MIM][PF_6]$	media for enzymatic enantioselective esterification	729
(*R*)-1-trimethylsilylethanol	key synthon for various silicon-containing drugs	$[C_4MIM][PF_6]$	IL phase, whole-cell catalysis	730
dronedarone intermediates	anticardiac arrhythmia drug	various imidazolium and pyridinium ILs	media	731
5-(α-haloacetyl)-8-substituted oxy-(1*H*)-quinolin-2-ones	intermediates of 5-[(*R*)2-(5,6-diethyl-indan-2-ylamino)-l-hydroxy-ethyl]-8-hydroxy-(1*H*)-quinolinone-2-one salts (bronchodilators, anti-asthmatic drugs)	various imidazolium ILs	media	732

[a]NSAID, nonsteroidal anti-inflammatory drug; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

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Chem. Rev. 2017, 117, 7132−7189

(NCT01968005), acute tendonitis and bursitis (NCT01161615, NCT01506154), and shoulder pain (NCT01506154) have been completed. In March 2016, a phase III trial in the treatment of acute delayed onset muscle soreness was announced (NCT02695381).[639] At the end of November 2016, MEDRx declared termination of the development of Etoreat due to unsatisfactory results of the trials.

4. CHEMICAL APPLICATIONS OF IONIC LIQUIDS IN PHARMACY

4.1. Ionic Liquids in Drug Synthesis

Ionic liquids are used in numerous chemical processes including fascinating application in the synthesis of pharmaceutical substances and drugs. ILs are employed in synthesis of heterocyclic molecules, such as imidazoles, furans, oxazoles, thiazoles, quinolines, and others, which are exploited in biology and medicine.[661] Because of their unique nature, ILs can simultaneously play dual roles of media and catalysts, thus allowing reduced volumes of volatile solvents and reduced quantities (or even elimination) of metal catalysts that may leach into the environment. ILs can also influence the selectivity of enzymes used in biotechnological processes. Previous excellent reviews cover these topical issues.[14,15,219,662,663] In this section, we discuss important issues of the IL employment in drug synthesis and point out on interactions between ILs and proteins, which may be responsible for the unique properties demonstrated by pharmaceutically significant enzymes in the presence of ILs.

Beause of their excellent solvent characteristics, ILs are often employed as reaction media and catalysts. Of note, upon dissolution in ILs, many substances display new behavior, which differs from that in molecular liquids. This phenomenon may be explained by intense intermolecular interactions between the solute and IL resulting in the formation of nanostructures (see section 1.2). In the case of uncharged solutes, the solute molecules are suggested to distribute in the polar or nonpolar nanodomains existing in ILs; small, charged solutes are supposed to undergo complete dissociation, and the ions are supposed to allocate in the polar IL nanodomains. According to several reports, transition metal ions form coordination complexes with IL anions, leading to local changes in the IL structure. Unfortunately, the case of bulkier charged solutes is significantly less studied.[67]

In 1997, hydrogenation of 2-arylacrilic acids in the $[C_4MIM][BF_4]$ media was published. The authors employed the procedure for producing the nonsteroidal anti-inflammatory drug (NSAID) (*S*)-naproxen.[664] In 2000, the first high-yield synthesis of a drug in an ionic liquid media was reported: the NSAID pravadoline was prepared by using $[C_4MIM][PF_6]$ as media.[665] Thus, the age of ionic liquids in the drug synthesis has begun.

In the last 15 years, many research groups have reported the employment of ILs in various chemical processes related to the production of pharmaceuticals, their precursors or intermediates, and other agents with proven or potential biological activity. In most cases, ILs are used as reaction media, which often also acts as catalyst, and the most popular ILs are salts of imidazolium (see Table 3). So far, the synthesis of several NSAIDs,[664,666−668] antiviral,[669−671] antimicrobial,[668,672−686] antimalarial,[687,688] and antitumor[669,689−701] agents, as well as cholinesterase inhibitors[702−705] and radiolabeled molecular imaging and therapy agents,[706] have been described. Table 3 shows important examples of advanced synthesis of drugs molecules using IL media. There are also many reports on the synthesis of molecules, which can be used as precursors for potential drugs with various activities and contain sulfonamide,[672] lactam,[675] imidazole,[707,708] pyrazolone,[709] thiazole,[710,711] or thiazolidine[712,713] cores.

One of the most interesting and promising discoveries concerns the employment of ILs for controlling the stability and selectivity of enzymes. ILs have recommended themselves as "chaperons", which interact both with water and with the protein surface in the solution. Usage of IL additives provides stabilization and enhanced activity of enzymes,[47,733] allows controlled, reversible folding/unfolding of proteins, and reduces protein aggregation.[96,734−737] Imidazolium-based cations with short alkyl side chains mostly stabilize the protein structure and preserve its activity.[734] However, the behavior of large, multidomain proteins in the IL media can be rather complex, and making general assumptions and conclusions on the basis of the existing data is a difficult task.[734,738]

In many cases, the IL impact on a protein structure seems to be related to interactions between ILs and the aqueous environment of a protein. Because hydration energies of charged molecules are typically rather large, the relocation of water bound to them should produce considerable energetic effects. Water possesses a high dielectric constant, which renders it an efficient solvent for ions and biological polyelectrolytes, such as proteins and DNA. In the case of proteins, surface water molecules interact preferentially with charged amino acids, as well as with other polar groups. Protein folding is known to be mediated by aqueous solvating: water hydrates the protein backbone and "guides" it toward a final active structure. At the protein surface, water molecules gather in clusters, which are governed by the hydrogen-bonding capacity and structure of the protein; some of these molecules occupy specific sites and are highly important for correct protein function. Such water molecules can be seen as a rightful part of the secondary structure of a protein, whereas ordered water molecules between donor and acceptor sites can promote proton and electron transfer. Being a nucleophile and proton donor, water can serve as a reagent in the active site of a protein. Moreover, hydrogen-bond networks are suggested to provide dielectric shielding between protein molecules, thus promoting directed electrostatic interactions between their hydrophilic groups.[739−742]

Most ILs, except highly hydrophobic ones, contain some water. Moreover, water can be easily adsorbed by ILs from humid air. According to molecular dynamics simulations, water molecules, which are present in IL, accumulate near charged electrodes, and their amount increases upon increasing the surface charge density.[743] This observation agrees with experimental studies, according to which water molecules form hydrogen-bond networks at the electrode interface[744] and interact with IL, therefore diminishing the interactions between the electrode surface and cations and anions.[745,746] Of note, the mechanisms of surface charging are suggested to influence the water impact on IL structuring significantly; this impact is supposedly related to balances between interactions between ions, surface, and water, which can vary depending on their combination.[747] Interestingly, water−IL systems demonstrate electrochemical anomalies, which depend on the amount of water. Thus, the ethylammonium nitrate−water system demonstrated electrochemical instabilities in the intermediate state between IL and bulk water (70−90% water in the system).[748] All

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of these data support the idea of water being a mediator of at least some effects imposed by ILs on proteins.

