Ionic Liquids Beyond Simple Solvents: Glimpses at the State of the Art in Organic Chemistry

Andrea Kuchenbuch and Ralf Giernoth*[a]

Within the last 25 years ionic liquids have written a tremendous success story, which is documented in a nearly uncountable amount of original research papers, reviews, and numerous applications in research and industry. These days, ionic liquids can be considered as a mature class of compounds for many different applications. Frequently, they are used as neoteric solvents for chemical tansformations, and the number of reviews on this field of research is huge. In this focused review, though, we are trying to evaluate the state of the art of ionic liquid chemistry beyond using them simply as solvents for chemical transformations. It is *not* meant to be a comprehensive overview on the topic; the choice of emphasis and examples rather refects the authors' personal view on the field. We are especially highlighting fields in which we believe the most fundamental developments within the next five years will take place: biomass processing, (chiral) ionic liquids from natural sources, biotransformations, and organic synthesis.

1 Introduction

Since the first break-through publication of air- and moisture-stable room-temperature-liquid salts in the beginning of the 1990s,[1] ionic liquids (or "ILs", for short) have attracted tremendous attention from virtually all major fields of chemistry.[2–6] Like all new "trendy" topics, ILs were expected to be the "solution" for all currently unsolved chemical problems. Soon, all kinds of experiments and synthetic procedures—sensible or not—were performed in IL solvents, and for quite a while, just using an IL for *something* safely guaranteed a publication in a chemistry journal.
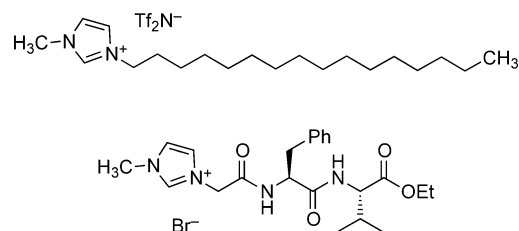
These days, ILs are typically applied as solvents for chemical transformations, and the huge choice of different ILs has led to the term "designer solvents" (see below). Early examples include all kinds of transition-metal catalysis—often with the twist that ILs are perfect media for biphasic processes.[7] Furthermore, since ILs are relatively polar and ionic interactions are strong, internal pressure effects like the ones known for reactions in water (i.e. solvophobic interactions) are also commonly applied. Classical examples include Diels–Alder reactions that show high efficiency, as well as endo selectivity in common ILs[8] (Scheme 1).

Now in the year 2015, this boom seems to be over. But, unlike other trend topics, ionic liquids are still here, and they appear to be there to stay. We know now that they can be
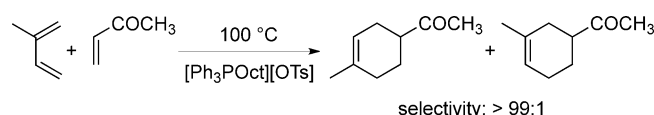
Scheme 1. Early example for the application of ionic liquids "just as solvent".[8]

used as solvents for *all* kinds of chemical transformations.[2,3,5,6] We also quite understand their somewhat unique properties. For example, ILs enable us to dissolve polar and nonpolar molecules simultaneously, for they can be designed to form regimes of different polarity within one homogeneous phase. (This behavior actually led to a new debate about the polarity concept and how to measure it.[9–11]) We understand the difference in dissolution behavior between simple inorganic salts and ILs as the presence or absence of dispersive interactions.[12] We even know these days that the low vapor pressures of these solvents will not render them "green solvents" per se, since many of them are considered quite toxic[13,14] (Figure 1), while others are not.[15] A recent review by Egorova and Ananikov gives a nuanced overview of biological systems for which an IL may or may not be considered toxic.[16]

[a] A. Kuchenbuch, Prof. Dr. R. Giernoth
Department für Chemie, Universität zu Köln
Greinstr. 4, 50939 Köln (Germany)
E-mail: ralf.giernoth@uni-koeln.de

Figure 1. Examples for "toxic" ionic liquids with antimicrobial activity.[13,14]

But aside from the solvent aspect, ionic liquids form a fascinating class of compounds that are utilized in many valuable applications. The major reasons are that it is quite easy to "tune" the IL according to the use case (by constructing one that exhibits the wanted properties), and that almost all of them display persistent ionic interactions combined with dispersive forces (the latter of which are completely absent in "simple" inorganic salts). Recent fields of application even extend this knowledge to using IL mixtures.[17] But more interestingly, the use of ILs as additives—for adapting the solvent's physical properties, as catalysts or auxiliaries, etc.—seems to be more like the current state of the art.

