Low melting carbohydrate mixtures as solvents for chemical reactions and the conversion of carbohydrates

Dissertation

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Meinen Eltern

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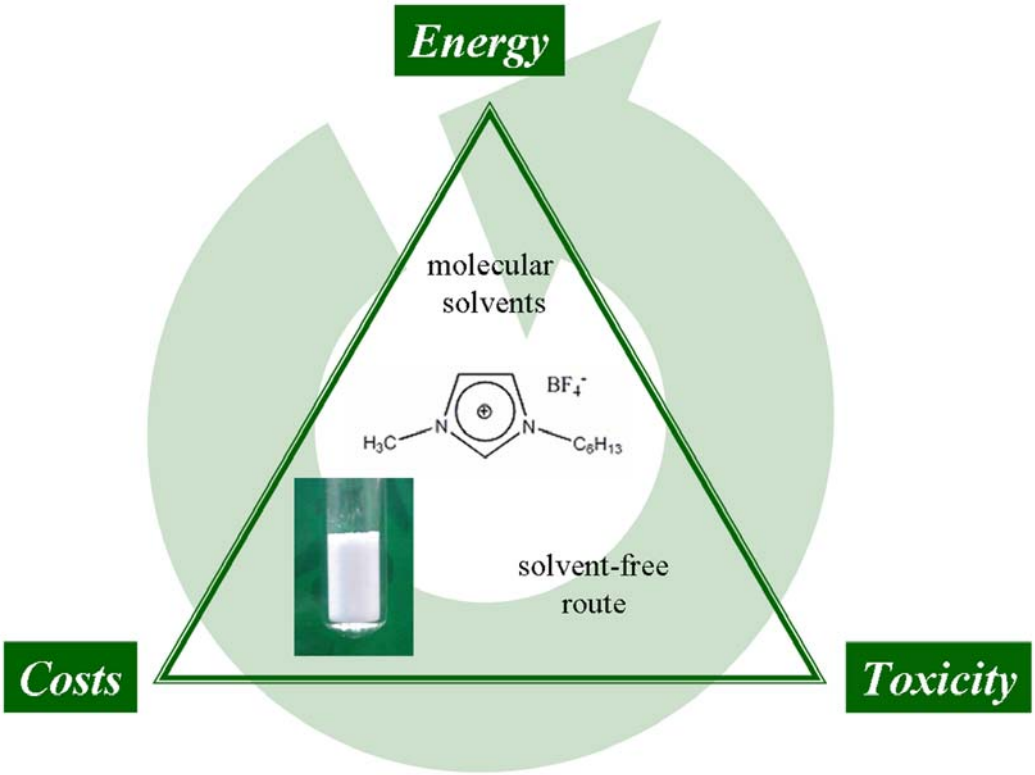
1. Evaluating the greenness of alternative reaction media*



* D. Reinhardt, F. Ilgen, D. Kralisch, B. König, G. Kreisel, *Green Chem.* **2008**, *11*, 1170-1182. Florian Ilgen validated and supplied the data for carbohydrate melts while Denise Reinhardt and Dana Kralisch performed all ecological evaluations and all other experiments. Florian Ilgen performed a recycling study in DMU/citric acid melt which was not part of this publication.

Introduction

Much effort has already been made to replace toxic and hazardous substances, *e.g.* solvents, auxiliaries or catalysts, by non-volatile, less hazardous and non-toxic alternatives, respectively. However, most organic solvents still used in chemistry are volatile and often hazardous both to humans and the environment. In order to substitute them and to create more environmentally benign chemical processes, solvent alternatives such as supercritical fluids,[1] water,[2] ionic liquids[3] or solvent-free processes[4] have been receiving growing interest.

As an example, the supercritical fluid $scCO_2$ benefits from the fact that it has a comparatively low toxicity due to the high concentrations needed for acute toxicity. Furthermore, it is relatively inert, easily removable and recyclable. The nature of this reaction medium benefits from both liquid and gaseous properties. The facilitated diffusion of the substrate to the catalyst and rapid dissociation after the chemical conversion, results in a positive effect on catalytic reactions. The drawback of supercritical fluids, however, is the demand for sophisticated equipment, exceeding the standard lab equipment, and thus resulting in a still limited use during R&D.

Water is considered to be the ideal solvent, being non-toxic, cheap and easily available. This solvent, however, has also some limitations due to the insolubility of nonpolar organic compounds and the instability of reactive reagents or substrates in this medium. A neglected topic in the context of water-chemistry is the effort of removing the reactants during the work-up procedure, consuming usually a large amount of organic solvent and energy, respectively. The extraction volume can exceed the volume of water by factors of up to 30.[5] Further, new reaction media consisting of carbohydrates and urea were investigated as solvents for organic reactions, *e.g.* Diels–Alder or Stille reactions.[6] Stable and clear melts can easily be obtained by reaching the melting points between 65 °C and 92 °C (depending on the composition). Fig. 1.1 shows a citric acid/*N*,*N*'-dimethyl urea (DMU) melt in the case of a Diels–Alder reaction.

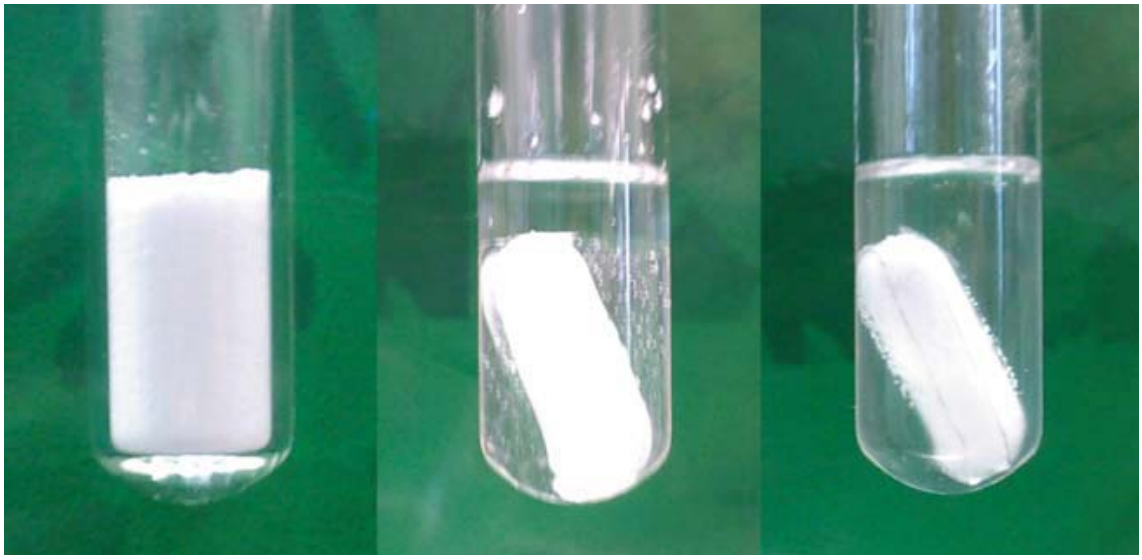


Fig. 1.1 left: citric acid/DMU mixture (rt); middle: citric acid/DMU melt (65 °C) with methyl acrylate/cyclopentadiene loading (separation); right: homogeneous melt with starting material after stirring for 5 min.

These mixtures benefit from the advantages of having a very low toxicity, being non-volatile and consisting of compounds from readily available resources, being in line with the majority of the 12 principles of green chemistry.[7] At first glance, these media seem to be a green alternative to conventional solvents.

Ionic liquids have been discussed as an alternative to conventional organic solvents as well, since they offer *e.g.* significant chemical advantages and have no relevant vapour pressure. However, results on their potential environmental impact, *e.g.* toxicity and environmental degradation, as well as the production effort required have led to a more differentiated point of view.

Nowadays, it is widely accepted that no solvent is *a priori* green; its greenness rather strongly depends on the specific application, its toxicological properties and on the environmental impact resulting not only from the production process but also from the whole life cycle.

While choosing a suitable solvent for a process or searching for alternative technologies, environmental, health and safety criteria should be considered in addition to physical and chemical properties of a solvent. With this in mind, the efforts to eliminate, replace, recycle or minimise the use of solvents should commence in the earliest stage of the product/process development. A number

of scientific groups have already published solvent selection/replacement tools in order to support this decisionmaking process.[8] These tools range from merely qualitative, semi-quantitative (*e.g.* ABC/XYZ-valuation[9]), to complex life cycle approaches. Some well-known computer aided methodologies and software tools, *e.g.* by Gani *et al.*,[10] EPA's SAGE (Environmental Protection Agency; Solvent Alternatives Guide) for surface cleaning processes[11] and PARIS II (Program for Assisting the Replacement of Industrial Solvents), reflecting solvent properties and environmental issues,[12] were developed.

In recent activities solvent selection tools were developed allowing for environmental, health and safety aspects at the R&D stage, partly under consideration of life cycle aspects/LCA (life cycle assessment),[13] as well as economic criteria.[14] For instance, the solvent selection guide by Capello *et al.*[13] integrates the life cycle assessment method as well as the EHS (environment, health, safety) method developed by Hungerbühler and co-workers.[15] Further, the Ecosolvent-Tool[13] is used as a life cycle assessment tool that facilitates the quantification of the environmental impact of waste–solvent treatment. For example, it is a useful tool to decide between "incineration *versus* distillation". Moreover, it contains life cycle inventories of the petrochemical production of the integrated solvents based on the ecoinvent database.[16] Kralisch *et al.*[17] suggested a holistic evaluation and optimisation approach considering ecological and economic aspects. The ECO (ecological and economic optimisation) method was in particular designed by the authors to accompany and optimise early stage development work in chemical R&D regarding the principles of ecological and economic sustainability. The ECO method uses a Simplified Life Cycle Assessment (SLCA) approach,[18] integrating all life cycle stages from the production of reactants, solvents *etc.*, synthesis, work-up, recycling and disposal. To evaluate the greenness of a product or process, the method uses three main criteria: the energy factor EF, the environmental and human health factor EHF and the cost factor CF, describing the energy demand, toxicity and cost of *e.g.* chemicals, auxiliaries, energies and equipment used during the life cycle stages of a product or process.

In this paper, ionic liquids and carbohydrate–urea mixtures are investigated regarding their ecological and economic sustainability for a typical organic reaction with the help of the ECO method. The Diels–Alder reaction was chosen

as an exemplary application, since the solvent effect on the reaction rate and selectivity has been widely examined and discussed, also in the case of the alternative solvents ionic liquids and carbohydrate–urea mixtures. Both media are compared to an assortment of conventional organic solvents as well as a solvent-free version (*i.e.* with no additional solvent within the Diels–Alder reaction), in order to demonstrate the process advantages, *e.g.* concerning product separation and catalyst recycling, but also to accentuate disadvantages and challenges, respectively.

Diels–Alder reaction

To perform a comprehensive assessment of solvent alternatives for a given chemical synthesis, starting material, auxiliaries and the energy demand for synthesis and work-up procedure have to be taken into account besides the solvent and its performance. Otherwise challenges and weak spots of processes/products during the whole life cycle can not be detected and improved. For our investigations, the Diels–Alder cycloaddition was chosen as a model reaction. The [4+2]-cycloaddition between a conjugated diene and a dienophile represents a widely used reaction to obtain fine chemicals, pharmaceuticals and bioactive molecules, respectively.[19] The pericyclic reaction proceeds *via* an aromatic transition state, typically resulting in the preferential formation of the *endo* diastereomer under kinetic control.

Both, efficiency and selectivity are significantly influenced by the acidity of the reaction medium. Up to now, Diels–Alder reactions have been investigated in several reaction media, like water, [20] $LiClO_4$/ether,[21] lithium amides,[22] as well as surfactants.[23] Studies reviewing the solvent effects, the polarity of the solvent or solvent mixtures focused predominantly on the stereoselectivity and reaction rate.[24] In this context, Cativiela *et al.* found out that with increasing polarity both the reaction rate and the *endo/exo* ratio increase. Experiments in aqueous solution[25] showed an even higher reaction rate enhancement due to “enforced hydrophobic interactions between diene and dienophile”. Engberts *et al.*[25] found that relatively nonpolar reactants are “forced” to perform a solvophobic binding process, and that this is more favoured in water or aqueous, polar media, than in conventional organic solvents. As early as 1980, Rideout and Breslow

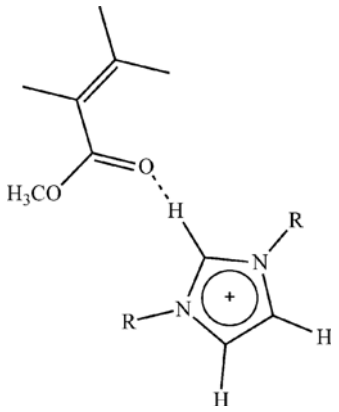
demonstrated that Diels–Alder reactions were dramatically accelerated in water due to the “hydrophobic effect”.[20]

In a comprehensive review, Cativiela *et al.* compared the theoretical and experimental results for solvent effects of diverse Diels–Alder reactions.[26] In this context, different solvents with polarities ranging from that of cyclohexane to acetic acid were tested in terms of reaction rate and three kinds of selectivity (*endo/exo*, regio- and diastereofacial). Experimental studies showed that the solvent polarity only has a marginal influence on the rate of some Diels–Alder reactions, whereas theoretical results pointed out that the activation barrier increases or decreases depending on the dienophile. However, solvent polarity enhanced the *endo/exo* selectivity, and, in agreement with theoretical calculations, the diastereofacial selectivity as well. In conclusion, solvent solvophobicity was established to be the main factor influencing reaction rate, accounting for the acceleration in aqueous media, and also the *endo/exo* selectivity of some Diels–Alder reactions.