The ability of ILs to stabilize protein molecules may be generally systemized similarly to small ions of the traditional salts. IL ions can be divided into kosmotropic (structuring) ions, which stabilize protein molecules, and chaotropic (destructing) ions, which destabilize protein molecules. Kosmotropes are intensively hydrated ions with pronounced salting-out activity; chaotropes are less hydrated ions with weak salting-out activity toward protein molecules. Thus, IL cations can be ascribed to chaotropic ions. However, due to the complex structure of IL ions and their capability to participate in various types of interactions, there are some difficulties in the unambiguous classification of IL ions to kosmotropic or chaotropic groups.[354,734]

According to molecular dynamics simulations, α-chymotrypsin[749] and lipases from *Candida* spp.[750] demonstrated higher stability in aqueous solutions of the $[C_4MIM]^+$ ILs, as compared to water. The ILs stripped nonlocalized water molecules from the protein surface, and the effect correlated with the solubility and hydrophobicity of the anions; thus, smaller anions with higher water solubility, such as chloride, were able to enter the protein core and caused its destabilization.[749,750]

A combined simulation and experimental study on the interaction of cytochrome *c* with ethylammonium nitrate showed that the IL formed a tight shell around the solvated protein supporting its renaturation.[751] On the contrary, ammonium-based ILs turned out to be powerful destabilizers of heme proteins. The length of the cation alkyl chains correlated with the effect: shorter chains imposed stronger destabilization, possibly due to stronger interactions with the hydrophobic regions of the proteins, which, in turn, might be related to the IL viscosity.[752] Similarly, aqueous $[C_2MIM][OAc]$ led to denaturation of a β-hairpin peptide.[753] Aqueous solutions of $[C_2MIM][OAc]$ and $[C_2MIM][C_2SO_4]$ interfered with the activity of xylanase from *Trichoderma longibrachiatum*, however, not due to denaturation of the enzyme but due to hindrance of its dynamic motion and kinetic trapping of the IL cations in its binding pocket.[754]

The existence of a hydration layer was crucial for the enzyme stabilization; thus, the structure of cutinase from the fungus *Fusarium solani* was dependent on the water amount in IL. $[C_4MIM][PF_6]$ removed water from the protein surface, but the remaining water molecules were enough for retention of the active structure; contrariwise, $[C_4MIM][NO_3]$ promoted more extensive water removal, which led to the enzyme inhibition. Strong interactions between $[NO_3]^-$ and hydrogen donor groups of cutinase were supposed to be the main cause of the structural destabilization.[755]

As was shown by classical MD simulation, cations of $[C_5MIM][Br]$ may replace water molecules in the solvation layer of lysozyme. This replacement caused the reduction of the size of the protein molecule (the hydrodynamic radius decreased from 18 Å in water to 11 Å in the water/IL mixture) and accelerated its conformational dynamics. The overall radius of the area of preferential solvation of the protein molecule by the IL cation was 42 Å.[756]

An experimental study on the stability of protein dispersions in aqueous solutions of $[C_nMIM][Cl]$ (n = 6, 8) suggested that the proteins preferentially bound to the IL via electrostatic interactions between charged areas of the protein molecule and the imidazolium part and chloride anion of the IL; the formation of hydrogen bonds and van der Waals interactions was also possible. Therefore, ILs penetrated the first hydration level of the protein and replaced it with an IL bilayer, which enhanced the stability of a nonaggregated protein fraction (monomers and dimers). The protein monomers subsequently adhered to each other due to overlapping of hydrophibic tails of the bound IL, which led to the formation of an aggregated fraction (bulky protein clusters). The presence of IL inhibited the pH-dependent protonation/deprotonation occurring in the protein dispersions in water, but had little impact on the protein integrity.[757] The authors suggested potential application of ILs as aggregation inhibitors for protein solutions (Figure 22).[758]

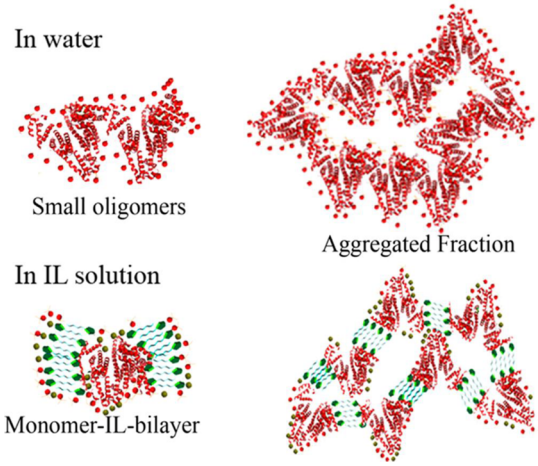

Figure 22. BSA aggregation in aqueous solutions in the presence/absence of $[C_8MIM][Cl]$. Reproduced with permission from ref 757. Copyright 2012 American Chemical Society.

Interestingly, positive supercharging of the surface of endoglucanase E1 from *Acidothermus cellulolyticus* assisted the maintenance of its wild-type activity in $[C_2MIM][OAc]$ and other ILs, which otherwise inhibited the enzyme.[759] According to a theoretical study, $[C_2MIM][OAc]$ demonstrated preferential solvation of positively charged solutes, possibly because of higher packing density in the first solvation shell formed by acetate ions; this result highlights the dominance of electrostatic interactions between the first solvent shell and the solute.[760]

According to the existing reports, the intact hydration layer is not always necessary for the protein integrity. Thus, anhydrous ILs were shown to solubilize dry proteins by forming surfactant nanostructures,[761] and ionization properties of IL were suggested to be responsible for the enzyme activation (Figure 23).[762]

According to a theoretical study on lipase B from *Candida antarctica* (CAL-B), the enzyme formed Coulomb interactions with the IL anions and van der Waals interactions with the cations; the ions, which formed strong hydrogen bonds with the enzyme, promoted conformational changes in the protein, leading to its denaturation. The butyl group of the $[C_4MIM]^+$ cation was able to penetrate into the active site of the lipase, possibly inhibiting its activity.[763] In the consecutive study, the authors investigated the process of CAL-B destabilization by ILs and defined two modes of the IL action: destabilization of the enzyme surface occurred mostly due to strong Coulomb interactions with the IL anions and polar cation groups, whereas destabilization of the enzyme core was due to conformational changes induced by long alkyl chains of ILs; in the latter case, these changes opened the access of IL ions into CAL-B.[764] Similar results were obtained in an experimental and theoretical study of interactions between bovine serum albumin (BSA) and

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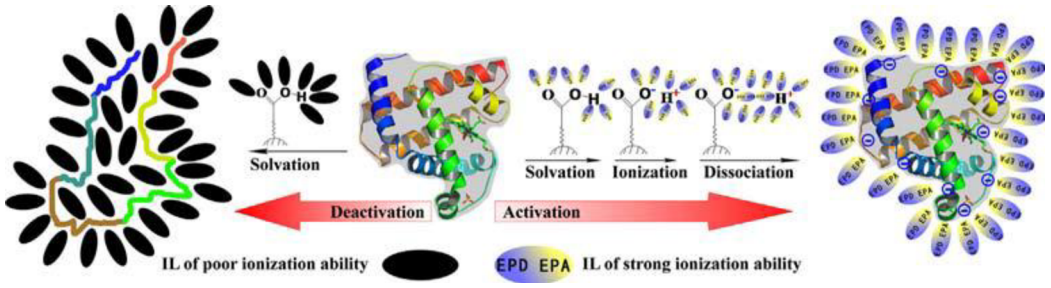

Figure 23. Enzyme activation/deactivation in ionic liquids. Reproduced with permission from ref 762. Copyright 2016 Elsevier.