Within this tutorial review (which is more of a personal choice of topics that the authors find important and mentionable, rather than a complete in-depth overview) we are trying to evaluate the state of the art of ionic liquid chemistry *beyond using them simply as modern solvents* for chemical transformations. Consequently, we are also leaving out the huge field of electrochemical applications (for which in-depth reviews can be found in the recent literature[5, 18–20]), as well as the field of hybrid materials and nanoparticles.

2 Biomass Processing

The quest for completely renewable resources has dominated fundamental research in the beginning of the 21st century. A huge, yet still largely unused, carbon source is plant waste. The challenge is that crop stems and wood waste consists of lignocellulose—the material that nature chose to render plants as resistant as possible.

Lignocellulose is a mixture of cellulose, hemicellulose, and lignin. From chemistry's point of view, lignin is the most challenging component: a complex polymer of carbohydrates and aromatics. Since lignin is insoluble in all common organic solvents, its use as source or raw material for the production of

valuables resembles more the classic oil cracking and refining rather than a controlled synthetic process.[21] Furthermore, cellulose processing, to produce paper, for example (known as the Kraft process[21]), is far from being "green" for it utilizes a strongly alkaline solution (known as white liquor) for breaking the bonds between lignin and cellulose. In addition, a lot of volatile sulfur-containing by-products are released into the air.

Interestingly, only twenty years after Paul Walden described the very first ionic liquids in 1914[22] (he did not use the term "ionic liquid" at that time, though), the first patent appeared in which the use of ILs for the dissolution of cellulose was presented.[23] In this light, the current boom of patents in this area is more than surprising. Nonetheless, until recently, there was apparently no urgent need for sustainable alternatives to dissolve and process cellulose.

These days, the use of ILs for this purpose seems to open up completely new perspectives,[3, 24–27] for cellulose is readily soluble in many ILs. Therefore, it is conveniently possible to separate cellulose from lignin this way. Furthermore, a room-temperature liquid homogeneous solution enables all kinds of possibilities for follow-up chemistry. This way, not only paper processing is simplified; many valuable and sustainable bulk chemicals like (bio-) ethanol, γ-valerolactone, or 5-hydroxymethyl furfural (HMF) also become accessible (Scheme 2).
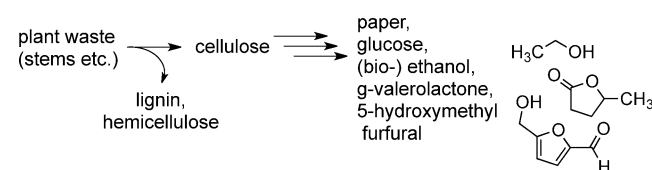
Scheme 2. Sustainable plant-waste processing in ionic liquids.

3 Chiral Ionic Liquids from Natural Sources

Ionic liquids have always been close to all fields of green chemistry. This has, of course, nothing to do with their (non)-toxicity—many of them are actually known to be quite toxic (see above). But the fact that many problems of sustainability in chemical processes are related to solvent issues has led to new ways of thinking about solvents. ILs can be "designed" to be perfect solvents for biphasic processes, and they can hardly evaporate under reaction conditions. Still, from a cradle-to-cradle point of view, it is necessary to consider the origin of these solvents, as well as their fate after having been used. Therefore, ILs being produced from natural sources (sustainable) can be expected to be readily biodegradable,[28, 29] as well as relatively nontoxic.[30]

The idea to design chiral ionic liquids for application in stereoselective catalysis is obvious and was born quite early in IL history.[31] And although only very few examples of chiral solvents for stereoselective synthesis can be found in the literature, hope was high that for ILs, things would be different due to their dominating ionic interactions. The concept of asymmetric counter-anion-directed catalysis (ACDC)[32] proved that it

Ralf Giernoth received his Diplom in 1996 and his Ph.D. in Chemistry in 1999 from the University of Bonn, Germany, under the supervision of Joachim Bargon. As a BASF research fellow, he did postdoctoral research at the University of Oxford, UK, together with John M. Brown. He then moved to the University of Cologne for independent research as a German Research Foundation (DFG) Emmy Noether fellow. In 2006, he received the *venia legendi* for organic chemistry. After a short intermezzo as interim professor at the University of Karlsruhe in 2009, he became professor for organic chemistry at the University of Cologne in 2014. His research interests are centered around ionic interactions, the application of in situ NMR and infrared spectroscopic techniques, and the development and application of task-specific ionic liquids.

is principally possible to get high stereoselection by using chiral ions as additives for organic transformations.