In spite of many advantages, water is not always the solvent of choice, as discussed above. One disadvantage can be *e.g.* the stability of the catalyst. As an example in the context of Diels–Alder reactions, Lewis acids as catalysts are, with a few exceptions like $Sc(OTf)_3$ and $Ce(OTf)_3$,[27] rather problematic in use because of their immediate reaction with water.

The above mentioned carbohydrate–urea mixtures were tested to be very polar reaction media[6] with polarities between dimethyl sulfoxide and ethylene glycol and are therefore suitable for organic reactions proceeding *via* polar or ionic intermediates or transition states. Such polar reactions are promoted by polar solvents like carbohydrate–urea melts due to a strong stabilisation by solvation of polar intermediates. The hydrogenation with a Wilkinson catalyst, the Suzuki reaction and the Stille cross-coupling are good examples for the applicability of carbohydrate–urea melts facilitating organic transformations in very high yields.[6] Apart from the efficient reaction procedure this alternative reaction medium has the advantage of consisting of mainly renewable components, which are vastly abundant and have a low impact on the environment and human health. Considering the risk for humans and the environment these melts should benefit from their very low (eco)toxicity compared with ionic liquids and conventional solvents.

Further, ionic liquids as reaction media and (acidic) catalysts for Diels–Alder reactions have also been the topic of numerous studies.[28] Aggarwal *et al.*[29] investigated the effect of possible hydrogen bonds between starting material and solvent molecules (ionic liquid) in terms of selectivity and reaction rate. The C2 imidazolium-proton shows a significant Lewis acid character and is able to coordinate the carbonyl oxygen in the methyl acrylate molecule during the reaction. The hydrogen bond formation between the cation of the ionic liquid and the dienophile, as a Lewis acid–base interaction, stabilises the transition state of the cycloadduct and leads to the preferential formation of the *endo* product (Scheme 1.1). By introducing sterically demanding residues (R), the preferred transition structure can be energetically disturbed, leading to a decrease in selectivity.



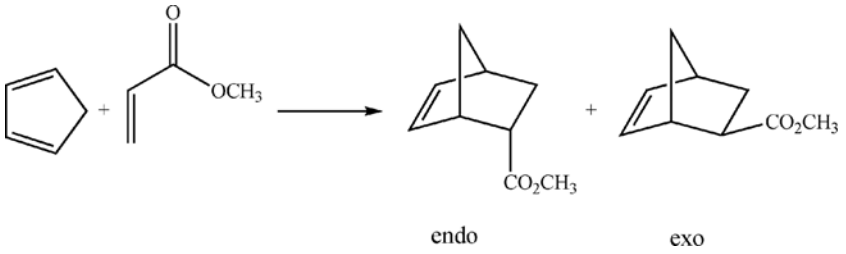
Scheme 1.1 Activated complex with the help of hydrogen bond interactions of an imidazolium cation with methyl acrylate. (in accordance to ref. 29).

In order to maximise the product yield, in some cases ionic liquids have the advantage that products can be simply removed by decanting the organic layer and the extraction phase, respectively, without time and energy consuming steps. Further, the performance of ionic liquid-based processes is improved significantly if the catalyst remains in the ionic liquid phase after separation (see *e.g.* ref. 30).

Results and discussion

Sample reaction

To compare the performance of alternative solvents the reaction of cyclopentadiene and methyl acrylate (Scheme 1.2) was investigated, leading to a mixture of *endo*- and *exo*-bicyclo[2.2.1]hept-5-en-2-carboxylic acid methyl esters. We assumed the *endo* molecule as the desired product of the synthesis. The reaction is typically performed at room temperature with stirring. Herein we compare different solvent systems in terms of their overall performance in the Diels–Alder cycloaddition, taking into account an ecological and economic assessment. For this purpose, ionic liquids were tested as solvents for Diels–Alder reactions and compared with the results obtained in solvent-free systems and conventional organic media. As a representative ionic liquid, 1-hexyl-3-methylimidazolium tetrafluoroborate, $[C_6mim][BF_4]$, was chosen. This ionic liquid does not show any Lewis acid character and hence does not interfere with a potentially used catalyst, shows moisture compatibility, is stable under air and thus simplifies the handling. Furthermore, 1-hexyl-3-methylimidazolium tetrafluoroborate allows for facile recycling of solvents, products and catalysts, and is easily accessible.[31] In addition, carbohydrate–urea mixtures as novel alternative solvents based on renewable components were compared regarding their performance, ecological and economic impact. Therefore, a melt consisting of citric acid/DMU (% w/w 40/60) was used. The conventional solvent systems evaluated in this work were acetone, methanol/deionised water, methanol, cyclohexane and a solvent-free reaction, respectively.



Scheme 1.2 Diels–Alder reaction of cyclopentadiene and methyl acrylate.

Evaluation

Assessment of the solvent performance

Table 1.1 summarises the results of the Diels–Alder reactions that were performed in different solvents (catalyst-free, without recycling). These experiments were carried out twice with no significant change neither in conversion nor selectivity. The evaluation was performed for reaction times of 8 h and 48 h, respectively, as can be seen in Table 1.1.

			Conversion of methyl acrylate		
Exp. Number	Solvent	Temp. [°C]	Time [h]	[%][a]	*endo/exo* ratio[a]
1	Methanol	25	48	95	4.9
2	Methanol/water% v/v, 50/50	25	48	98	5.5
3	Acetone	25	48	83	3.3
4	Cyclohexane	25	48	90	2.6
5	$[C_6mim][BF_4]$	25	48	92	3.8
6	Citric acid/DMU % w/w, 40/60	65	8	99	3.7
7	$[C_6mim][BF_4]$	65	8	98	3.3
8	Solvent-free	25	48	98	2.9

[a] Determined by gas chromatography

Table 1.1 Solvents used in the Diels–Alder reaction and their performances.

These reaction times, yields and selectivities represent the basis for the evaluation, since in all cases similar and nearly quantitative conversion and high product yields were reached. Furthermore, the conversions and yields reached a plateau during this time (see also Fig. 1.2).

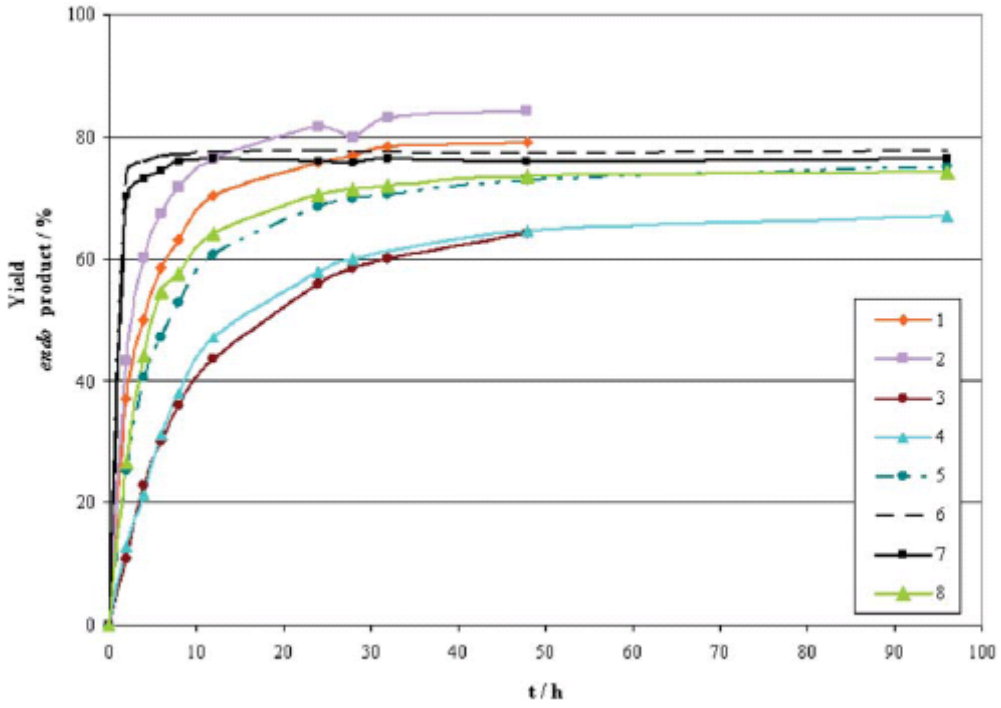


Fig. 1.2 Yield of *endo*-bicyclo[2.2.1]-hept-5-en-2-carboxylic acid methyl ester in dependence of the time and solvent system (see Table 1.1).

Fig. 1.2 shows the time-dependent synthesis of *endo*-bicyclo[2.2.1]-hept-5-en-2-carboxylic acid methyl ester. In general, the ionic liquid $[C_6mim][BF_4]$ showed a similar performance in the Diels–Alder reaction compared to conventional solvent systems at room temperature. The solvents methanol and methanol/water, respectively, appear to be the best choice among the tested solvents for the Diels–Alder reaction at room temperature (in accordance to the literature).

Further, the citric acid/DMU mixture would be a good choice, if accepting a higher energy demand for heating and a slightly reduced *endo/exo* ratio. In the case of $[C_6mim][BF_4]$, with increasing temperature higher conversion rates, but decreasing *endo/exo* ratios were observed.

In the case of the solvent-free route, good results were obtained too, even if the *endo/exo* ratio is lower than for the reactions with added solvents.

Ecological assessment

The experimental work was accompanied by the application of the ECO method in order to compare the solvent performances in a holistic approach and to identify improvements regarding the objectives EF, EHF and CF. For this study, the disposal of the ionic liquid was not included, due to lack of data concerning the end of life information. Since this study represents a screening of all solvent alternatives, only the upstream chains, the Diels-Alder reaction, the recycling considerations and work up were part of the calculation. To demonstrate the influence of $[C_6mim][BF_4]$ when released into the environment, a qualitative (Fig. 1.5) and quantitative assessment (environmental and human health factor) was made. The data obtained during the assessment procedure are very extensive and thus, only selected and significant findings will be discussed in detail below.

Evaluation of the energy factor EF

The energy factor EF sums up the cumulative energy demand (CED)[32] resulting from the supply of the reactants, solvents and auxiliaries (*E*S), the performance of the reaction (*E*R), the energy demand necessary for the work-up (*E*W), the application of the products (*E*A) and the disposal of waste (*E*D), related to a product-based benefit *e.g.* the product molarity (eqn (1)) or the product mass.

$$\mathrm{EF} = \frac{\sum_{i=1}^{x_S} E_i^S + \sum_{i=1}^{x_R} E_i^R + \sum_{i=1}^{x_W} E_i^W + \sum_{i=1}^{x_A} E_i^A + \sum_{i=1}^{x_D} E_i^D}{n_{\mathrm{product}}} \qquad (1)$$

The EF was determined using the Life Cycle Assessment software Umberto,[33] incorporating the database Ecoinvent,[16] which contains literature references as well as a pool of data concerning the supply of organic and inorganic chemicals, electrical energy, inert gases *etc.*, starting from their primary sources. If specific data were not available, the energy demand for the supply of structurally similar

compounds available from the database was used as an approximation. The CED for cyclopentadiene was determined using the inventory data of "chemicals organic, at plant" (ecoinvent v. 1.3).

Fig. 1.3 demonstrates the EF for the synthesis of 1 mol *endo*-bicyclo[2.2.1]-hept-5-en-2-carboxylic acid methyl ester.

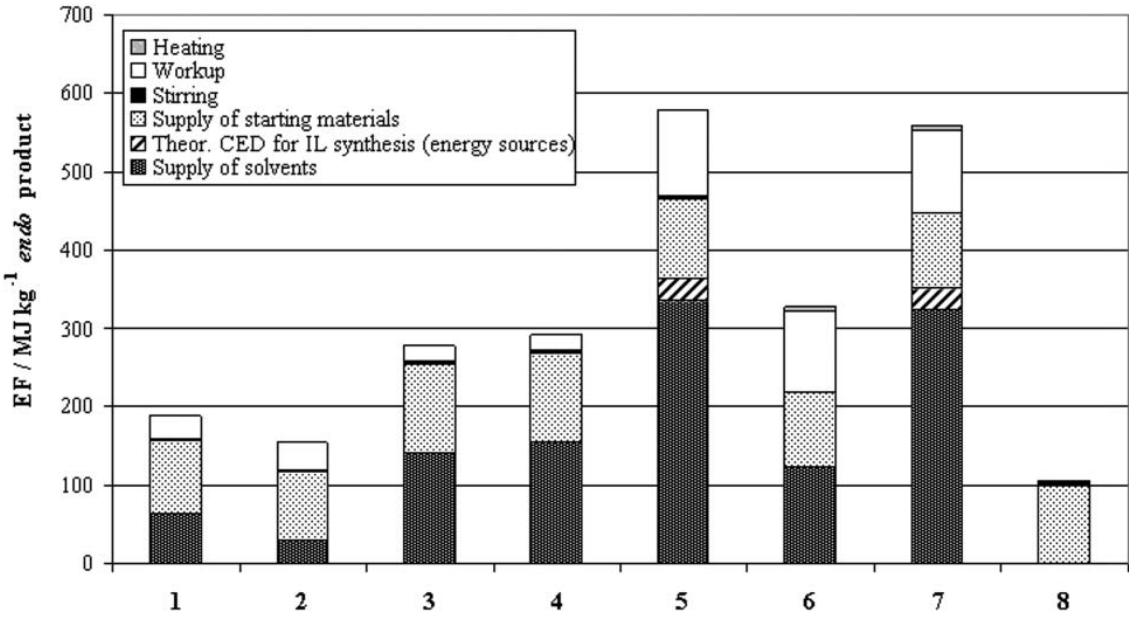


Fig. 1.3 Dependence of EF on the choice of solvent for the Diels–Alder reaction of methyl acrylate and cyclopentadiene (T = 25 °C or 65 °C, t = 48 h or 8 h, solvent systems methanol, methanol/water, acetone, cyclohexane, [C_6mim][BF_4], citric acid/DMU, solvent-free, see Table 1.1).