imidazolium ILs: ILs led to unfolding of the protein. The imidazolium moiety entered the BSA subdomains and formed contacts with hydrophobic amino acids. The process depended on the anionic moiety of ILs: thus, the presence of the $[NO_3]^-$ anion resulted in significantly stronger interactions between the IL and BSA, in comparison with the $[Cl]^-$ anion.[765] A study on the interaction between BSA and $[C_n MIM][Br]$ (n = 4, 6, 8, 10) demonstrated that in the case of $[C_{10}MIM][Br]$, hydrophobic interactions were predominant, whereas in the case of $[C_4MIM][Br]$, $[C_6MIM][Br]$, and $[C_8MIM][Br]$, hydrogen bonds and van der Waals interactions played the major role. Accordingly, $[C_{10}MIM][Br]$ caused significant changes in the secondary structure of BSA.[766]

Molecular dynamics modeling of the *Candida rugosa* lipase 1 in $[C_4MIM][PF_6]$ and $[C_4MIM][NO_3]$ demonstrated that even at 310 and 375 K the ILs significantly decelerated the protein dynamics and detained the system near its starting structure. The interactions between the enzyme surface and the solvent were dominated by the IL anion, possibly due to a broader spatial distribution of positively charged residues of the protein and limited mobility of the bulky cation.[767] According to a subsequent MD investigation of the native and modified *C. rugosa* lipase in the aqueous ionic liquids $[C_4MIM][Cl]$ and $[C_2MIM][C_2SO_4]$, there was no indication of structural destabilization of either modified or unmodified enzyme on the 50 ns time scale. In the modified lipase, the surface lysine residues were randomly mutated to glutamate, which effectively decreased the net surface charge. Changes in the surface characteristics of the protein were shown to impact the close-range ion solvation shells; thus, a decrease in the local concentration of anions and an increase in the bound cations or water molecules were observed due to the increase of the number of negatively charged residues. The solvent reorganization was suggested to be crucial for the protection of the enzyme from smaller anions, which could permeate its surface and disrupt its structure.[768] Therefore, targeted modification of enzymes can be an effective way to regulate their tolerance toward IL action and their biopharmaceutical activity.

According to MD simulation, $[C_1C_4Pyr][NTf_2]$ could dramatically decrease the mobility of a 20-residue tryptophan (Trp) cage mini-protein. The unfolded Trp cage folded in water at 298 K in less than 500 ns of simulation; on the contrary, it demonstrated very limited mobility in IL at the same temperature, possibly due to higher IL viscosity. Nevertheless, the folded Trp cage in IL closely resembled that in water. Similar theoretical results were obtained for amino-acid-based ILs.[769] Complete substitution of water by organic cations and anions further hampered the conformational flexibility of the Trp cage, suggesting that such ILs could protect proteins from thermal denaturation. Comparison of the Trp cage solution in the amino-acid IL and in water showed that the amino acid anions dominated in the first coordination sphere of positively charged sites of the Trp cage, whereas water molecules dominated in the first coordination sphere of negatively charged sites of the Trp cage.[770] ILs also selectively promoted folding of various secondary structures of proteins,[771] implying possible application of ILs as stabilizers.

All of these data also suggest the possibility of modulating the structure and activity of an enzyme by tuning the structure of an IL supplement. Thus, cocosalkylpentaethoxymethylammonium methyl sulfate was found to induce changes in the secondary and tertiary structures of β-galactosidase from *Thermus thermophilus*; according to experimental and theoretical studies, the presence of IL led to increased flexibility of the enzyme and subsequent modifications in its activity and regioselectivity.[772] Similarly, the presence of $[C_4MIM][PF_6]$ changed the substrate specificity of β-galactosidase from *Aspergillus oryzae*.[773] $[C_8MIM][Cl]$ and $[C_{10}MIM][Cl]$ stimulated the activity of the firefly luciferase: the imidazolium ring of the ILs blocked the entrance into the AMP pocket of the enzyme; the ILs acted as competitive inhibitors of AMP and luciferun, which resulted in low-concentration hormetic stimulation. For $[C_6MIM][Cl]$ and $[C_{12}MIM][Cl]$, the effect was less pronounced, whereas $[C_2MIM][Cl]$ and $[C_4MIM][Cl]$ demonstrated no hormesis.[774] To overcome inhibitive effects of ILs on biocatalytically demanded enzymes, targeted protein engineering for diminishing unfavorable interactions between ILs and proteins was proposed.[775,776]

$[C_4MIM][PF_6]$ provided a suitable environment for kinetic resolution of (*R*,*S*)-ibuprofen by native lipases from *Candida rugosa* and *Aspergillus*,[666,667] whereas $[C_8C_1Py][BF_4]$ allowed efficient production of (*S*)-ibuprofen from racemic ibuprofen ethyl ester by thermostable esterase (EST10) from *Thermotoga maritime*.[715] The ability of ILs to affect the enzyme regioselectivity was exploited in lipase-catalyzed synthesis of esters of nucleoside drugs (derivatives of ribavirin, cytarabine, and inosine), where 10% supplement of $[C_4MIM][BF_4]$ accelerated the reaction and led to significantly higher yields.[669] $[C_4MIM][NTf_2]$ turned out to be a promising solvent for *trans*-esterification of methyl caffeate by lipase B from *Candida antarctica*; the obtained esters demonstrated antiproliferative activity;[694] this enzyme also effectively synthesized caffeic acid phenylethyl ester in $[C_2MIM][NTf_2]$.[777] $[C_4MIM][PF_6]$ and $[C_4MIM][BF_4]$ showed good results when used as cosolvents in *trans*-esterification of (*R*,*S*)-1-chloro-3-(3,4-difluorophenoxy)-2-propanol, which was an intermediate in the synthesis of the neuroprotector (*S*)-lubeluzole, by lipases from *Pseudomonas aeruginosa*.[727] $[C_2MIM][Br]$ facilitated enantioselective production of (*R*)-modafinil by chloroperoxidase from *Caldariomyces fumago*.[716]

Recently, a water-soluble artificial enzyme demonstrated a significantly enhanced ability to promote a dephosphorylation reaction, when bearing an ionic imidazolium tag. The

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Table 4. Application of ILs in the Preparation of Drug Delivery Systems

drug delivery system	IL	role of IL	ref
microporous poly(lactic acid) scaffolds	[C_4MIM][OTf], [C_4MIM][Cl], [C_4MIM][BF_4], [C_4MIM][SbF_6]	microporosity enhancers	784
polylactic acid and polycaprolactone membranes and microspheres	[$(C_8)_3C_1$N][Cl], [C_4MIM][NTf_2], [C_4MIM][PF_6], [C_4MIM][BF_4], [C_4MIM][OTf], [C_4MIM][Cl], [C_4MIM][SbF_6]	additive for microsphere preparation	785−788
cellulose-biopolymer composite hydrogel	[C_2MIM][OAc]	solvent	793
cellulose-*graft*-poly(L-lactide)	[C_4MIM][Cl], [AlkMIM][Cl]	solvent	794,814
cellulose/SWCNT complex	[C_4MIM][Br]	solvent	795
cellulose-nanohydroxyapatite composite scaffolds	[C_4MIM][Cl]	solvent	796
cellulose, keratin, and chitosan composite materials	[C_4MIM][Cl]	solvent	800
chitosan-based nanocarriers	[C_4MIM][Cl]	solvent	801
linoleic acid-grafted chitosan micelles	[C_4MIM][OAc]	solvent	802
biopolymeric chitosan Schiff bases with salicylidene IL brushes	IL-based salicyldehyde	functionalization agent	803
benzylpyrazolyl coumarin scaffolds	[C_5MIM][Br]	catalyst and reaction media	782
fullerenes	[C_4MIM][BF_4]	fullerene dispersion enhancer	781
curcumin-loaded platinum-phytase nanospheres	[C_4MIM][BF_4]	media for self-assembly of enzyme nanospheres	783
silica particles	[C_4MIM][BF_4]	solvent	805
Ag-NPs	[HOC_2C_{14}IM][Br], [$((HO)_2C_3)C_{14}$IM][Cl], [$HOC_2C_1C_{14}$IM][Cl], [$HOC_2C_1C_{16}$IM][Cl], [C_{16}Py][Sal]	dispersing agent	628,812
starch nanoparticles	[C_{16}MIM][Br] + [C_8MIM][OAc], [C_{16}MIM][Br], [C_4MIM][PF_6], [C_8MIM][NTf_2] + [C_{16}MIM][Br]	microemulsion cross-linking reaction	806−809
polyphosphate nanogel	[C_4MIM][BF_4]	solvent	789
magnetic mesoporous CoNi@Au nanorods	[C_4MIM][PF_6]	IL-in-water microemulsion as electrochemical media	811
Au-NPs	bis-imidazolium amphiphiles	ligands acting as transfer agents and NP stabilizers	810