The synthesis of amino-acid-derived ILs is well established.[33, 34] Unfunctionalized amino acids can form the anion, as well as the cation of the IL, in combination with all sorts of established IL cations and anions. Amino acids can also be used as the basis for modified ionic structures. What all these examples have in common as the source of chirality is a natural, readily available one. Much to our surprise, the Ananikov group has very recently found that amino-acid-containing ILs are relatively toxic, especially with the amino acid as part of the cation.[35]

Other sources of natural chirality for ionic liquids include choline, tartrate, lactate, and sugars,[30, 36] but also more esoteric examples like nicotine or ephedrine.[28] A selection of representative structures is depicted in Figure 2. Interestingly, these motifs are seemingly more likely to render nontoxic ILs that are readily biodegradable.[37]
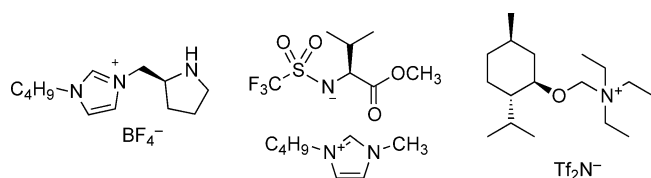

Figure 2. Selection of representative ionic liquid structures that are derived from natural chiral sources.

Armstrong and co-workers have assembled a comprehensive collection of all sorts of chiral ILs and have reported their successful use in synthesis.[36] A few results are highlighted in the following section.

4 Applications in Organic Synthesis

Against high hopes, chiral ionic liquid solvents seem to *not* be able to induce high levels of stereoselectivity when used as solvents. Nonetheless, they have found their way into chemical synthesis as catalysts and additives.

Not surprisingly, many (especially early) attempts for stereoselective synthesis using ionic liquids were inspired by organocatalysis, a field of research that developed historically in parallel to the chemistry of ILs. Thus, classical aldol-type conversions were early goals.[38] What also proved quite successful were the closely related class of Michael additions (Scheme 3), which
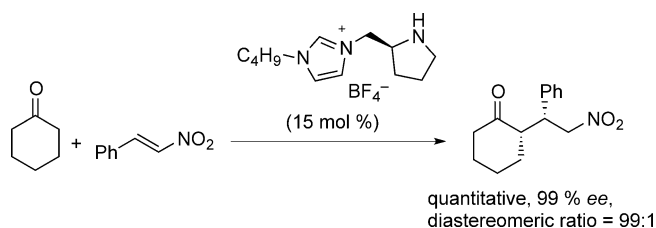
were easily and efficiently catalyzed by ionic liquids, especially by ones being derived from L-proline.[39, 40]

The example shown in Scheme 3 is one in which the organocatalyst is covalently attached to an IL cation. In a recent review, Headley and Ni have called this concept *ionic-liquid-supported* (ILS) catalysis.[41] Apart from this organocatalytic niche, hardly any convincing example of succesful and sensible or useful stereoselective reactions that use chiral ILs can be found in the literature.

Classical transition-metal catalysts readily dissolve in many common ILs. Therefore, it comes as no surprise that organometallic catalysis—especially homogeneous hydrogenation—was among the first examples for using ILs as solvents for chemical synthesis. (Scheme 4).[42] In transition-metal catalysis using un-
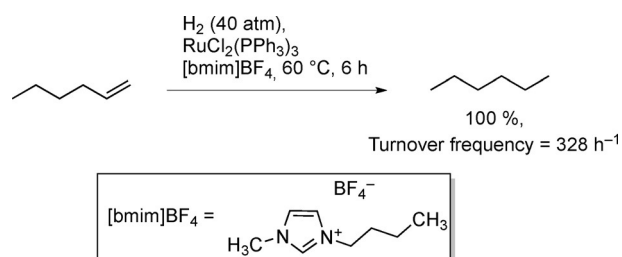
Scheme 4. One of the first historical examples of successful transition-metal catalysis in an ionic liquid.[42]

conventional solvents, the fundamental goal is to immobilize a homogeneous catalyst in a liquid phase for easy product separation and efficient catalyst recycling. Sometimes, the organometallic catalyst can also be covalently attached to the ionic liquid, which effectively renders an ionic-liquid transition-metal catalyst useful without the need for an IL solvent. This way, it is obvious to extend the ILS concept to transition-metal catalysis.[41] An insightful example by Geldbach and Dyson, a hydrogenation catalyst for acetophenone, is shown in Figure 3.[43]
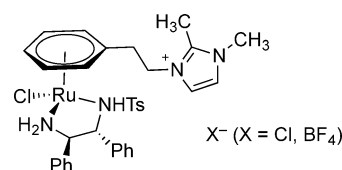
Figure 3. Ionic-liquid-bound transition-metal catalyst.[43]