The best results were obtained for methanol, methanol/water and for the solvent-free system. On the one hand, this can be explained by the comparatively low energy demand for the supply of the solvents and on the other hand by the solvent performance during the Diels–Alder reaction. Due to the low *endo/exo* selectivity, the EF for the supply of the reactants for the solvent-free route is higher than for methanol and methanol/water. In spite of this, the EF per kg *endo* product is comparably low, since no additional energy demand for the solvent supply is necessary. Further, the work-up procedure involves no additional solvent distillation steps increasing the EF.

In the case of acetone, cyclohexane and DMU, the CEDs for solvent supply are generally higher than for methanol or water. In addition, the reaction in acetone

and cyclohexane gave lower yields and selectivities, which results in higher EF values. For citric acid/DMU, a lower EF for the supply of starting material can be expected. However, for the synthesis at 65 °C, the higher energy demand for heating has to be taken into account. Further, the work-up procedure of the media citric acid/DMU and $[C_6mim][BF_4]$ is more complex and results in a higher EF, since additional organic solvents become necessary to extract the product from the stationary phase having no relevant vapour pressure. However, in some cases the organic phase can be removed from the stationary phase by decanting, resulting in a lower energy demand.

Comparability of upstream processes for solvent supply

One of the main requirements for a well-founded comparison is to ensure comparability. In this case, a direct comparison of the alternative solvents was difficult, since the same scale of production data for all solvents considered is necessary. The supply of acetone, methanol, deionised water, cyclohexane as well as of carbohydrates and urea derivatives can be evaluated on industrial production scale using the Ecoinvent-database, while such data were not available for the supply of $[C_6mim][BF_4]$. The energy demand for a lab scale synthesis (batchwise) of the ionic liquid, known from our experiments, allows no energetic comparison to the supply of the other solvent systems. Whereas, especially the alkylation step of *N*-methylimidazole and *n*-hexyl chloride is exceedingly energy demanding. To guarantee comparability, the energy requirements for heating, stirring and distillation processes within upstream chains were theoretically calculated by means of thermochemical data. The amount of energy which is theoretically required (calculated by means of heat capacity, enthalpy of vaporisation, standard enthalpy change of formation, standard enthalpy change of reaction; assumed efficiency for heating: 80%) amounts to less than 10% of the overall result (Fig. 1.3).

Against this background, the approach seems to be sufficient regarding the task of our investigations.

The results presented in Fig. 1.3 point out that the energy demand for the supply of both reaction media, the melt system as well as the ionic liquid, is

higher than that for the supply of the conventional solvents. In order to become an energetically favourable alternative, further synthesis optimisation, new synthetic strategies and/or other techniques, *e.g.* process intensification *via* microreactors, as studied in the case of [C_4mim]Br,[34] have to be considered. Another promising possibility of increasing the energy efficiency of the Diels–Alder synthesis could be an appropriate solvent recycling strategy. This aspect will be discussed in the following.

Effects of solvent recycling

To investigate a particular process advantage of ionic liquids, [C_6mim][BF_4] was recycled and reused for 3 times. After three recycling steps, a mass loss of 5% was determined, while the solvent performance seems to remain unchanged (Table 1.2).

If ionic liquids (or carbohydrate–urea melts) should represent an ecological and further economic alternative to conventional solvent systems, their process advantages like solvent recovery or catalyst recycling are of particular importance. Therefore, we assumed a 100-fold use in order to demonstrate the impact on ecological and economic criteria.

For the determination of EF including recycling, the assumption was made, that the solvent performance does not diminish within 100 runs and the mass loss of 5% for 4 runs does not increase. Carbohydrate–urea mixtures benefit from their simple work-up. Addition of water to the still warm melt solubilises carbohydrates and urea derivatives, leaving behind a supernatant of products and starting material, which can be decanted. However, the energy demand for the supply of the melt components is higher than for conventional solvents, and therefore recycling is desired. For the calculation, we assumed that the changes in solvent performance and mass loss are equal to the results obtained in the ionic liquid. In the case of the conventional solvents, a mass loss of 10% per run was assumed.

Fig. 1.4 shows a significant improvement in energy efficiency concerning the supply of [C_6mim][BF_4], resulting in a lower EF (reduction of approx. 98%) and

in a better comparison to the other solvent systems in the case of a hundred-fold solvent use.

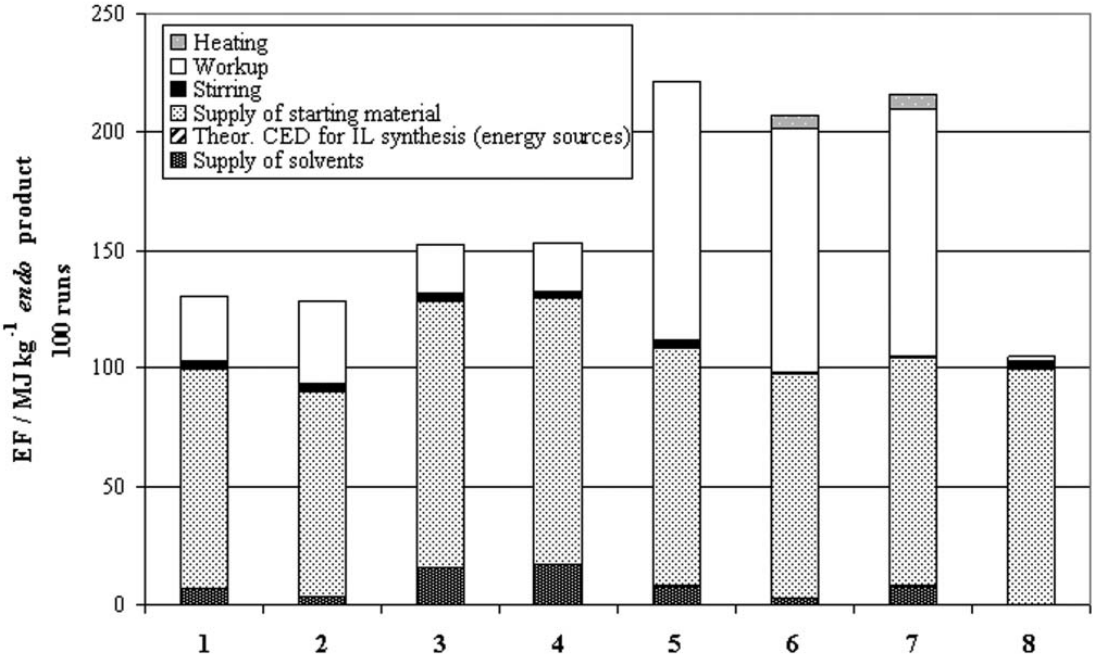


Fig. 1.4 Dependence of EF on the choice of solvent for the Diels–Alder reaction of methyl acrylate and cyclopentadiene (T = 25 °C or 65 °C, t = 48 h or 8 h, solvent systems methanol, methanol/water, acetone, cyclohexane, [C_6mim][BF_4], citric acid/DMU, solvent-free, see Table 1.1), per 100 cycles.

The EF for the supply of the [C_6mim][BF_4] and of the citric acid/DMU melt is nearly equal to the energy demand for the supply of the conventional solvents. With the possibility of recycling the reaction medium easily, ionic liquids as well as carbohydrate–urea mixtures become a suitable alternative to conventional solvents (black bars in Fig. 1.4).

However, a disadvantage for media having no relevant vapour pressure or being non-volatile became clear for the work-up procedure, where additional solvents are needed to extract the organic reaction products and non-reacted reactants.

Although the work-up procedure has not been optimised yet, we tried to estimate the additional energy demand for the supply of an extraction solvent and distillation steps. As shown in Fig. 1.4 (white bars), additional work-up steps to extract starting material and products from the stationary phase ([C_6mim][BF_4], citric acid/DMU) before reuse decrease the energy efficiency of

the Diels–Alder reaction. Although these alternative media feature non-volatility and therefore contribute to safety aspects, the work-up regarding the Diels–Alder reaction seems to be the bottle-neck and accentuate the need for an assessment *via* a life cycle approach.

Evaluation of the environmental and human health factor EHF

We started our investigations addressing toxicological aspects of the solvent choice by means of qualitative criteria concerning aspects of mobility, acute toxicity and chronic toxicity for humans, acute toxicity for aquatic organisms, persistency in the environment and bioaccumulation, using the data given in safety data sheets.[35] These results are demonstrated in Fig. 1.5.
Against this background, water seems to be an environmentally benign solvent alternative, followed by the melt components DMU[36] and citric acid, which are harmless to human health and the environment. The classification of $[C_6mim][BF_4]$ turned out to be difficult, since quantitative data regarding toxicity for humans, ecological effects, information about accumulation and biodegradability of this product are hardly or not available at all. Since $[C_6mim][BF_4]$ is classified by a water hazard class (WGK) of 3, the acute toxicity for aquatic organisms was assumed to be “high”.

Solvent	Acetone	Cyclohexane	Methanol	Water	[C_6mim][BF_4]	DMU	Citric acid
Environmental effects							
Mobility							
Acute toxicity for humans							
Chronic toxicity for humans							
Acute toxicity for aquatic organisms							
Persistency in environment							
Bioaccumulation							

Colour definition (qualitative)

No/low
Low to medium
Medium
Medium to high
High
No data

Effect	Data base
Mobility	boiling point, temperature diff. betw. boiling point and process temperature, vapour pressure
Acute toxicity for humans	EC classification (Xn, T, T+), GK, R-codes, LD50 (inhal., oral, dermal)
Chronic toxicity for humans	carcinogenity, mutagenicity *etc* ., R-codes, MAK, EC classification (Xn, T, T+)
Acute toxicity for aquatic organisms	WGK (German water hazard class), R-codes, EC50/LC50
Persistence in environment	OECD, EU classification (readily, inherent, no)
Bioaccumulation	log k_{ow}, qualitative info

Fig. 1.5 Qualitative assessment of the ecological impact of the used solvents (database: safety data sheets).

To quantify the environmental effects and to integrate the quantity of the solvents used under consideration of technical constraints (*e.g.* safety issues), the environmental and health factor EHF was used. The EHF allows a comparison of different chemical substances used, *e.g.* as reactants, solvents or auxiliaries regarding the resulting risks for human and environment during their supply (RPoDS), product synthesis (RPoDR), product work-up (RPoDW), product application (RPoDA) and disposal (RPoDD). EHF sums up the RPoD*ij*, calculated according to Koller *et al.*,[15] and relates this input to the molarity (or mass) of the product. The EHF is divided into three sub-objectives: EHF(AcT), EHF(ChT) and EHF(WmE), referring to the categories acute toxicity, chronic toxicity and water mediated effects. Their calculation is demonstrated using the example of EHF(AcT) (eqn (2)).

$$\mathrm{EHF(AcT)} = \frac{\sum_{i=1}^{x_S} \mathrm{RPoD(AcT)}_i^S + \sum_{i=1}^{x_R} \mathrm{RPoD(AcT)}_i^R}{n_{\mathrm{product}}} + \frac{\sum_{i=1}^{x_W} \mathrm{RPoD(AcT)}_i^W + \sum_{i=1}^{x_A} \mathrm{RPoD(AcT)}_i^A + \sum_{i=1}^{x_D} \mathrm{RPoD(AcT)}_i^D}{n_{\mathrm{product}}} \quad (2)$$

As mentioned in safety data sheets, hazardous properties of $[C_6mim][BF_4]$ can not be excluded. In the absence of bioaccumulation and persistency data, we assumed the risk as high as possible.

Fig. 1.6 demonstrates the criteria EHF in the special case of acute toxicity regarding the alternative solvents used. Methanol is classified as a toxic substance and has therefore a significant impact on the human health. Although the risk is assumed to be high in the case of $[C_6mim][BF_4]$, the resulting acute toxicity for humans is lower than for methanol-systems, since $[C_6mim][BF_4]$ has no relevant vapour pressure and thus represents a low imminent hazard. Further, Fig. 1.6 gives an in-depth view into the toxicological impact of the starting-materials used as well. In the case of cyclopentadiene, the resulting EHF is about in the same order of magnitude compared to the influence of the solvents. A possible negative effect resulting from the release potential of cyclopentadiene and methyl acrylate at $T = 65$ °C was avoided by working under reflux to minimise the hazard potential.