phenomenon was explained in the terms of IL effects: the imidazolium cation was supposedly responsible for the substrate activation.[135]

Another area of IL usage in pharmaceutical synthesis is closely related to the previous one and also exploits unique IL abilities to affect enzymatic activity and selectivity. In whole-cell biosynthetic processes, ILs are used as components of ionic liquid/water solvent systems to overcome low water solubility and toxicity of substrates and products.[778−780] Thus, [C_4MIM][NTf_2] was used for promoting *Escherichia coli*, which expressed reductase from *Saccharomyces cerevisiae* and glucose dehydrogenase from *Bacillus subtilis*, to enantioselectively convert 3-chloro-1-phenyl-1-propanone to (*S*)-3-chloro-1-phenyl-1-propanol, which was a building block for the synthesis of antidepressant drugs.[724] A biphasic system consisting of [C_4MIM][PF_6] and buffer was employed for enantioselective reduction of acetyltrimethylsilane to (*R*)-1-trimethylsilylethanol, a precursor of silicon-containing drugs, by *Candida parapsilosis*. Both the substrate and the product were toxic for the immobilized cells, but the IL system allowed separating the dangerous substances from the biocatalyst.[730] Another example of successful employment of an IL system containing [C_4MIM][PF_6] in the whole-cell biocatalysis is hydroxylation of 16α,17-epoxyprogesterone, an important stage in the synthesis of steroidal drugs, by *Rhizopus nigricans*.[729]

There are also numerous reports on using ILs for production of diverse drug delivery systems. According to Table 4, which includes examples of current IL applications in preparation of drug delivery systems, in this case, imidazolium ILs also seem to be the substances of choice and are mostly used as media and dispersion agents. Thus, [C_4MIM][BF_4]−water mixtures allowed effective dispersion of hydrophobic C_{60} fullerenes, which showed high biomedical potential.[781] Benzylpyrazolyl coumarin scaffolds, which presumably possessed inhibitory activity toward the cyclooxygenase COX-II, were synthesized by using [C_5MIM][Br] as catalyst and reaction media.[782] The enzyme phytase self-assembled into active nanospheres in [C_4MIM][BF_4], and these nanospheres were subsequently used for production of platinum-decorated, curcumin-loaded phytase nanospeheres, which the authors considered "multifunctional protein-based drug delivery vehicles".[783]

[C_4MIM][OTf], [C_4MIM][Cl], [C_4MIM][BF_4], and [C_4MIM][SbF_6] were employed for developing tissue-compatible microporous poly(lactic acid) scaffolds with enhanced cell adhesion properties and drug loading capacity.[784] Highly porous polylactic and polycaprolactone membranes and microspheres were prepared using [$(C_8)_3C_1$N][Cl] or [C_4MIM] ILs with various anions.[785,786] The polycaprolactone microspheres were subsequently modified with water-soluble carbon nanotubes and paclitaxel or NGF-containing gelatin to obtain model drug delivery systems.[787,788] IL miniemulsions were employed for the synthesis of a biocompatible branched polyphosphate nanogel.[789]

There are several patents on cellulose dissolution and processing in ILs,[790−792] and ILs turned out to be helpful in the preparation of cellulose-based polymers with possible biomedical applications (see examples in Table 4). Thus, dissolution of cellulose in [C_2MIM][OAc] with subsequent addition of lipase from *Candida rugosa* allowed efficient entrapping of the enzyme in the cellulose hydrogel.[793] Microcrystalline cellulose-*graft*-poly(L-lactide) copolymers were synthesized in [C_4MIM][Cl]; micelles of these copolymers demonstrated high efficiency in drug loading.[794] A biocompatible complex of cellulose with single-walled carbon nanotubes was prepared in [C_4MIM][Br].[795] Employment of [C_4MIM][Cl] allowed better dispersion of hydroxyapatite in cellulose when preparing cellulose−nanohydroxyapatite composite scaffolds for drug encapsulation.[796]

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It should be mentioned that the solubility of natural polymers, such as cellulose, in ILs is a very important topic. Thus, cellulose is poorly soluble in water and common organic solvents; application of ILs allows one to realize the chemical conversion of plant biomass, which has been considered a rather difficult task before.[34,36,797,798] Similarly, imidazolium-based ILs turned out to be appropriate solvents for chitin.[799]

Cellulose, keratin, and chitosan composite materials suitable for controlled drug release,[800] as well as temperature- and pH-sensitive chitosan-based nanocarriers,[801] were prepared by using [C_4MIM][Cl] as solvent. Micelles of linoleic acid-modified chitosan were produced in [C_4MIM][OAc].[802] Recently, biopolymeric chitosan Schiff bases with salicylidene IL brushes complexed with Ag(I) were suggested to be used for the development of potent anticancer and antimicrobial agents.[803]

The first theoretical study of cellulose dissolution in ILs by classical MD was carried out for [C_2MIM][OAc] as solvent. The energy of the interaction between the polysaccharide chain and IL was higher than that for either water or methanol. The anion formed strong hydrogen bonds with hydroxyl groups of cellulose, whereas some cations established hydrophobic interactions with the polysaccharide, confirming the hypothesis that the cation was important for the dissolution of cellulose in IL.[804]

ILs were also used for the preparation of various biomedical nanoparticles from silica,[805] starch,[806−809] silver,[93,94] gold,[810] and cobalt−nickel−gold[811] (see Table 4). In the case of silver, the particle size and dispersivity of nanoparticles depended on the IL structure.[812] Of note, Ag nanoparticles with enhanced antimicrobial activity were produced using [C_{16}Py][Sal] as dispersing agent.[628]

At the end of this section, we would like to mention a recent report on the application of ILs for skin tissue engineering. [C_4MIM][OAc] was proposed to be used as solvent for muga fibroin from cocoons of the silkworm *Antheraea assama*. The resulting solution was subsequently used for electrospinning of nanofibrous mats, which could become a promising alternative to xenotransplants or allotransplants.[813]

4.2. Ionic Liquids in Biomedical Analytics

Because of their unique and flexible properties, ionic liquids find application in numerous fields, including those related to chemical analysis. ILs are employed in electrophoresis,[80,81,815] extraction,[81,85,87,488−490,816,817] gas and liquid chromatography,[80,81,818,819] UV−visible, IR, Raman, and fluorescence spectroscopy,[80,81] NMR,[81,164,165,167−169,820] and mass spectrometry,[80,81,170,821,822] as well as in various sensor systems (Figure 24).[80−82,823−825] Several comprehensive reviews have been published on the topic recently.[80−82,818,825] Therefore, in this section we discuss only some representative examples of successful application of ILs in the detection of natural and pharmaceutical substances.