5 Biotransformations

The ability to fine-tune polarity and interactions in solution with the help of ILs also has a great potential for biocatalysis and poses an obvious alternative to protein engineering. Enzyme chemistry is normally limited to aqueous systems, simply due to solubility issues. In biocatalysis, enzymes are used for highly selective organic transformations. The general scope of biotransformations is growing each day, since more

Scheme 3. Ionic-liquid-catalyzed Michael addition reaction.[39] *Reagents and conditions*: CF$_3$COOH (5 mol%), rt, 8 h, 100%.

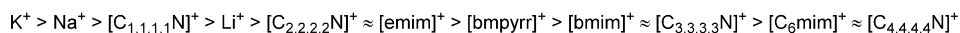and more non-natural biocatalytic processes are being discovered.

Enzyme activity in solution has long been connected with (and explained by) the Hofmeister series of ions.[44] Back in 1888, Hofmeister studied the stability of aqueous solutions containing egg white protein in the presence of varying concentrations of different anions. The results of these experiments led to the so-called Hofmeister series of ions (Figure 4).

Anions:

$SO_4^{2-} > HPO_4^{2-} > Cl^- > EtOSO_3^- > BF_4^- \approx Br^- > MeOSO_3^- > TfO^- > SCN^- \approx N(CN)_2^- > Tf_2N^-$

Cations:

$K^+ > Na^+ > [C_{1,1,1,1}N]^+ > Li^+ > [C_{2,2,2,2}N]^+ \approx [emim]^+ > [bmpyrr]^+ > [bmim]^+ \approx [C_{3,3,3,3}N]^+ > [C_6mim]^+ \approx [C_{4,4,4,4}N]^+$
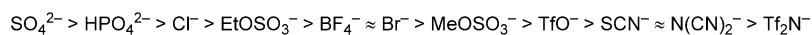
Figure 4. The Hofmeister series of ions, as determined by Weingärtner and co-workers,[45] sorted by their kosmotropicity: ions at the beginning of the series are called *kosmotropic*, ions at the end are *chaotropic* (cf. text).

Anions that stabilize the native structure of water are called *kosmotropic*, while structurally destabilizing anions are called *chaotropic*. Kosmotropic anions also stabilize the native structure of a protein, since they do not interact strongly with the protein; chaotropic ones interact with the protein and therefore destabilize it.

Weingärtner and co-workers have systematically studied the stabilizing and destabilizing effects of ionic liquids on proteins, very much in line with Hofmeister.[45] These experiments also led to an extension of Hofmeister's series to IL cations. Interestingly, for cations, everything seems to be "upside down": kosmotropic cations that stabilize the native structure of water destabilize proteins, while chaotropic cations stabilize the proteins. An overview on the nature of interactions between ILs and small peptides has been assembled by Tietze and co-workers.[46]

Based on this knowledge, it seems logical and obvious to exploit the use of ionic liquids as cosolvents with water for biotransformation reactions. Very low quantities of ILs have been reported to substantially enhance biocatalytic processes in terms of stability and selectivity, although current applications seem to be limited (or focused) to lipases as enzymes.[47] Only very few biotransformations have already been successfully carried out in neat ILs;[48] as an example, Lozano, Vaultier, and co-workers reported a pronounced stabilization effect of the enzyme α-chymotrypsin in transesterification reactions.[49] Recently, in another case, Imhof and co-workers have found that oxidative folding of certain cysteine-rich conotoxin peptides went along successfully only in the IL [emim]OAc, although various other ILs have been tested.[50]

In summary, one can say that the combination of biotransformations and ionic liquids has great potential for future applications. To date, unfortunately, general trends or even sensible conclusions are not yet available.[51] Most investigations are still in the early stage of development.[52]

6 Conclusions

The chemistry of ionic liquids in the year 2015 is obviously chemistry beyond the simple neoteric solvent. Surely, ILs provide a modern "solvent construction kit" with the potential to choose (or "design") exactly the properties that are needed for almost any given chemical reaction. But obviously ILs are far more than that, with virtually endless possibilities. Ionic liquids are able to dissolve mixtures of polar and unpolar substrates in one homogeneous phase, or provide the perfect choice for a biphasic system. They can dissolve biomolecules for subsequent processing that can otherwise only be processed with the aid of toxic or highly reactive chemicals. They can easily introduce chirality into a given process, either as a solvent or—much more frequently by reason of efficacy—as an ionic additive. The possibilities seem endless.