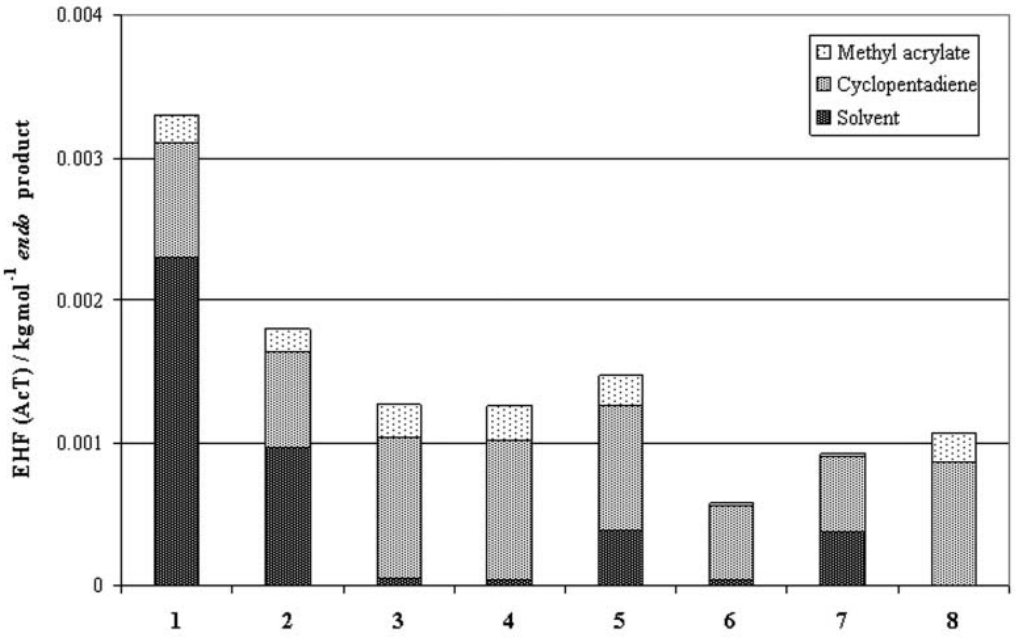


Fig. 1.6 Dependence of EHF(AcT) on the choice of the solvent for the Diels–Alder reaction of methyl acrylate and cyclopentadiene (*T* = 25 °C or 65 °C, *t* = 48 h or 8 h, solvent systems methanol, methanol/water, acetone, cyclohexane, $[C_6mim][BF_4]$, citric acid/DMU, solvent-free, see Table 1.1).

Fig. 1.7 demonstrates the EHF for water mediated effects. The EHF(WmE) for $[C_6mim][BF_4]$ is extremely high in comparison to the other solvent systems. This effect is a result of its high classification in the German water hazard class as well as the low biological degradation[37] and has to be regarded as worst case scenario.

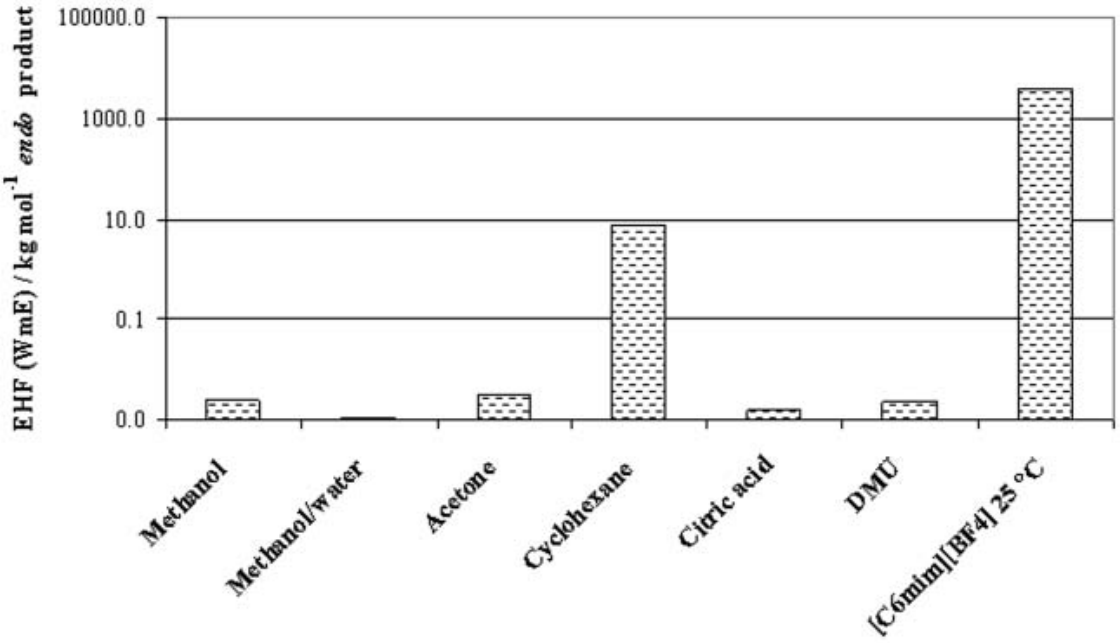


Fig. 1.7 Dependence of EHF(WmE) on the choice of the solvent for the Diels–Alder reaction of methyl acrylate and cyclopentadiene (see Table 1.1).

Cyclohexane is classified as N-substance, *i.e.* environmentally dangerous substance. Further, cyclohexane is specified with R-codes 50/53, indicating a substance as very toxic to aquatic organism, and may cause long-term adverse effects in the aquatic environment. Acetone, methanol, methanol/water and citric acid/DMU have no significant influence on aquatic organisms, since the systems are classified with WGK 1. For the latter solvent systems and the solvent-free alternative, respectively, Fig. 1.8 shows the resulting EHF(WmE). Here the environmental impact is significantly affected by the performance of the solvent.

In general, reactions in the citric acid/DMU melt are well suited regarding toxicological aspects, since their low impact on the environment and human health as well as their solvent performance.

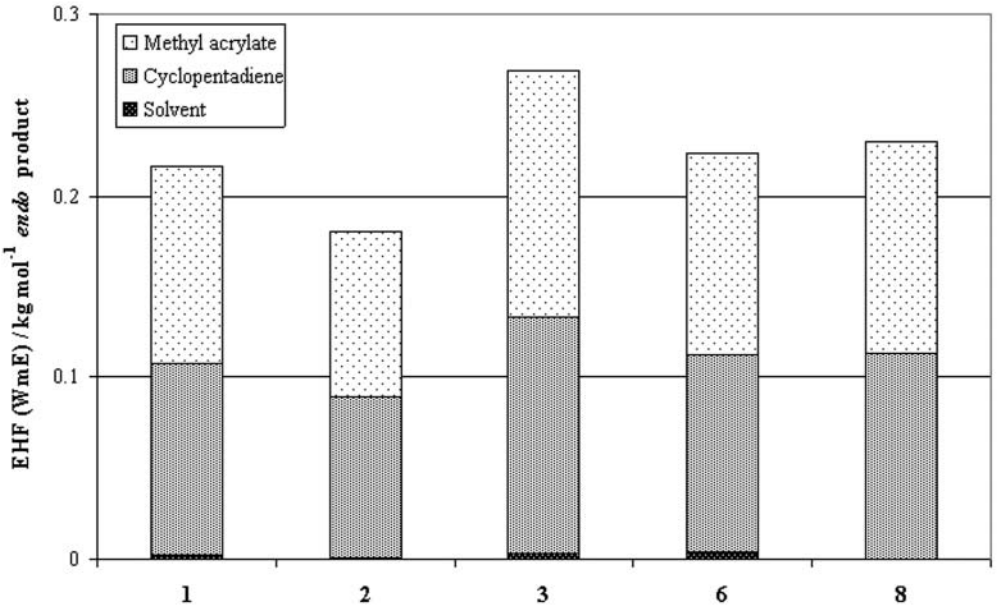


Fig. 1.8 Dependence of EHF(WmE) on the choice of the solvent system for the Diels–Alder reaction (T = 25 °C or 65 °C, t = 48 h or 8 h, solvent systems methanol, methanol/water, acetone, cyclohexane, $[C_6mim][BF_4]$, citric acid/DMU, solvent-free, see Table 1.1).

For the solvent-free experiment, reduced *endo/exo* ratios and yields were obtained, resulting in a slightly higher consumption of starting material and therefore higher EHF values.

Evaluation of the cost factor CF

The cost factor CF is determined in analogy to EF and EHF and sums up all occurring costs, *i.e.* the prices of the chemicals, energy, disposal, equipment and personnel as well as process expenditure *etc.*, related to the molarity (or mass) of the product.

Fig. 1.9 represents the cost factor CF for the synthesis of 1 kg *endo*-bicyclo[2.2.1]hept-5-en-2-carboxylic acid methyl ester under consideration of a 100-fold use strategy.[38] Therein, the costs for starting-materials, solvents for reaction and work-up as well as energy costs were considered. Personnel costs were not included yet, since their calculation on laboratory scale would not be representative.

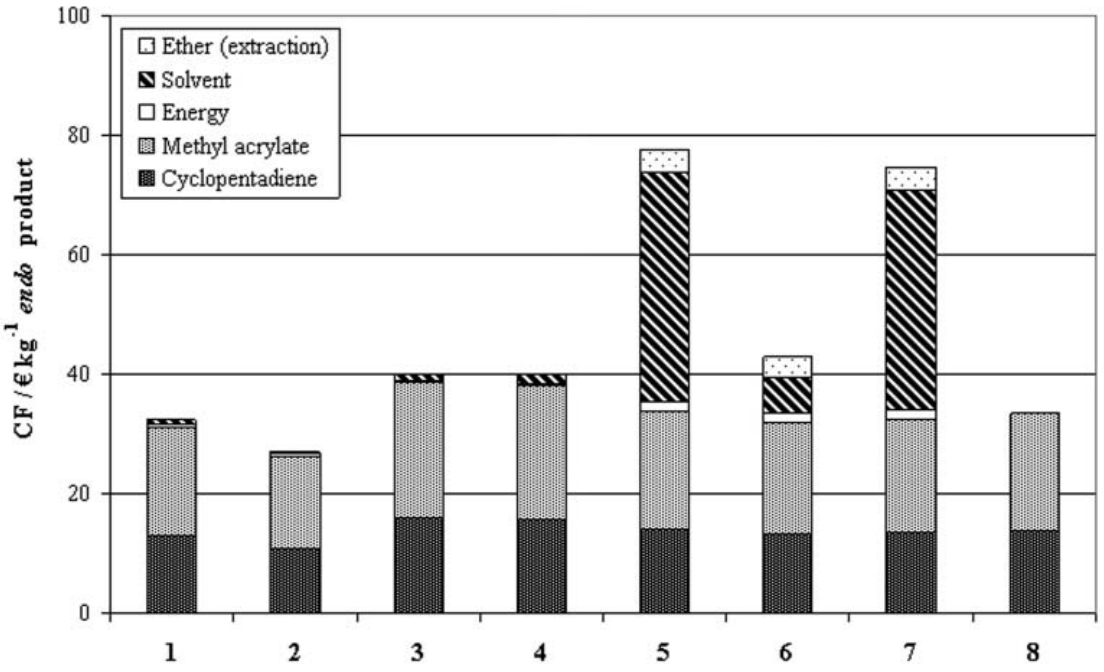


Fig. 1.9 Dependence of CF on the choice of the solvent for the Diels–Alder reaction of methyl acrylate and cyclopentadiene (*T* = 25 °C or 65 °C, *t* = 48 h or 8 h, solvent systems methanol, methanol/water, acetone, cyclohexane, $[C_6mim][BF_4]$, citric acid/DMU, solvent-free, see Table 1.1).

The conventional solvents are easily available and relatively cheap, that is why the cost factor is mainly defined by the supply of the starting materials. Therefore, in case of a 100-fold use, CF mainly depends on the performance of the different reaction media. In the case of the ionic liquid as well as the carbohydrate–urea melt, the additional solvent demand for extraction and further higher costs for the supply of these media, lead to a comparably higher CF than for the reactions in conventional solvents and the solvent-free synthesis route. Taking into account the specific application for ionic liquids discussed herein, the price for $[C_6mim][BF_4]$ should not exceed 22 € kg^{-1} in order to be in the range with the conventional solvents (40 € kg^{-1} *endo* product). This is in accordance with Hilgers and Wasserscheid. They expected that a range of ionic liquids will become commercially available for 25–50 € L^{-1} on a ton scale.[39]

Conclusion

Within this study, new, potentially green, solvent alternatives for the Diels–Alder reaction between methyl acrylate and cyclopentadiene were compared to conventional solvents and a solvent-free version, too. The ionic liquid [C_6mim][BF_4] and carbohydrate–urea melt citric acid/DMU were chosen as two representative examples for those alternative reaction media. They were investigated regarding their performance and their ecological as well as economic sustainability.

One major disadvantage of the melt system can be its relatively low thermal and pressure stability compared to the other solvents used, since *N*,*N*'-dimethyl urea and carbohydrate components like glucose tend to decompose at high temperatures. However, within our investigations the system showed no thermal decay since the reactions and work-up procedures were performed well below the decomposition temperature. In addition, the melt components feature very low (eco)toxicity, simplifying the handling.