In one of the first reports on the application of ILs in analytical techniques, an imidazolium IL-coated capillary was used for the determination of sildenafil and its metabolite in the human serum by capillary zone electrophoresis−ion-trap mass spectrometry. The IL coating provided improved resolution and precluded absorption of the substances on the capillary wall.[815] Usage of imidazolium-based ILs as mobile phase additives in the reversed-phase liquid chromatography enhanced separation of basic drugs by alleviating the issue of broad chromatographic peaks, which arose through interactions of the positively charged drugs with free silanol groups of the reverse phase.[826,827] In addition, employment of chiral ILs as electrolyte additives during

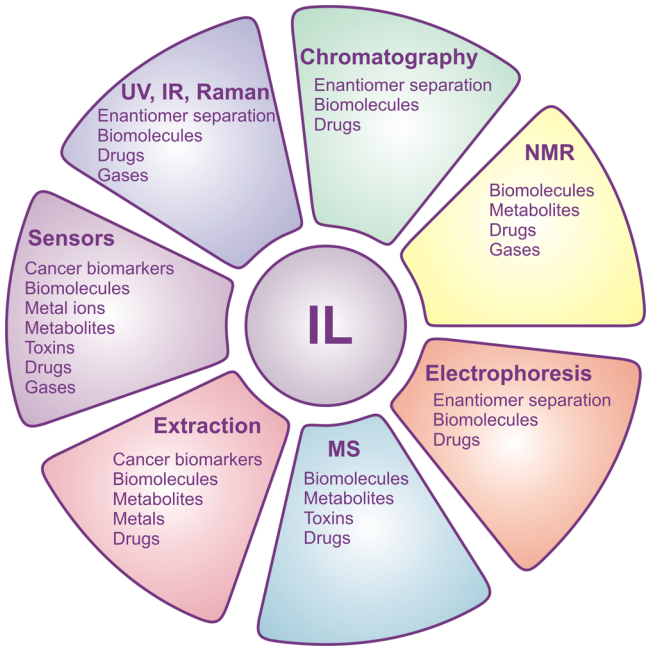

Figure 24. Graphical summary of application of ionic liquids in biomedical analytics.

electrophoresis allowed separating enantiomers of various active pharmaceutical ingredients.[828−830] Similarly, an IL-functionalized β-dextrin was successfully used as chiral selector in capillary electrophoresis.[831] A fluorescence technique based on interactions of enantiomers with optically active ILs was proposed for establishing enantiomeric composition of drugs.[832]

Excellent extraction properties of ILs have stimulated the development of numerous IL-based extraction systems for chemical and pharmaceutical analysis. There are three possible mechanisms of extraction: the solute can move between the phases in the form of supramolecular associates; partial mixing of the solvents may lead to transition of both solute and solvent molecules from one phase into the other and therefore to the nonuniformity of the phase boundary; and pure molecular extraction can occur, with solute molecules passing the boundary individually (Figure 25). For extraction of peptides from IL to the organic phase, the third mechanism (molecular diffusion) was found to be preferable.[488]

The IL-based microextraction combined with capillary electrophoresis was employed for the detection of analytes in

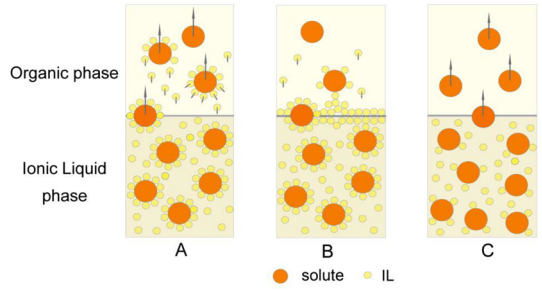

Figure 25. Possible mechanisms of solute transition from IL to organic phase: (A) Solute molecules move as supramolecular associates; (B) partial mixing of the phases occurs; and (C) solute molecules pass the boundary individually by molecular diffusion. Reproduced with permission from ref 488. Copyright 2015 American Chemical Society.

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Chem. Rev. 2017, 117, 7132−7189

biological samples and provided up to 1000-fold sensitivity enhancement.[833] Microextraction coupled with gas chromatography and mass spectrometry was proposed to be used for the determination of cancer biomarkers in urea samples. The suggested method was fully automated and allowed high-throughput analysis.[834] The IL-based microextraction coupled with liquid chromatography and UV detection was developed for analysis of the levels of the drugs nifurtimox and benznidazole in the plasma; the method demonstrated very low detection limits and required low amounts of sample.[835]

Among other analytical methods, NMR and mass spectrometry are highly demanded.[164,165,168,170] Thus, UV-light absorbing IL-based matrices were efficiently used in matrix-assisted desorption/ionization mass spectrometry (MALDI-MS) for biosensing bacterial toxins without preliminary separation and purification.[836]

As in many other scientific and industrial areas, the tunability of ILs has won them an important place in the field of electrochemical sensors. ILs are characterized by wide electrochemical windows and good electrochemical stability, which make them promising electrolytes.[82,825] However, ionic conductivity of ILs strongly depends on their chemical structure and viscosity; thus, imidazolium ILs demonstrate higher conductivity than pyrrolidinium or tetraalkylammonium ones. Therefore, IL-based electrolytes do not necessarily perform better than conventional ones, and the favorable combination of the electrode structure and material is the key to success.[825] Nevertheless, ILs are broadly employed in various electrochemical biosensors, which are based on carbon nanotubes (CNT), metal nanomaterial, graphene, carbon paste, and other materials.[82,823,825]

The IL-containing electrodes are used for the detection of low-level target molecules in biological fluids. A multiwall carbon nanotube (MWCNT)-ionic liquid electrode doped with gold nanoparticles and antibody was applied as immunosensor for human serum albumin.[837] An MWCNT-IL-modified electrode was used for developing an immunosensor for the tumor marker prostate specific antigen (PSA) in the serum; the immunosensor was produced by a simple one-step method and showed high sensitivity and reasonable accuracy.[838] An electrochemical immunosensor based on IL-doped graphene/gold nanoparticles with alkaline phosphatase as enhancer was used for the detection of the cancer biomarker APE1.[839] A carbon IL paste electrode with a graphene/MWCNT composite film successfully detected carbamazepine in the presence of paracetamol in tablets or urine samples.[840] A nanocomposite from IL-functionalized graphene and gold nanoparticles was used in an electrochemical immunosensor with the detection range from 1 fg mL^{-1} to 100 ng mL^{-1}; the sensor was efficiently applied for analysis of human serum samples;[841] similarly, an immunosensor based on IL-functionalized reduced graphene oxide and gold nanoparticles was proposed to be employed for simultaneous detection of multiple analytes.[842] A polymerized IL film-tin oxide electrode containing ZnCdHgSe quantum dots was decorated with antibody against the serum tumor marker neuron-specific enolase and demonstrated the wide detection range from 1 pg mL^{-1} to 100 ng mL^{-1}.[843]