The understanding of ionic liquid chemistry is currently in a state in which a knowledge-driven development of IL processes (rather than a trial-and-error approach) is feasable. Beyond using them for chemical synthesis, we already see ILs as technical materials in industry (lubricants, gas absorbants, etc.), so they surely are here to stay.

In the future, we believe we shall see more technical, as well as chemical, applications. We strongly believe that some of the fundamental challenges in the near future will be tackled using ionic liqids, including the future of energy sources, sustainability, and the production of building-block chemicals from renewable sources.

7 Acknowledgements

[1] J. S. Wilkes, M. J. Zaworotko, *Chem. Commun.* **1992**, 965–967.
[2] J. P. Hallett, T. Welton, *Chem. Rev.* **2011**, *111*, 3508–3576.
[3] S. S. Y. Tan, D. R. MacFarlane, *Top Curr. Chem.* **2009**, *290*, 311–339.
[4] N. V. Plechkova, K. R. Seddon, *Chem. Soc. Rev.* **2008**, *37*, 123–150.
[5] G. Gebresilassie Eshetu, M. Armand, B. Scrosati, S. Passerini, *Angew. Chem. Int. Ed.* **2014**, *53*, 13342–13359; *Angew. Chem.* **2014**, *126*, 13558–13576.
[6] R. Ratti, *Adv. Chem.* **2014**, *2014*, 1–16.
[7] P. Wasserscheid in *Transition Metal Catalysis in Ionic Liquids, Vol. 6* (Ed.: P. T. Anastas), Wiley-VCH, **2010**, pp. 65–91.
[8] P. Ludley, N. Karodia, *Tetrahedron Lett.* **2001**, *42*, 2011–2014.

[9] M. Schmeisser, P. Illner, R. Puchta, A. Zahl, R. van Eldik, *Chem. Eur. J.* **2012**, *18*, 10969–10982.

[10] P. G. Jessop, D. A. Jessop, D. Fu, L. Phan, *Green Chem.* **2012**, *14*, 1245–1259.

[11] M. A. Ab Rani, A. Brant, L. Crowhurst, A. Dolan, M. Lui, N. H. Hassan, J. P. Hallett, P. A. Hunt, H. Niedermeyer, J. M. Perez-Arlandis, M. Schrems, T. Welton, R. Wilding, *Phys. Chem. Chem. Phys.* **2011**, *13*, 16831–10.

[12] S. Zahn, F. Uhlig, J. Thar, C. Spickermann, B. Kirchner, *Angew. Chem. Int. Ed.* **2008**, *47*, 3639–3641; *Angew. Chem.* **2008**, *120*, 3695–3697.

[13] J. Łuczak, C. Jungnickel, I. Lacka, S. Stolte, J. Hupka, *Green Chem.* **2010**, *12*, 593–601.

[14] D. Coleman, M. Spulák, M. T. Garcia, N. Gathergood, *Green Chem.* **2012**, *14*, 1350–1356.

[15] M. Petkovic, K. R. Seddon, L. P. N. Rebelo, C. S. Pereira, *Chem. Soc. Rev.* **2011**, *40*, 1383–1403.

[16] K. S. Egorova, V. P. Ananikov, *ChemSusChem* **2014**, *7*, 336–360.

[17] M. T. Clough, C. R. Crick, J. Grasvik, P. A. Hunt, H. Niedermeyer, T. Welton, O. P. Whitaker, *Chem. Sci.* **2015**, *6*, 1101–1114.

[18] M. C. Buzzeo, R. G. Evans, R. G. Compton, *ChemPhysChem* **2004**, *5*, 1106–1120.

[19] F. Endres, D. MacFarlane, A. Abbott, *Electrodeposition from Ionic Liquids*, John Wiley & Sons, Inc., New York, **2008**.

[20] H. Ohno, *Electrochemical Aspects of Ionic Liquids*, John Wiley & Sons, Inc., Hoboken, NJ, **2011**.

[21] C. J. Biermann, *Handbook of Pulping and Papermaking*, Academic Press, San Diego, CA, **1996**.

[22] P. Walden, *Bull. Acad. Imper. Sci. St. Petersbourg* **1914**, *8*, 405–422.