Further, ionic liquids and carbohydrate–urea melts can become attractive alternatives to conventional solvents, if their separation efficiency and recyclability are high. The production stage of ionic liquids turns out to be disadvantageous in most cases and further research work has to be done in this context. In the case of the investigated reaction, the solvent system methanol/water or the solvent-free synthesis seem to be the most ecological sustainable alternatives, yet. This has been proven within a decision support software. With the help of the outranking procedure PROMETHEE,[40] the different reaction media have been compared in an objective way under consideration of EF, EHF and CF. The outranking of the different solution candidates under consideration of a 100-fold reuse resulted in the following order of preference: solvent-free ≥ methanol/water > methanol > acetone > cyclohexane > citric acid/DMU > [C_6mim][BF_4]. This result is valid under the following regulations: minimise EF, EHF(AcT), EHF(ChT), EHF(WmE), CF, weight: 33 : 11 : 11 : 11 : 33, preference function: linear, threshold unit: percent, and was determined using the software Decision Lab 2000.[41]

The use of ionic liquids or carbohydrate–urea melts within the Diels–Alder reaction instead of water containing systems may be preferred, since these media allow the use of moisture sensitive reagents, and organic materials can be removed *in vacuo.* In addition, the use of Lewis acid catalysts, like $Sc(OTf)_3$, in these media is advantageous compared to conventional solvents, if the catalyst remains in the reaction medium after work-up. Addressing these issues, processes based on non or low-volatile solvents can be improved significantly regarding their environmental and reaction performance. However, reactions in media with no relevant vapour pressure often require additional solvents during work-up, which might affect environmental aspects adversely. Therefore, multiphasic systems, which often can be established in ionic liquid processes, probably provide more efficient pathways for practical applications.

If the costs of producing bulk ionic liquids remain at their current level, difficulties in adopting ionic liquids in industrial processes in order to replace volatile organic solvents can not be overcome.[42] The carbohydrates and urea components are easily available, but purity specifications for organic synthesis actually inhibit their cheap disposal.

The considered ionic liquid $[C_6mim][BF_4]$ presents only one example of the huge class of ionic liquids, and there is, for instance regarding the factor of human and environment, great potential for further optimisation by changing the solvent and using other synthesis strategies (see *e.g.* review by Stark and Seddon[3]). Nevertheless, the ECO method was used to accentuate the need for the assessment of alternative reaction media in a more holistic approach and to demonstrate the opportunities and challenges of these alternative media.

The presented results are part of a long-term investigation regarding the optimisation of synthesis pathways and assessment of applications of ionic liquids *via* life cycle approach.

Experimental Section

$[C_6mim]Cl$ was synthesised *via* the Menschutkin reaction. This synthesis of $[C_6mim]Cl$ was part of an optimisation study in earlier work.[17] It was performed in a 250 mL round bottom flask, fitted with a reflux condenser. The mixture of

0.21 mol *N*-methylimidazole and 0.21 mol *n*-hexyl chloride (1.0 mol equivalents) was stirred for 30 h (100 °C, oil bath) and cooled down to room-temperature afterwards. The work-up procedure was carried out by dissolving the crude reaction mixture in water, followed by the extraction of the remaining *N*-methylimidazole content with diethyl ether. The yield of 98% was determined after removing of all volatiles *in vacuo* (rotary evaporator, water bath T = 80 °C, t = 1.5 h, p = 10 mbar). The purity was checked by ^{1}H-NMR-spectroscopy. [C_6mim][BF_4] was synthesised *via* reaction of [C_6mim]Cl with HBF_4: 1 mol [C_6mim]Cl was dissolved in 150 mL of water and stirred at rt for 3 h together with 1 mol HBF_4 (48% aqueous solution). After the synthesis, the crude mixture was dissolved in methylene chloride, followed by an aqueous extraction. The yield of 80% was determined after removal of all volatiles *in vacuo* (rotary evaporator, water bath T = 80 °C, t = 1.5 h, p = 10 mbar). The purity was verified by ^{1}H-NMR-spectroscopy and the water content by means of Karl Fischer titration. By $AgNO_3$ test and halide titration with 0.1M $AgNO_3$ using 1 g of the ionic liquid (automated Mettler Toledo titration), no chloride content could be detected (halide < 200 ppm, water 0.02% by mass). The resulting ionic liquid was dried *in vacuo* immediately prior to use. Compared to commercially available [C_6mim][BF_4], *e.g.* from Merck (specification: high purity; halide < 200 ppm, water 0.05 % by mass), no changing in performance properties concerning the Diels–Alder reaction of methyl acrylate and cyclopentadiene could be detected.

With regard to the citric acid/DMU mixture, 10.5 g DMU and 7 g citric acid were blended and led to a stable melt at 65 °C. For a typical Diels–Alder reaction, 15 mL of solvent (acetone, cyclohexane, methanol, methanol/water (% v/v 50/50), [C_6mim][BF_4], citric acid/DMU (% w/w 40/60)), cyclohexanone (1 mL) as internal standard, methyl acrylate (5.34 mL, 59 mmol) and freshly cracked cold cyclopentadiene (5.85 mL, 71 mmol) were added into a Schlenk flask containing a small stirring bar. The reaction took place at 25 °C (controlled by a cryostat) or at 65 °C, respectively (see Table 1.1). The progress of the reaction was monitored at appropriate time intervals by extraction of aliquots with cyclohexane (for [C_6mim][BF_4] and citric acid/DMU), appropriate dilution and GC analysis (conditions below). The yield of products and *endo/exo* ratios were calculated based on the GC analysis.

In the case of recycling experiments ([C_6mim][BF_4]), cyclohexane or diethyl ether (5x30 mL) were added to extract non-reacted starting material and products. Afterwards, the cyclohexane phase including impurities was decanted. The purity of the cyclohexane phase was tested *via* GC. Before each run, the ionic liquid was dried *in vacuo.* Mass losses and performance properties can be seen in Table 1.2. In the case of citric acid/DMU, the same assumptions were made. For the conventional solvents, a solvent loss of 10% for each run was assumed. In general, the work-up was performed by distillation steps to remove solvents and starting material from the product phase.

Run	Mass loss [g]	Mass loss [%]	*endo*/ *exo* ratio[a]	Conversion of methyl acrylate [%][a]
1			3.8	92
2	0.52	3.1	3.7	96
3	0.72	4.3	3.7	97
4	0.84	5.0	3.7	97

[a] Determined by gas chromatography

Table 1.2 Reaction conversions and *endo*/*exo* ratios with recycled [C_6mim][BF_4]

GC-measurements were performed using a Hewlett Packard, 8890 Series II apparatus; column HP 5 (Chrompack), length 30 m, diameter 0.32 mm, 0.25 mm film thickness. The following conditions were used: column pressure 5 psi, flow rate 75 mL min^{-1} of hydrogen; inlet temperature: 200 °C, detector temperature: 250 °C; oven conditions: 50 ºC for 6 min, then ramped at 15 °C min^{-1} to 110 °C, maintained for 10 min, then ramped at 25 °C min^{-1} to 250 °C, maintained for 2 min. Total run time: 27.6 min. FID-detector.

The energy demand for heating, stirring and distillation for the Diels–Alder reaction was determined using an energy monitoring socket (Energy Monitor 3000, Voltcraft), and in the case of the ionic liquid synthesis calculated with the help of thermochemical data.

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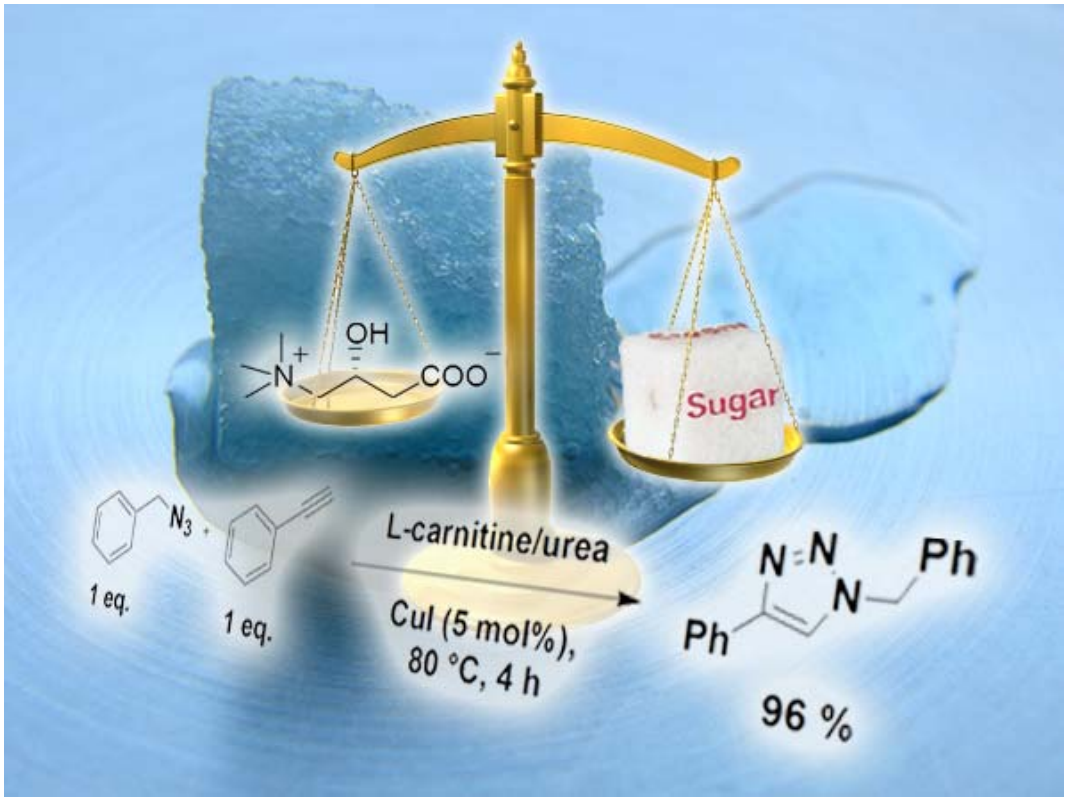
2. Organic reactions in low melting mixtures based on carbohydrates and L-carnitine – A comparison*



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Introduction

The use of appropriate alternative solvents for chemical transformations is becoming increasingly important for sustainable development in R&D and for the chemical industry. The use of alternative solvents is one of the 12 principles of Green Chemistry postulated by Anastas and Warner and has gained growing interest as a response to legislative and social pressure and an increasing greener awareness of the industrial community.[1] Green solvents are meant to successively replace conventional solvents which continue to dominate processes and (to lesser extent) products.[2]

Classical organic solvents used for reactions in the laboratory or industrial processes may cause environmental problems, if they belong to the class of volatile organic compounds (VOC), such as chlorinated hydrocarbons derived from methane, ethane and propane. Because of their persistence, they accumulate in the atmosphere, contribute to ozone depletion and smog in urban areas.[3] Conventional solvents show a high (eco)toxicity, are flammable and expensive. Despite the intrinsic drawbacks of solvents most chemical transformations are performed in solution to efficiently control the heat flow, ensure rapid and safe conversion to avoid undesired side products by dilution and to stabilise transition states, thus enhancing the reaction rate. Only a small number of organic reactions proceed in the solid state[4,5] and such approaches, like the ball mill, are restricted by small reaction rates and difficult heat flow control.

To address the drawbacks of conventional solvents and still benefit from solvent effects, “green solvents” for synthetic organic chemistry have been developed, finding their way into laboratories and chemical production. These new “green” solvents include supercritical fluids,[6] ionic liquids,[7] water,[8] and fluorous biphasic mixtures[9] and have received growing interest over the last two decades.[10,11] Supercritical fluids like $scCO_2$ are beneficial because they are non-toxic, relatively inert, easily removable, and recyclable. A widespread application in research and development, however, is hampered by the demand for advanced apparatus. Ionic liquids, usually based on 1,3-dialkyl imidazolium or pyridinium cations, which have a weakly coordinating counter-ion, currently receive much attention, because of their thermal stability, a negligible vapour

pressure, being inflammable and their catalytic effects on many types of reactions. Although industry has already started to incorporate IL-based applications like the BASIL or the Dimerosol process, the wider use of ILs has to be evaluated because they are still mainly based on non-renewable resources, the long term toxicity is unclear, while acute toxicity has already been tested positively.[12,13]

Water can be considered an ideal solvent, because it is non-toxic, cheap and easily available. However, limitations arise, especially when extraction with organic solvents becomes necessary or the water has to be removed, which is energy consuming.

We have recently introduced low melting mixtures consisting of carbohydrates, urea and optionally inorganic salts as new alternative solvents for organic transformations.[14] The stable melts of the mixtures are environmentally benign, because they are easily biodegradable, relatively non-toxic and are available from bulk renewable resources without numerous energy consuming modification steps. Their simple production is advantageous for the use as materials or replacement of organic solvents in developing countries with limited industrial infrastructure. In preliminary studies, the physical and physicochemical properties were determined. Melting points were measured with differential scanning calorimetry (DSC) and found to be in the range of 65 to 85 ^{o}C. The solvent polarity, an important reaction parameter, especially when the transition state of a reaction is polar or ionic, was determined by UV measurements with Nile red and Reichardt's dye as solvatochromatic probes. The melts are very polar and exhibited polarities between DMSO and ethylene glycol.[15] Carbohydrate urea melts have very good solvent properties and were successfully used for chemical transformations such as Diels-Alder reactions, Stille and Suzuki cross-couplings and for hydrogenation reactions, illustrating the general use of the melts in organic synthesis.[16] A sustainability assessment of the melts, where solvent performances and ecological (dis)advantages of different solvent systems for the Diels-Alder reaction of cyclopentadiene and methyl acrylate were investigated, rated the new alternative media to be less toxic compared to other conventional and alternative solvents.[17]

Apart from sugar as a melt component, other renewable materials are suitable to form melts, which can be considered as alternative solvents. As a

consequence, a broad spectrum of melts with different compounds is available with different solvent properties like polarity, melting point, dissolving ability, and the price of the raw materials. Here, the right choice of solvent system for a specific chemical transformation becomes difficult and it is necessary to compare the performance of different melt systems based on renewable materials to reach high reaction rates and selectivities.