In the end of the section, important reports on employing ILs in DNA studies should be also mentioned. It is well-established knowledge that highly charged counterions have an impact on DNA compaction.[844] Therefore, it is unsurprising that ILs can influence the DNA structure. Multicharged ions may possibly form by hydrogen bonding in ILs, which overcomes the electrostatic repulsion between similarly charged ions. Iron-containing magnetic hydrophobic ILs were found to perform excellently as solvents in efficient extraction of single- and double-stranded DNA molecules, as well as bacterial plasmid DNA. The obtained results suggested the possibility of selective extraction due to IL structural fine-tuning.[845] Of note, a $[C_4MIM][PF_6]$-containing extraction system was proposed to be used for direct DNA quantification,[846] whereas bis(dialkylamino)cyclopropenium chloride-based poly(ILs) formed complexes with plasmid DNA and were proposed to be used for efficient transfection of cells.[847]

ILs of various classes maintained the native double-strand DNA B structure; the cations mostly formed electrostatic interactions with the DNA phosphate groups, whereas the anions established hydrogen bonds with the nucleobases.[848−851] Hydrated choline dihydrogen phosphate stabilized the formation of a DNA triplex due to the binding of the choline cations to the third DNA strand.[852] DNA stored in IL showed enhanced resistance against nuclease-induced degradation,[853,854] and the IL guanidinium tris(pentafluoroethyl)trifluorophosphate was shown to induce DNA compaction.[855] The authors suggest that multicharged micellar aggregates of the IL are involved in this process: the positively charged part of the IL neutralizes the DNA negative charge (phosphate groups), whereas the anions participate in the formations of micelles; consequently, the DNA strands are attracted to the micellar surface (Figure 26).[855] $[C_nMIM][Cl]$ (n = 8, 12, 16) intercalated into double-stranded DNA, and the binding increased with the increasing alkyl side chain.[856]

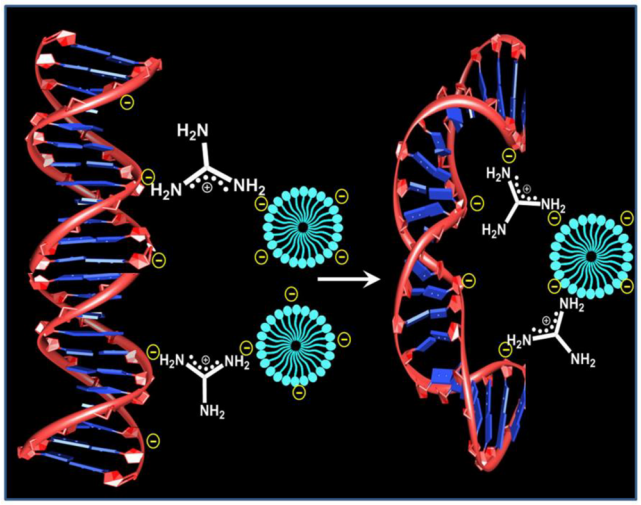

Figure 26. Possible mechanism of ionic liquid-driven DNA compaction. The positively charged part of IL neutralizes the DNA phosphate groups, whereas the anions form micelles to which the DNA strands are subsequently attracted. Reproduced with permission from ref 855. Copyright 2015 Nature Publishing Group.

Molecular dynamics simulations, docking studies, fluorescence, and electrochemical techniques suggest that, similarly to inorganic ions, IL cations interact both with the minor and with the major grooves of DNA. This interaction is mostly realized via the Coulomb attraction of cations to the diffuse negative charge of DNA, but hydrogen bonding, hydration, and dispersion forces also may be important (Figure 27).[354]

For $[C_1MIM][Cl]$, $[C_1MIM][PF_6]$, and $[C_1MIM][NTf_2]$, it was established that larger anions possessed higher ability to

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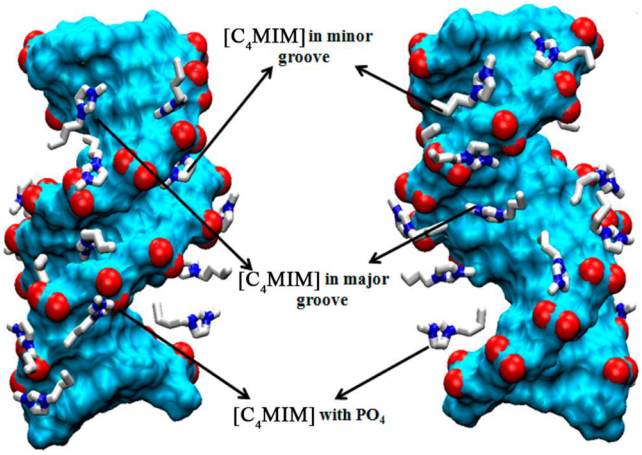

Figure 27. Interaction of [C_4MIM] cation with DNA backbone and grooves. Reproduced with permission from ref 849. Copyright 2012 American Chemical Society.

associate with π-systems of organic molecules ($[Cl]^- < [PF_6]^- < [NTf_2]^-$).[193] Evidence of $[Cl]^- \cdots \pi$ interactions was found within [C_4MIM][Cl] by DFT and ab initio methods; it should be noted that to produce correct theoretical results, the method must be capable of accurate description of the dispersion interaction.[187] Thus, bulky organic ions of ILs may interact with DNA by dispersion forces, which are especially pronounced in large aromatic molecular systems[857] and are particularly important for DNA–substrate complexes[858] and for stabilization of the double-helical DNA structure.[859]

5. CONCLUSIONS

During the last decades, the field of drug delivery has undergone dramatic changes. Medicine has turned from oral and transdermal formulations to sophisticated medium-sensitive carriers and nanoparticles for targeted delivery (Figure 28).[860] Accordingly, pharmaceutical formulations have changed from powders to diffusions in polymers to micelles and nanoparticles.[860,861]

Ionic interactions have been undoubtedly shown to take an important part in the formation and function of various drug carriers. As a leading example, block ionomer complexes, or polyion complex micelles, were designed as a class of carriers for charged molecules.[541−543] These complexes are formed via interactions between ionic block copolymers and macromolecules of opposite charge (DNA, proteins, etc.). Block ionomer complexes are characterized by high efficiency of loading, ease of preparation, and preservation of biomolecule activity, and are suggested to be used for overcoming the blood–brain barrier and delivering active substances into the brain.[542,543]

Another promising property of ionic carriers is the possibility of targeted release of their cargo. Biomolecules can leave the carrier not only via diffusion or carrier degradation, but also due to a pH shift or displacement by environmental counterions. Thus, anionic 5′-triphosphates of nucleoside analogues left the cationic nanogel upon interaction of the latter with cellular membranes, whereas cytochrome *c* exited the anionic gel upon acidification or addition of Ca^{2+} ions (Figure 29).[541]

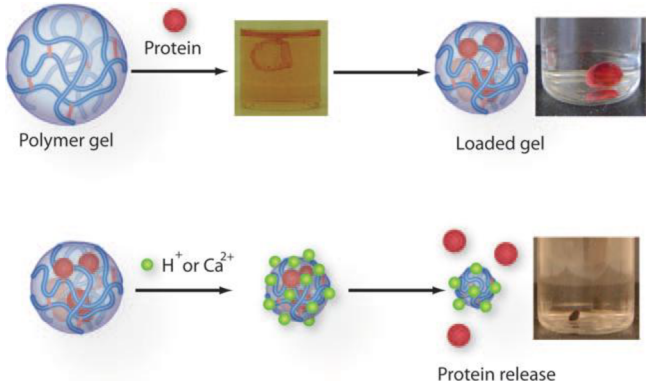

Figure 29. Loading and release of cytochrome *c* from anionic gel. Cytochrome *c* spontaneously forms a complex with anionic chains of the gel; upon acidification or addition of calcium ions, the protein is released due to gel protonation or competitive binding. Reproduced with permission from ref 541. Copyright 2009 Wiley-VCH Verlag GmbH & Co. KGaA.