[23] C. Graenacher, (Basel, Switzerland), US Patent No.1943176, **1934**.

[24] R. Kordala-Markiewicz, *Przem. Chem.* **2013**, *92*, 1615–1617.

[25] P. Domínguez de María, *J. Chem. Technol. Biotechnol.* **2014**, *89*, 11–18.

[26] M. Isik, H. Sardon, D. Mecerreyes, *IJMS* **2014**, *15*, 11922–11940.

[27] K. M. Gupta, J. Jiang, *Chem. Eng. Sci.* **2015**, *121*, 180–189.

[28] G. Imperato, B. König, C. Chiappe, *Eur. J. Org. Chem.* **2007**, 1049–1058.

[29] D. Coleman, N. Gathergood, *Chem. Soc. Rev.* **2010**, *39*, 600–637.

[30] W. Gouveia, T. F. Jorge, S. Martins, M. Meireles, M. Carolino, C. Cruz, T. V. Almeida, M. E. M. Araújo, *Chemosphere* **2014**, *104*, 51–56.

[31] S. T. Handy, *Chem. Eur. J.* **2003**, *9*, 2938–2944.

[32] K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561; *Angew. Chem.* **2013**, *125*, 558–588.

[33] X. Chen, X. Li, A. Hu, F. Wang, *Tetrahedron: Asymmetry* **2008**, *19*, 1–14.

[34] N. V. Plechkova, K. R. Seddon in *Ionic Liquids Uncoiled* (Eds.: J. Kagimoto, H. Ohno), John Wiley & Sons, Inc., Hoboken, NJ, **2012**, chap. 7, pp. 231–250.

[35] K. S. Egorova, M. M. Seitkalieva, A. V. Posvyatenko, V. P. Ananikov, *Toxicol. Res.* **2015**, *4*, 152–159.

[36] T. Payagala, D. W. Armstrong, *Chirality* **2012**, *24*, 17–53.

[37] X.-D. Hou, Q.-P. Liu, T. J. Smith, N. Li, M.-H. Zong, *PLoS ONE* **2013**, *8*, e59145.

[38] W. Miao, T. H. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1711–1718.

[39] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; *Angew. Chem.* **2006**, *118*, 3165–3169.

[40] T. Miao, L. Wang, P. Li, J. Yan, *Synthesis* **2008**, 3828–3834.

[41] B. Ni, A. D. Headley, *Chem. Eur. J.* **2010**, *16*, 4426–4436.

[42] P. Suarez, S. Dullius, S. Einloft, R. F. deSouza, J. Dupont, *Inorg. Chim. Acta* **1997**, *255*, 207–209.

[43] T. J. Geldbach, P. J. Dyson, *J. Am. Chem. Soc.* **2004**, *126*, 8114–8115.

[44] T. Hofmeister, *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247.

[45] D. Constantinescu, H. Weingärtner, C. Herrmann, *Angew. Chem. Int. Ed.* **2007**, *46*, 8887–8889; *Angew. Chem.* **2007**, *119*, 9044–9046.

[46] A. A. Tietze, F. Bordusa, R. Giernoth, D. Imhof, T. Lenzer, A. Maa, C. Mrestani-Klaus, I. Neundorf, K. Oum, D. Reith, A. Stark, *ChemPhysChem* **2013**, *14*, 4044–4064.

[47] M. Goldfeder, A. Fishman, *Appl. Microbiol. Biotechnol.* **2014**, *98*, 545–554.

[48] A. Tavares, E. A. Macedo, O. Rodríguez in *New Generations of Ionic Liquids Applied to Enzymatic Biocatalysis* (Ed.: J.-I. Kadokawa), InTech, Rijeka, **2013**, chap. 20.

[49] P. Lozano, T. de Diego, J. P. Guegan, M. Vaultier, J. L. Iborra, *Biotechnol. Bioeng.* **2001**, *75*, 563–569.

[50] P. Heimer, A. A. Tietze, M. Böhm, R. Giernoth, A. Kuchenbuch, A. Stark, E. Leipold, S. H. Heinemann, C. Kandt, D. Imhof, *ChemBioChem* **2014**, *15*, 2754–2765.

[51] Q. Yan, H. Zang, C. Wu, J. Feng, M. Li, M. Zhang, L. Wang, B. Cheng, *J. Mol. Liq.* **2015**, *204*, 156–161.

[52] A. A. Tietze, P. Heimer, A. Stark, D. Imhof, *Molecules* **2012**, *17*, 4158–4185.