We report here a comparison of the performance of a new L-carnitine urea melt to established sugar and sugar alcohol melts using several important organic reactions for benchmarking. The Heck and Sonogashira cross-coupling, as well as the 1,3-dipolar copper catalysed cycloaddition reactions were performed in the alternative media to compare the systems. Apart from the chemical reactions, the polarity of the new L-carnitine urea melt was determined with a solvatochromatic probe and found to be even higher than the typical sugar melt.

Results and discussion

Reactions in sugar and sugar alcohol melts

Mixtures based on carbohydrate, urea and salt were reported by us to form stable and clear melts with melting points between 65 and 85 ^{o}C and were successfully applied as solvents for Diels-Alder cycloadditions, catalytic hydrogenation and Suzuki and Stille cross-coupling reactions. The work-up of the melts is conducted simply by the addition of water leading to phase separation,[18] allowing for the collection of starting material and crude product by pipetting off the supernatant.

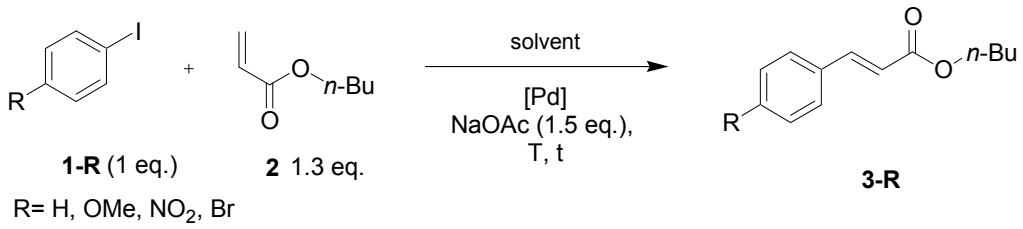
To prove the general applicability of sugar/urea/salt melts for chemical transformations, further typical reactions were tested using the melt as a solvent. Especially transition metal catalysed reactions were investigated, because of their good efficiency.

Heck cross-coupling

A widely used palladium-catalysed process in contemporary organic chemistry is the Heck-type coupling. In most cases, catalytic amounts of a palladium complex, often with phosphine ligands, is used in a polar solvent at moderate temperatures. [19] Heterogeneous catalyst systems facilitate the catalyst recycling[20] and avoid contamination of products by the palladium catalyst.[21]

To compare the difference in performance of homogeneous and heterogeneous palladium catalysts in this alternative media we used both types of catalysts and the results were compared between conventional and alternative solvents. Firstly, palladium on activated carbon (Pd/C) as a heterogeneous catalyst was used, because this catalyst is reported to have high activity and enjoys general use even for one-pot multi step reactions.[22]

The Heck cross-coupling of iodobenzene (**1-H**) and *n*-butyl acrylate (**2**) was studied using different catalysts and reaction conditions to afford *n*-butyl cinnamate (**3-H**) (Scheme 2.1). The use of a heterogeneous palladium catalyst was compared with homogeneous Pd-sources and with reactions in high boiling solvents like DMF and in $[C_4mim][PF_6]$ as a representative room temperature ionic liquid (RTIL).



Scheme 2.1 Palladium-catalysed Heck cross-coupling with *n*-butyl acrylate and iodobenzenes in several solvent systems using different reaction conditions.

R	Pd-source	reaction conditions	time [h]	isolated yield [%]
H	Pd/C	melt, 80 °C	12	63
H	Pd/C	melt, us, 73 °C	3	69
H	Pd/C	DMF, 80 °C	1	67
H	$PdCl_2$	$[C_4mim][PF_6]$, 120 °C	6	91
H	$Pd(OAc)_2$	melt, us, 73 °C	2	81
Br	$Pd(OAc)_2$	melt, 80 °C	4	85
H	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	77
OMe	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	86
NO_2	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	85
Br	$PdCl_2(PPh_3)_2$	melt, 80 °C	4	91

us = ultra sound, melt = D-mannose/DMU (3:7, w/w)

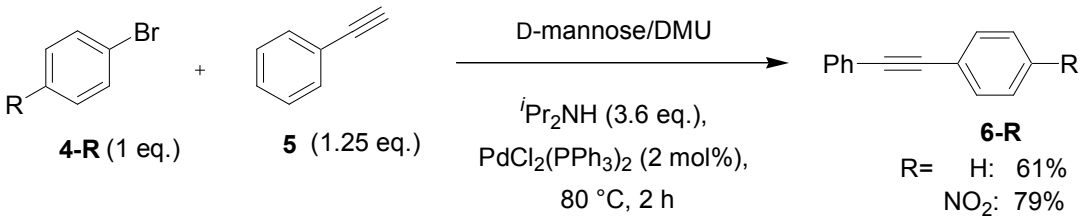
Table 2.1 Isolated yields of the cross-coupling product under different reaction conditions

Table 2.1 shows the yields of the cross-couplings, indicating the use of heterogeneous Pd/C catalysts (grey background) less suitable in melts, presumably due to their higher viscosity. To increase the reaction rate ultrasound agitation was applied resulting in a significantly shorter reaction time with a slightly increased yield.[23] Using a homogeneous catalyst still gave a higher yield, which is comparable to isolated yields reported for conversions in classical organic solvents.

After identifying the best source of metal catalyst for the Heck-reaction in the melt, the addition of ligands to the homogeneous Pd salt was investigated, where $PdCl_2(PPh_3)_2$ seemed to be the catalyst of choice. The scope of the melt reaction conditions was investigated with a small series of substituted iodobenzenes (**1-R**), giving good to excellent isolated chemical yields of the reaction products. 1-Bromo-4-iodobenzene was found to be a good electrophile for the Heck reaction in this alternative medium. Reactions with this electrophile in melts were compared with different homogeneous catalysts in conventional ($AcNMe_2$, 87%) [24] and alternative solvents ($[C_4mim][PF_6]$, 33%)[25] to show the general applicability of sugar and L-carnitine melts. The comparison shows that good to excellent yields (62-91%) can be obtained using the carbohydrate melts at lower reaction temperatures compared to organic solvents or an ionic liquid.

Sonogashira cross-coupling

Another important palladium/copper-catalysed reaction for the synthesis of substituted alkynes from aryl halides and terminal acetylenes is the Sonogashira coupling.[26] The Sonogashira reaction is frequently used as a key step in natural product chemistry and for the synthesis of acetylene compounds for optoelectronic applications.[27] This well-established methodology has seen a huge variety of modifications during recent years. Remarkably is the elimination of the copper salt which was used to suppress the undesired homocoupling by the in-situ generated copper acetylides (the Glaser-coupling) to diynes by oxidative agents or air.[28] In our experiments a D-mannose/urea melt was used to couple aryl halides (**4-R**) and phenyl acetylene (**5**) without the use of a copper co-catalyst. Like in the Heck cross-coupling described above, the homogeneous catalyst $PdCl_2(PPh_3)_2$ was used due to better performance compared to the heterogeneous Pd/C (Scheme 2.2). As expected, the nitro-substituted electrophile **4-NO_2** gave better yields (79%) after 2 h at 80 °C.

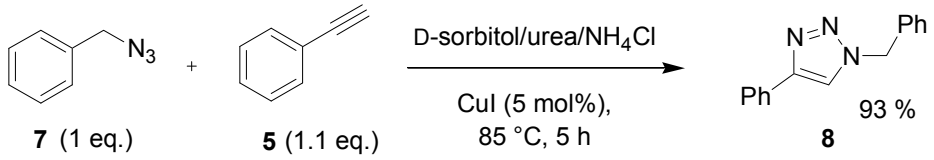


Scheme 2.2 Homogeneous Sonogashira cross-coupling with D-mannose/DMU as a solvent at 80 °C.

Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition

The Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC), a Cu^I-catalysed version of the Huisgen 1,3-dipolar cycloaddition, [29] has been established as a reliable method for the preparation of triazoles and is performed in conventional organic solvents,[30] ionic liquids[31] and water.[32] Here, a D-sorbitol/urea/NH_4Cl (7:2:1, w/w/w) melt was used rather than a mannose

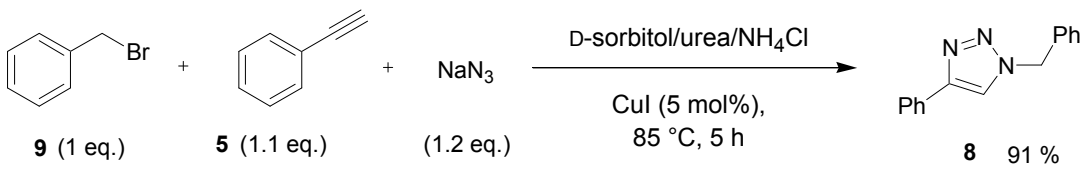
melt due to its higher chemical stability avoiding potential side reactions induced by the strong nucleophile sodium azide. The sugar alcohol sorbitol is chemically less reactive than mannose and hence a good solvent for the reaction of benzyl azide (**7**) with phenyl acetylene (**5**) at 85 °C (Scheme 2.3) providing excellent isolated product yields.



Scheme 2.3: Cu(I) catalysed formation of 1,4-substituted 1,2,3-triazoles in the melt.

After isolation, the 1,4-regioisomer **8** was found to be formed exclusively.[33] Best yields were obtained using CuI as copper source, $CuSO_4$ with sodium ascorbate as reducing agent, used in many cases for the CuAAC, yielded only 84%. Upon ultrasound irradiation the conversion increased drastically, but the regioselectivity of the reaction decreased. After 30 min of reaction time a 4:1 mixture of the 1,4- and the 1,5- triazole was isolated, which indicates that under these conditions the non-catalysed reaction pathway is promoted.[34]

Reducing the number of individual synthetic steps to a product is economically and environmentally advantageous.[35] Therefore, a “one-pot” modification of the CuAAC was investigated. The azide formation and cycloaddition can be performed in one step (Scheme 2.4) in the D-sorbitol melt, still giving excellent yield (91%). The conversions in the melt systems require no additional base, similar to the findings of CuAAC reactions in water.[36]



Scheme 2.4 One-pot fashion formation of 1,4-substituted 1,2,3-triazoles in the melt.

The discussed examples illustrate that many modern transition metal catalysed reactions can be performed in low melting mixtures of sugars, urea and salt.[37] Depending on the catalytic system used, the reaction benefits from the highly polar medium and simple and efficient work-up procedures. However, the higher viscosity of the melt compared to conventional organic solvents limits the use of heterogeneous catalyst systems, even if ultrasound was employed.

Properties and chemical reactions in L-carnitine based melts

Looking for new alternative melt systems consisting of renewable feedstock, L-carnitine (Fig. 2.1) was investigated. L-Carnitine, a natural betain, is biotechnologically accessible via both γ-butyrobetain and crotonbetaine and an interesting renewable bulk product. [38] This non-toxic (rat oral LD_{50} > 5,000 mg kg^{-1}) and non-mutagenic (Ames-test negative) natural product shows almost no skin irritation and is reported to be a stable compound. L-carnitine is used as renewable building block for biomaterials like polycarnitine, polycarnitine allylesters and poly crotonbetaines, retaining the initial properties of the monomers e.g. the “stiffening” effect.[39]

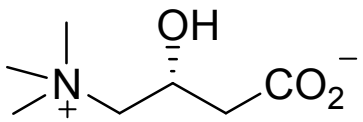


Fig. 2.1 L-Carnitine: Carboxy-2-hydroxy-*N,N,N*-trimethyl-hydroxide

Screening the best combinations between L-carnitine and different substances like urea, DMU and NH_4Cl, which are known for potential melting point depression, DSC measurements gave the lowest melting point of 74 °C for a 2:3-mixture of L-carnitine/urea (w:w). For all further measurements and chemical reactions this ratio was used without further addition of melt components.

Solvatochromatic measurements were carried out to determine the polarity of the new L-carnitine/urea melt and compared with other melts (Fig. 2.2). Nile red

was used as solvatochromatic probe in the melt and E_T values were calculated from UV-Vis measurements.