In view of state-of-the-art tendencies in the development of new drugs, the following advantages and opportunities of ILs in the field of pharmaceutics and medicine can be summarized on the basis of the literature discussed in this Review:

(I) It is a straightforward and cost-efficient way to generate highly tunable, diverse libraries of biologically active compounds with a virtually unlimited number of combinations of anions and cations.

(II) ILs exhibit control of ion formation in solution and adjustment of solvation properties in water and biological fluids to provide a flexible approach for alleviation of solubility,

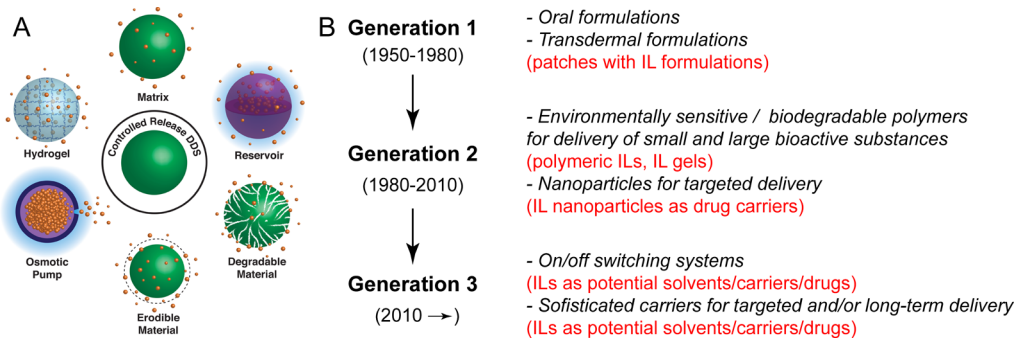

Figure 28. Evolution of controlled drug delivery systems: from oral and transdermal formulations to "clever" environmentally sensitive carriers. Part (A) reproduced with permission from ref 861 (Copyright 2016 American Chemical Society), and part (B) (in adapted form) reproduced with permission from ref 860 (Copyright 2014 Elsevier).

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bioavailability, and polymorphism limitations of conventional drugs.

(III) ILs allow easy incorporation of readily developed ionic cores into existing drug molecules, as well as design of novel drugs and biologically active molecules.

(IV) It is a powerful API-IL concept to fine-tune hydrophobic/hydrophilic properties, nature of ionic core, covalent/ionic binding, linker size, and characteristics via simple organic synthesis procedures (Figure 21).

(V) ILs show intrinsically tunable structural organization (section 1.1) reflected at the nanoscale and microscale levels (section 1.2) with access to various types of biological activity (sections 2 and 3).

(VI) Application of ILs allows one to advance (bio)synthetic processes and to optimize the cost of production/analytics of pharmaceutical compounds (section 4).

The active development of the field has raised a number of important questions. Thus, the following challenges can be formulated upon the analysis of the current literature:

(I) Mechanisms of action of many biologically active compounds with ionic nature are poorly understood and require more detailed studies.

(II) Systematic comparative studies on different types of IL-based drug development systems are currently missing, because most of the reported results are focused on particular types of IL systems.

(III) Most of the studied systems utilize only a combination of ions (section 3) and Type I of the API-IL concept (Figure 21), whereas powerful but more complicated systems remain a future challenge.

(IV) The studies on the relationship between the molecular structure and nano-/microscale organization and translation of molecular properties into self-organized structures are only at the early stage of development.

(V) The fundamental nature of the systems involving formation, organization, and chemical reactivity of ions in the liquid phase urgently appeals for the development of new experimental and theoretical methods to gain the necessary understanding.

Research activity in the area of ionic liquids has reached an astonishing level with an enormous number of studies (Figure 30). The number of publications and the growth trend show a behavior similar to that of the mature life-science fields, such as genomics and proteomics, which have a principal influence on the progress in pharmaceutics and medicine.[862−864]

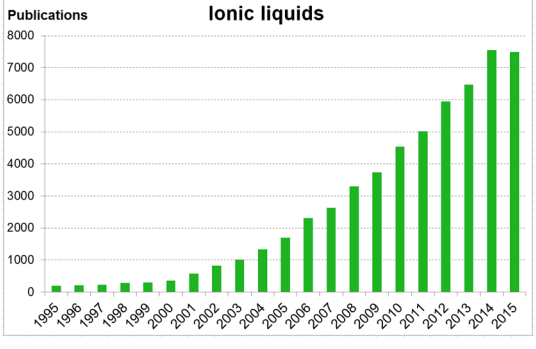

Figure 30. Number of publications on the subject of ionic liquids and molten salts (according to the Web of Science database, http://www.webofknowledge.com/).

Ioliomics, the studies of ions in liquids, is the key point of the ionic liquid rise, which has already made a valuable contribution to synthesis, catalysis, and material science.[865] Ioliomics should cover not only the pool of ions in biological systems, but also a broad range of studies on their properties and applications, which vary from classical chemical reactions to nanotechnology and drug delivery systems. Now it is clearly established that ionic interactions and ions themselves play important roles in building and maintaining structures of biological molecules and artificial materials, in enzymatic reactions and various chemical processes. The time is ripe now for fundamental insight into more complex chemical phenomena involving ILs and for their application in pharmaceutics and medicine.

As highlighted in the recent literature, ILs are anticipated to find several applications in drug delivery systems, from well-known conventional formulations to state-of-the-art carriers. The main subject of this Review deals with the rapidly developing area of in-depth studies on biological activity of ILs, and our aim is to attract the attention of a broad audience of readers to the challenges and opportunities of this fascinating interdisciplinary research. The emerging applications of ionic liquids in pharmaceutical science and drug development represent a collaborative effort between chemical, biological, and medical scientists, which will certainly uncover even more striking possibilities in the near future.

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Notes

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Biographies

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Evgeniy Gordeev completed his M.Sc. (2004) and Ph.D. in theoretical modeling and computations chemistry (2007) at the Lomonosov Moscow State Academy of Fine Chemical Technologies. Since 2011, he has been a researcher at the Zelinsky Institute of Organic Chemistry Russian Academy of Sciences. His research interests include theoretical studies, molecular modeling, reaction mechanisms, and scientific visualization.

Valentine Ananikov received his M.Sc. degree in 1996 (biochemistry), Ph.D. degree in 1999 (organic chemistry and catalysis), Habilitation in 2003, and in 2005 he was appointed Professor and Laboratory Head of the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences. In 2008 he was elected as a Member of the Russian Academy of Sciences. In 2012 he became Professor of the Chemistry Department of Moscow State University. He was a recipient of the Russian State Prize for Outstanding Achievements in Science and Technology (2004), an Award of the Science Support Foundation (2005), a Medal of the Russian Academy of Sciences (2000), Liebig Lecturer by German Chemical Society (2010), the Balandin Prize for outstanding achievements in the field of catalysis (2010), Organometallics Distinguished

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Chem. Rev. 2017, 117, 7132−7189

Author Award Lectureship by American Chemical Society (2016), and the Hitachi High-Technologies Award in Appreciation for Novel Approach and Outstanding Contribution to Setting New Standards for Electron Microscopy Applications in Chemistry (2016). His research interests are focused on mechanistic studies, catalysis, ionic liquids, and molecular complexity.