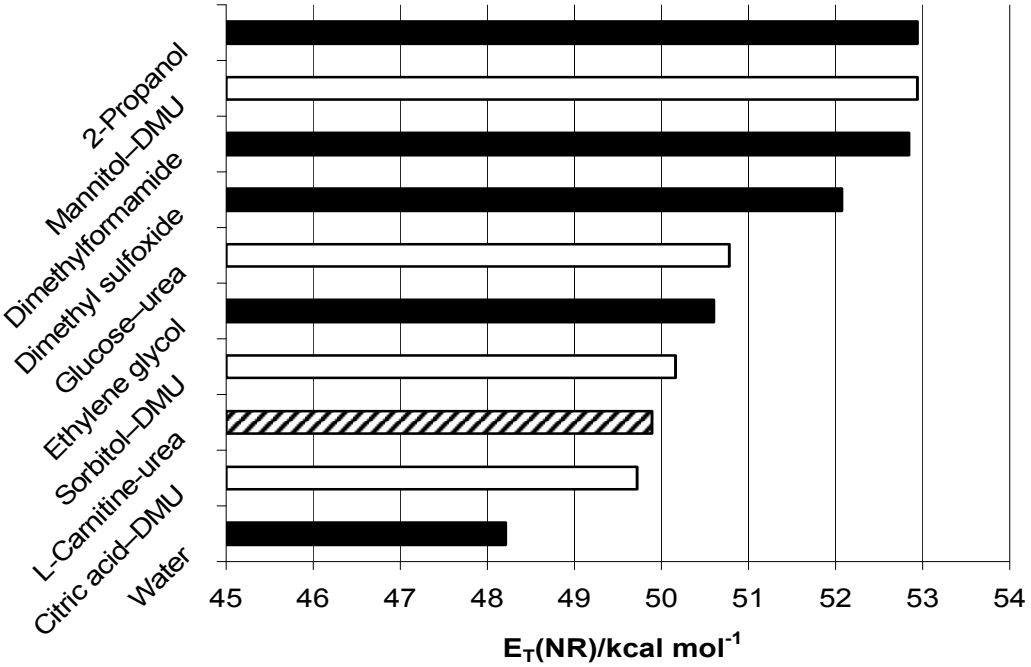


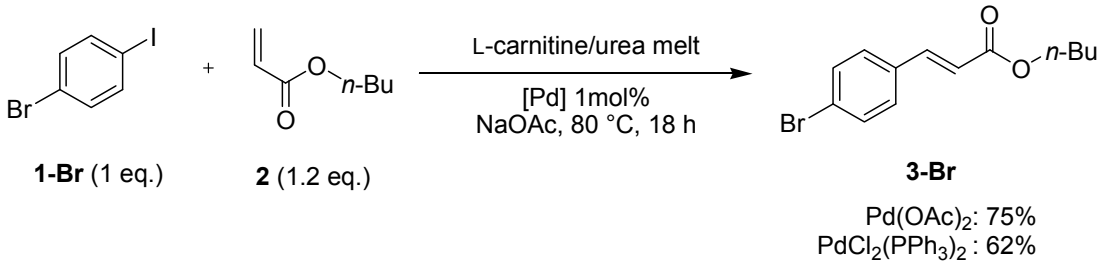
Fig. 2.2 Solvent polarity values E_T in L-carnitine/urea melt (dashed) and other solvents (black) and melts (white) for comparison at 80 °C; determined with Nile red as probe.

In comparison to other melts based on renewable feedstock the L-carnitine/urea mixture showed a rather high polarity with an E_T(NR) value of 49.89 kcal mol^{-1}. The E_T(NR) value is between the value of D-sorbitol/DMU and citric acid/DMU melts with 50.16 and 49.72 kcal mol^{-1}, respectively, and only slightly higher than the value for water.

Heck cross-coupling

Like the previously reported sugar based urea mixtures, the L-carnitine/urea mixtures show good solvent properties for chemical transformations. The viscosity, however, is slightly higher than in the case of the sugar melts.

First, the Heck cross-coupling reaction was investigated. Different palladium sources were tested and $Pd(OAc)_2$ worked best in this media for a reaction of *n*-butyl acrylate with 1-bromo-4-iodobenzene, which was found to be the best electrophile for the carbohydrate melts (Scheme 2.5). Similar as in the sugar melts, palladium on charcoal as a catalyst, exhibited lower conversions.



1-Br (1 eq.) **2** (1.2 eq.) **3-Br**

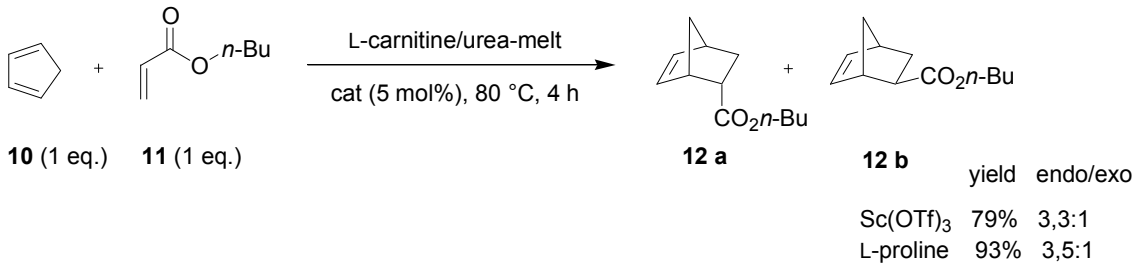
$Pd(OAc)_2$: 75%
$PdCl_2(PPh_3)_2$: 62%

Scheme 2.5 Homogeneous Heck cross-coupling with *n*-butyl acrylate and 1-bromo-4-iodo benzene.

The work up of the reaction mixture is easy since both components of the melt have a high solubility in water, like the sugar melts. Activation by ultrasound was tested in the case of the Heck reaction, but gave very low conversions. We explain the low yields by the partial decomposition of L-carnitine under the reaction conditions poisoning the catalyst.

Diels-Alder cycloaddition

The Diels-Alder cycloaddition is widely used in organic synthesis.[40] The reaction proceeds in organic solvents and alternative solvents like ILs, $scCO_2$ and water. Scheme 2.6 shows the Diels-Alder reaction of cyclopentadiene and *n*-butyl acrylate with catalytical amounts of $Sc(OTf)_3$ or L-proline as catalysts.

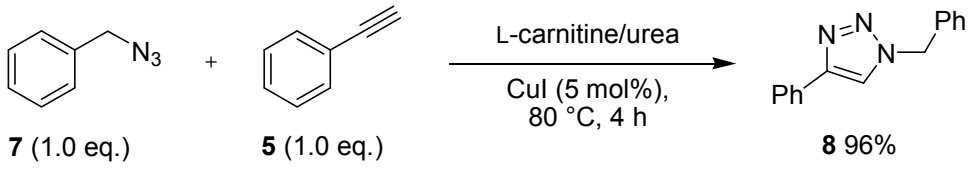


Scheme 2.6 Diels-Alder cycloaddition of cyclopentadiene and *n*-butyl acrylate.

The reaction with 5 mol% L-proline as organocatalyst instead of $Sc(OTf)_3$ gave an excellent yield of 93% for **12 a** and **12 b**. The results obtained in the L-carnitine/urea melt are comparable to the previous findings in carbohydrate melts, where overall yields of **12 a** and **12 b** range from 72 to 95% for a D-fructose and lactose melt, respectively.[14]

Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition

Interestingly, the copper catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) proceeded slightly better in an L-carnitine based melt than in the sugar melt (Scheme 2.7).



Scheme 2.7 Cu(I) catalysed formation of 1,4-substituted 1,2,3-triazole in the L-carnitine melt.

A possible coordination of the carnitine molecule to the Cu^{I} ion, resulting in a stabilising effect during the cycloaddition, may promote the reaction. An analogue effect was demonstrated by the group of Ma where L-proline functions as a ligand in Cu^{I} catalysed C-N bond formation reactions.[37] Fig. 2.3 shows the proposed coordination of the copper ion during amino acid promoted reactions.

An analogous coordination of copper by L-carnitine is proposed to explain the better yields in the carnitine melts compared to the carbohydrate melts.[41]

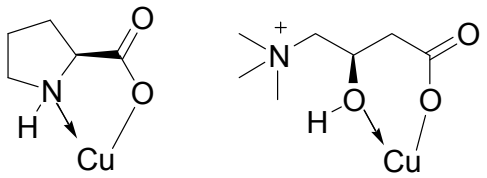


Fig. 2.3 Proposed coordination of copper(I) ions by L-proline and L-carnitine.

The use of $CuSO_4$ instead of CuI was tried, but resulted in a reduced yield (81%) similar to the reaction performed in a carbohydrate melt. In all cases reported here no additional base was necessary, because of the reversible proton accepting property of the melt. This effect was observed for CuAAC reactions in water, as well.[32] The results obtained in carnitine and carbohydrate melt systems are compared with the outcome of the reaction in other commonly used organic solvents (Fig. 2.4). A comparison of CuAAC reactions starting from either benzylazide (benzylazide) or the benzylbromide (chloride) (one-pot) are given. The one-pot approach in L-carnitine melt resulted in a lower overall yield of 55%, which is attributed to the higher chemical reactivity of the melt. However, both melts showed very good applicability compared to aqueous and organic solvents.

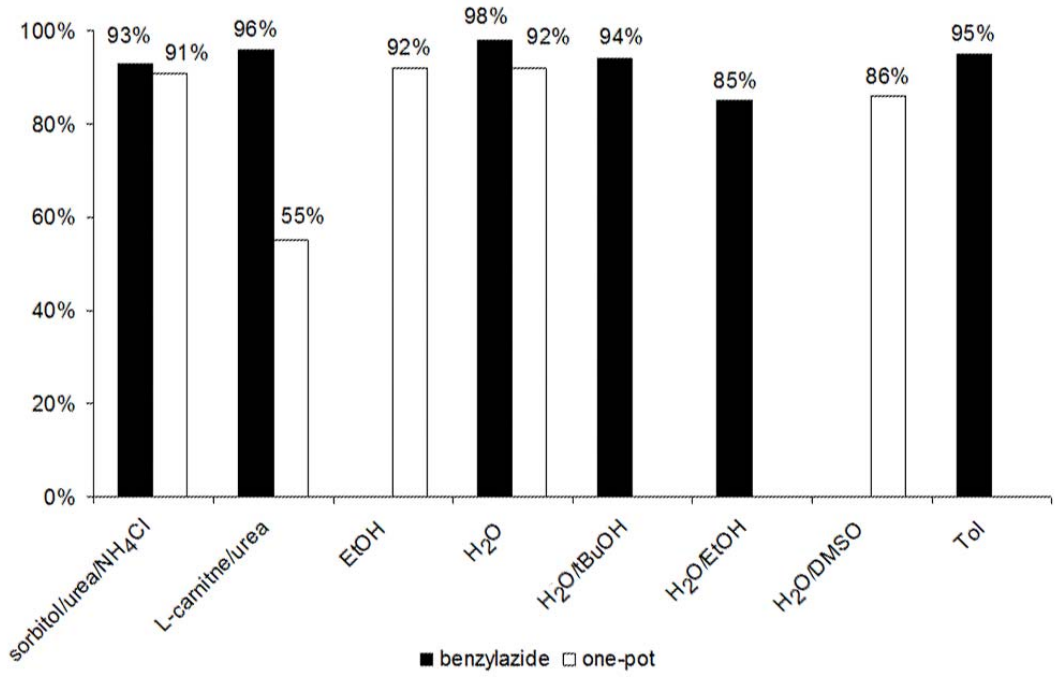


Fig. 2.4 Bar graph comparing click reactions yielding 1,4-substituted 1,2,3-triazoles in different solvent systems. Reactions starting from benzylazide and one-pot reactions using benzylbromide are shown separately. Reaction conditions for EtOH: 78 °C, 24 h; H_2O: 25 °C, 24 h, 25 °C, 1 h; $H_2O/^tBuOH$: 25 °C, 24 h; H_2O/EtOH: 25 °C, 3 h; H_2O/DMSO: 25 °C, 15 h; toluene: 60 °C, 24 h.[42]

Conclusion

Melts based on an L-carnitine/urea mixture show an overall lower efficiency as alternative solvents compared to established carbohydrate melts. The new medium was found to have a melting point of 74 °C for a 2:3-mixture of L-carnitine/urea (w:w) and a relatively high solvent polarity between the E_T values of ethylene glycol and water, as determined by solvatochromatic probes. For comparison, transition metal catalysed reactions were performed in the new melt and the previously reported carbohydrate melts. The Heck cross-coupling reaction with heterogeneous Pd/C showed low reaction rates, due to the high viscosity of the melts. Using a homogeneous Pd-source, the carbohydrate melts gave yields up to 91%, whereas the L-carnitine melt afforded only 75% yield for

$Pd(OAc)_2$. Sonication increased the reaction rate in carbohydrate melts, but gave lower yields in L-carnitine/urea melts indicating a decomposition of the melt component. The Diels-Alder reaction gave comparable yields and selectivites in both melt systems when L-proline was used as an organocatalyst. The yields for Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) were slightly better (96%) in the L-carnitine/urea when compared to the carbohydrate melt reactions. The “one-pot” procedure of subsequent azide formation and conversion gave excellent results in the sugar based melts, while the yield for the L-carnitine melt was much lower (55%). A side reaction of the azide nucleophile with the carnitine melt component may account for the reduced yield. When $CuSO_4$ with sodium ascorbate was used as catalyst, the yields were found to be lower than for CuI: From carbohydrate melts 84% and from the L-carnitine melt 81% of the desired product were isolated.

Comparing the performance in chemical transformations of the new L-carnitine melt to carbohydrate melts, L-carnitine was not as effective as a solvent for organic transformations. L-Carnitine contains a quaternary ammonium ion leading to chemical instability[43] in the presence of nucleophiles, like azides. Irradiation with ultrasound causes partial decomposition of the L-carnitine melt. Another aspect of evaluating alternative solvents is the price of the melt components. Considering the various parameters the carbohydrate melts have an advantage over L-carnitine melts. Fig. 2.5 summarises the results from Heck-type and click reactions in carbohydrate and carnitine melts in terms of chemical yields. Carbohydrate melts, based on D-mannose or D-sorbitol, showed very good solvent properties for the Heck reaction with homogeneous Pd-sources, the Cu-catalysed azide-alkyne 1,3-dipolar cycloaddition, performed well in “one-pot” CuAAC procedures and gave good results for the Sonogashira cross-coupling, while L-carnitine/urea is only suitable for some of these standard transformations in organic synthesis and therefore limited in general applicability.