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ABBREVIATIONS

Cations of ILs

[Im]	imidazolium
[AlkMIM]	1-alkyl-3-methylimidazolium
[AMIM]	1-allyl-3-methylimidazolium
[AEIM]	1-allyl-3-ethylimidazolium
[C_1MIM]	1,3-dimethylimidazolium
[C_1C_1MIM]	1,2,3-trimethylimidazolium
[C_2MIM]	1-ethyl-3-methylimidazolium
[C_4MIM]	1-butyl-3-methylimidazolium
[C_4C_1MIM]	1-butyl-2,3-dimethylimidazolium
[C_5MIM]	1-pentyl-3-methylimidazolium
[C_6MIM]	1-hexyl-3-methylimidazolium
[C_8MIM]	1-octyl-3-methylimidazolium
[C_{10}MIM]	1-decyl-3-methylimidazolium
[C_{12}MIM]	1-dodecyl-3-methylimidazolium
[C_{14}MIM]	1-tetradecyl-3-methylimidazolium
[C_{16}MIM]	1-hexadecyl-3-methylimidazolium
[$C_{16}C_1$MIM]	1-hexadecyl-2,3-dimethylimidazolium
[HOC_2MIM]	1-(2-hydroxyethyl)-3-methylimidazolium
[C_1OC_2MIM]	1-methoxyethyl-3-methylimidazolium
[C_2OC_2MIM]	1-ethoxyethyl-3-methylimidazolium
[HOC_2OC_2MIM]	1-(4-hydroxy-2-oxybutyl)-3-methylimidazolium
[HOC_3MIM]	1-(3-hydroxypropyl)-3-methylimidazolium
[HOC_2C_{14}IM]	1-(2-hydroxyethyl)-3-tetradecylimidazolium
[$((HO)_2C_3)C_{14}$IM]	1-(2′,3′-dihydroxy)propyl-3-tetradecylimidazolium
[$HOC_2C_1C_{14}$IM]	1-(2-hydroxyethyl)-2-methyl-3-tetradecylimidazolium
[$HOC_2C_1C_{16}$IM]	1-hexadecyl-3-(2-hydroxyethyl)-2-methylimidazolium
[$SalOC_2$MIM]	1-(2-((2-hydroxybenzoyl)oxy)ethyl)-3-methylimidazolium
[$SalOC_3$MIM]	1-(3-((2-hydroxybenzoyl)oxy)propyl)-3-methylimidazolium
[C_2Py]	1-ethylpyridinium
[C_{16}Py]	1-hexadecylpyridinium, 1-cetylpyridinium
[C_4C_1Py]	1-butyl-3-methylpyridinium
[C_8C_1Py]	1-octyl-3-methylpyridinium
[C_6C_6OCOPy]	1-hexyl-3-hexyloxycarbonylpyridinium
[C_8OC_1HOPy]	3-hydroxy-1-octyloxymethylpyridinium
[C_1C_3Pyr]	*N*-methyl-*N*-propylpyrrolidinium
[C_1C_4Pyr]	*N*-methyl-*N*-butylpyrrolidinium
[HOC_2Pyr]	*N*-(2-hydroxyethyl)-pyrrolidinium
[C_2C_1Pip]	1-ethyl-1-methylpiperidinium
[$C_{10}C_1$Pip]	1-decyl-1-methylpiperidinium
[$C_{12}C_1$Pip]	1-dodecyl-1-methylpiperidinium
[C_2C_1Mor]	1-ethyl-1-methylmorpholinium
[$C_{10}C_1$Mor]	1-decyl-1-methylmorpholinium
[$(C_1)_4$N]	tetramethylammonium
[$(C_2)_4$N]	tetraethylammonium
[$(C_4)_4$N]	tetrabutylammonium
[$(C_1)_3C_4$N]	trimethylbutylammonium
[$(C_1)_3C_8$N]	trimethyloctylammonium
[$(C_1)_3C_{10}$N]	trimethyldecylammonium
[$(C_1)_3C_{12}$N]	trimethyldodecylammonium
[$(C_1)_3C_{16}$N]	trimethylhexadecylammonium, cetyltrimethylammonium
[$(C_4)_3C_1$N]	tributylmethylammonium
[$(C_8)_3C_1$N]	trioctylmethylammonium
[$(C_{10})_2(C_1)_2$N]	didecyldimethylammonium
[$(C_{11})_2(C_1)_2$N]	diundecyldimethylammonium
[Cho]	trimethylethanolammonium, cholinium
[$(C_2)_3$NH]	triethylammonium
[$(HOC_2)_3$NH]	triethanolammonium
[$(C_4)_3C_1$P]	tributylmethylphosphonium
[$(C_8)_3C_1$P]	trioctylmethylphosphonium
[$(C_4)_4$P]	tetrabutylphosphonium
[$(C_6)_3C_{14}$P]	trihexyl(tetradecyl)phosphonium
[$HOC_2(C_4)_3$P]	tributyl(2-hydroxyethyl)phosphonium
[$(C_1)_2(C_1)_2$G]	1,1,3,3-tetramethylguanidine
[HDBU]	1,8-diazabicyclo[5.4.0]undec-7-en-8-ium
[Benzalk]	benzalkonium
[Benzeth]	benzethonium
[Bupiv]	bupivacainum
[Lid]	lidocainium
[Metf]	metformin
[Pril]	prilocainum
[Proc]	procainium
[ProcA]	procainium amide
[Tet]	tetracycline

Anions of ILs

[Acesulf]	acesulfame
[Amp]	ampicillin
[ASal]	acetylsalicylate
[BF_4]	tetrafluoroborate
[Br]	bromide
[Bz]	benzoic acid
[HSO_4]	hydrogensulfate
[C_1SO_4]	methyl sulfate
[C_2SO_4]	ethyl sulfate
[C_8SO_4]	octyl sulfate
[$C_{10}SO_4$]	decyl sulfate
[$C_{12}SO_4$]	dodecyl (lauryl) sulfate
[$C_{18}SO_4$]	octadecyl sulfate
[Dic]	diclofenac
[DMP]	dimethylphosphate
[Doc]	docusate
[Fluf]	flufenamate
[Flurb]	flurbiprofenate
[Ibu]	ibuprofenate
[IBut]	isobutanoate
[ICl_2]	dichloroiodate
[Lac]	lactate
[Ms]	methanesulfonate
[$N(CN)_2$]	dicyanamide
[Nal]	nalidixate
[NO_3]	nitrate
[NTf_2]	bis(trifluoromethylsulfonyl)amide
[OAc]	acetate

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Chem. Rev. 2017, 117, 7132−7189

[OTf]	trifluoromethanesulfonate
[PF_6]	hexafluorophosphate
[Pro]	propanoate
[Sac]	saccharinate
[Sal]	salicylate
[Sulf]	sulfacetamide
[TFa]	trifluoroacetate
[Theophyl]	theophyllinate
[Trp]	tryptophan

Other

IL	ionic liquid
API-IL	active pharmaceutical ingredient-ionic liquid
BSA	bovine serum albumin
CNT	carbon nanotubes
CPMD	Car−Parinello molecular dynamics
DFT	density functional theory
GED	gas-phase electron diffraction
MD	molecular dynamics
MWCNT	multiwall carbon nanotubes
NGF	nerve growth factor
NSAID	nonsteroidal anti-inflammatory drug
PSA	prostate specific antigen
SANS	small-angle neutron scattering
SWCNT	single-wall carbon nanotubes
TSIL	task-specific ionic liquid

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