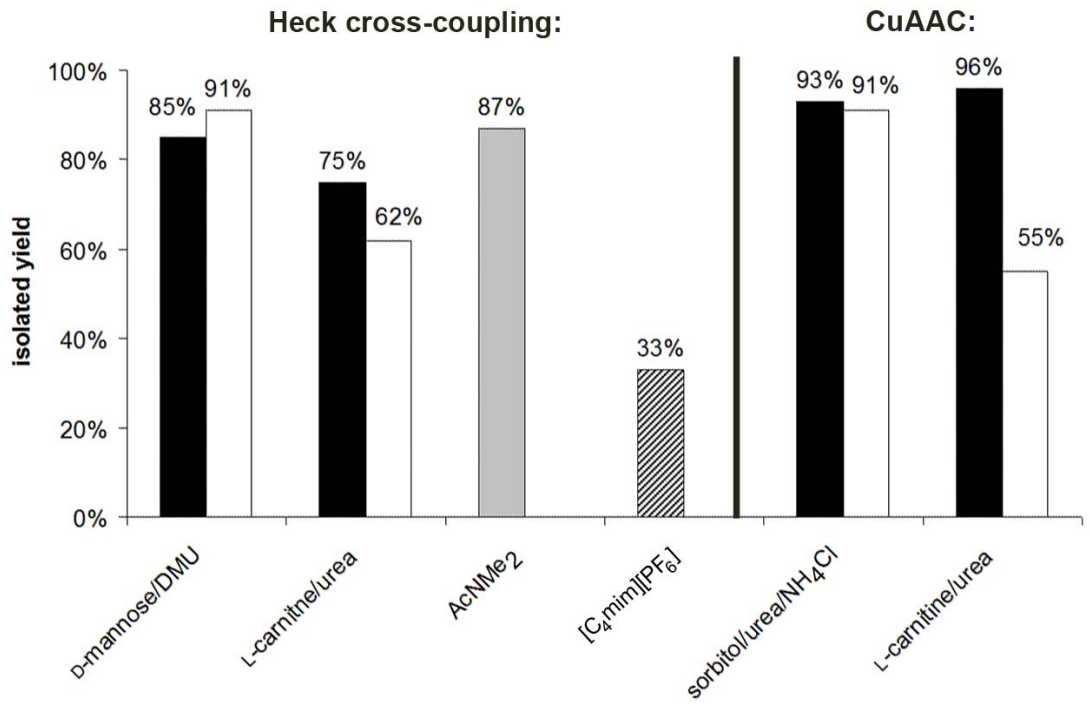


Fig. 2.5 Typical chemical yields of reactions in carbohydrate and carnitine melts. Heck cross-coupling (left): Reactions of 1-bromo-4-iodobenze using $Pd(OAc)_2$ (black bar), $PdCl_2(PPh_3)_2$ (white bar), a furancarbothioamide derived palladacycle (grey),[24] or (bis-*N*-methylimidazole)$PdCl(CH_3)$[25] (dashed) as catalyst. CuAAC (right): 1,4-substituted 1,2,3-triazoles were obtained either from benzylazides (black bar) or in one-pot fashion (white bar).

Experimental Section

General

All chemicals were used without further purification as received with the exception of $^{i}Pr_2NH$ which was distilled before use.

Benzyl azide was prepared following the procedure of Alvarez and stored in the refrigerator.[44]

Preparation of melts

Unless otherwise stated, the constituents of the melts were ground with a mortar and pestle, filled into a resealable vial equipped with a stirring bar and placed into an oil bath. Upon formation of the melt, the reactants were loaded under nitrogen before the vial was sealed.
For the Sonogashira reaction, liquid reactants were deaerated with nitrogen prior to use. After formation of the melt the vial was evacuated and flushed with nitrogen to remove any oxygen from the melt. This procedure was repeated three times before the reactants were added.

For experimental accuracy the work-up was carried out by extraction with organic solvents in commonly used amounts. For larger scale, however, liquid extraction with organic solvents can be significantly reduced. Here, even with the small testing reactions (1 mmol) a separation with little organic solvents was successful: The addition of water (50 mL), brine (10 mL) and just 3 mL of EtOAc to the reaction mixture will dissolve all melt components and separates the organic layer containing product and starting material after extraction. For analytical investigations the remaining aqueous phase was extracted with EtOAc (3x20 mL) and the combined organic phase was analysed by gas chromatography (GC). For D-mannose/DMU (3:7) (Fig. ES2.5), D-sorbitol/urea/NH_4Cl (7:2:1) (Fig. ES2.6) and L-carnitine/urea (2:3) (Fig. ES2.7) melt no starting material or product could be detected by GC analysis confirming their complete extraction by 3 mL of EtOAc.
To test the recyclability of the Pd containing melt a recycling experiment over three cycles was performed with *p*-iodo anisole and 1-bromo-4-iodobenzene as electrophiles in a sorbitol/urea melt (5:5). The catalyst remains active during the experiment, but its activity drops significantly with each reuse of the melt. The decreasing catalytic activity of the catalyst in reused melts is in agreement with earlier observations of Stille cross-coupling reactions in the melt.[16] After the last run of the recycling experiment the melts were dissolved in water (50 mL) and extracted with EtOAc (3x20 mL). GC analysis of the organic phase gave no

detectable signals for starting material or product indicating its quantitative extraction during the recycling runs (Fig. ES2.3 and Fig. ES2.4).

Typical procedure for homogeneous Heck reactions in D-mannose/DMU melt

In a 10 mL Schlenk tube containing deaerated D-mannose/urea-melt (2 g, D-mannose/DMU, 3:7, w/w) 4-iodoanisole (0.23 g, 1.0 mmol), *n*-butyl acrylate (0.19 mL, 1.3 mmol), sodium acetate (0.2 g, 1.5 mmol) and bis-(triphenylphosphin)-palladium(II)-chloride (0.007 g, 0.01 mmol) were added at 80 °C under nitrogen. The reaction was stirred for 18 h at this temperature, water (3 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (EtOAc:PE = 1:6, R_f = 0.32) to yield the desired product as colourless oil (0.2 g, 86%). The ^{1}H and ^{13}C-NMR-spectroscopic data are in accordance with the literature.[45]

Typical procedure for Sonogashira cross-coupling in D-mannose/DMU melt

In a 10 mL Schlenk tube containing deaerated D-mannose/urea-melt (2 g, D-mannose/DMU, 3:7, w/w) 1-bromo-4-nitrobenzene (0.202 g, 1.0 mmol), phenylacetylene (0.128 g, 1.25 mmol), diisopropylamine (0.26 mL, 3.6 mmol) and dichloro-bis(triphenylphosphine)palladium(II) (0.014 g, 0.02 mmol) were added at 80 °C and under nitrogen. The reaction mixture was stirred for 2 h. After the reaction was stopped, water (3 mL) was added. After extraction with EtOAc (3x20 mL) the combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give the brown crude product. The crude solid was subjected to column chromatography (EtOAc:PE = 1:19, R_f = 0.48) to obtain **6-NO_2** in 79% yield (0.176 g). The ^{1}H and ^{13}C- NMR-spectroscopic data are in accordance with the literature.[46]

Cu-catalysed azide-alkyne cycloadditions in D-sorbitol/urea/NH_4Cl melt

To a capped vial equipped with a stirring bar containing D-sorbitol/urea/NH_4Cl melt (2 g, D-sorbitol/urea/NH_4Cl, 7:2:1, w/w/w) benzyl bromide (0.12 mL, 1 mmol), phenyl acetylene (0.12 mL, 1.1 mmol), copper(I) iodide (9 mg, 0.05 mmol) and sodium azide (78 mg, 1.2 mmol) were added and the reaction was stirred for 5 h at 85 °C. At the end of the reaction water (3 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The organic phase was dried over $MgSO_4$, evaporated and the crude product was subjected to column chromatography (EtOAc:PE = 1:3, R_f = 0.31) to yield the 1,4-substituted 1,2,3-triazole as pale yellow solid (210 mg, 91%). The ^1H and ^{13}C- NMR-spectroscopic data and the melting point are in accordance with the literature.[47]

The Heck and CuAAC reactions were performed in analogy to the carbohydrate melts using L-carnitine instead of the sugar component.

Diels-Alder cycloaddition in L-carnitine/urea melt

To a capped vial equipped with a stirring bar containing L-carnitine/urea melt (2 g, 2:3, w/w) cyclopentadiene (0.16 mL, 2.0 mmol), *n*-butyl acrylate (0.29 mL, 2.0 mmol) and scandium-trifluoromethane sulfonate (0.01 g, 0.1 mmol) were added and the reaction was stirred for 4 h at 80 °C. At the end of the reaction water (3 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The organic phase was dried over anhydrous $MgSO_4$, evaporated and the crude product was subjected to column chromatography (PE, R_f = 0.39) to yield the product as colourless oil (0.306 g, 79%).

Determination of the polarity

Solvatochromatic measurement of the solvent polarity with Nile red (NR) as solvatochromatic probe: L-carnitine (10 g), urea (10 g) and Nile red (0.3 mg)

were ground with a mortar and pestle. The mixture was filled into a reaction flask, stirred in an oil bath at 80 °C and equilibrated for 5 h until a transparent purple homogeneous melt was formed. A blank melt for comparison was prepared using L-carnitine (2 g) and urea (2 g) and stirred for 5 h. While still hot, the melts were consecutively transferred into preheated UV cuvettes and instantly measured with a UV-Vis spectrometer. The blank sample was used for background subtraction. λ_{max} was determined and used in the formula E_T(NR) kcal mol^{-1} = $hc\lambda_{max}N_A$ = 28591/λ_{max} to obtain E_T(NR). The measurement and determination of the polarity was repeated two times to confirm the reproducibility without significant variations.

Recycling study

The recycling experiments were conducted in resealable vials (5 mL) with septum. For work-up deaerated EtOAc (3 mL) was added through a septum into the vial and the mixture was stirred at the reaction temperature for 5 min. The organic phase was pipetted or after resolidification of the melt simply decanted off. This procedure was repeated five times (total of 15 mL EtOAc), the combined organic phases were washed with water and analysed by GC using toluene as internal standard. After the first run (75% yield, 89% conversion for 1-bromo-4-iodobenzene) yield and conversion dropped significantly to 32% and 45%, respectively. In a third run, GC analysis revealed 8% yield and 27% conversion. For *p*-iodo anisole the measured yields and conversions for the three runs were 62%/87%, 41%/63% and 32%/55%.

GC study:

To the withdrawn samples toluene (20 µmol/L) was added as internal standard. The mixture (200 µL sample and 200 µL standard) was filtered and injected for quantification.

J+W Scientific / DB-5MS / 30 m x 0.25ID / 0.25 µm Film, GC: HP5890 II, Pressure Control: Panel Hydrogen: 14 psi (100 kPa), Panel Air Pressure: 40 psi (260 kPa), Column Head Pressure: 14.5 psi-> 100 kPa -> ~1.7 mL/min, Split: (40 ml/min), Septum Purge: 6 mL/min, Liner: Supelco split/splitless Injection Sleeve, Septum: Agilent Inlet Septa Part 5183-4757, Bleed/Temp Optimized Non-Stick 11 mm.

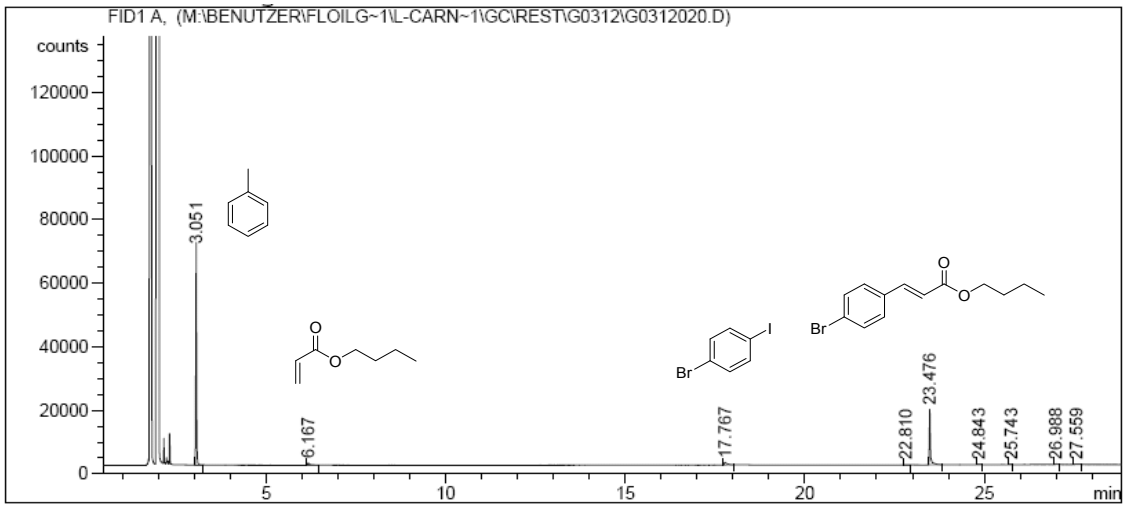


Fig. ES2.1 Chromatogram for the reaction of 1-bromo-4-iodo benzene with *n*-butyl acrylate in sorbitol/urea (1:1, w/w) (Toluene is used as tracer).

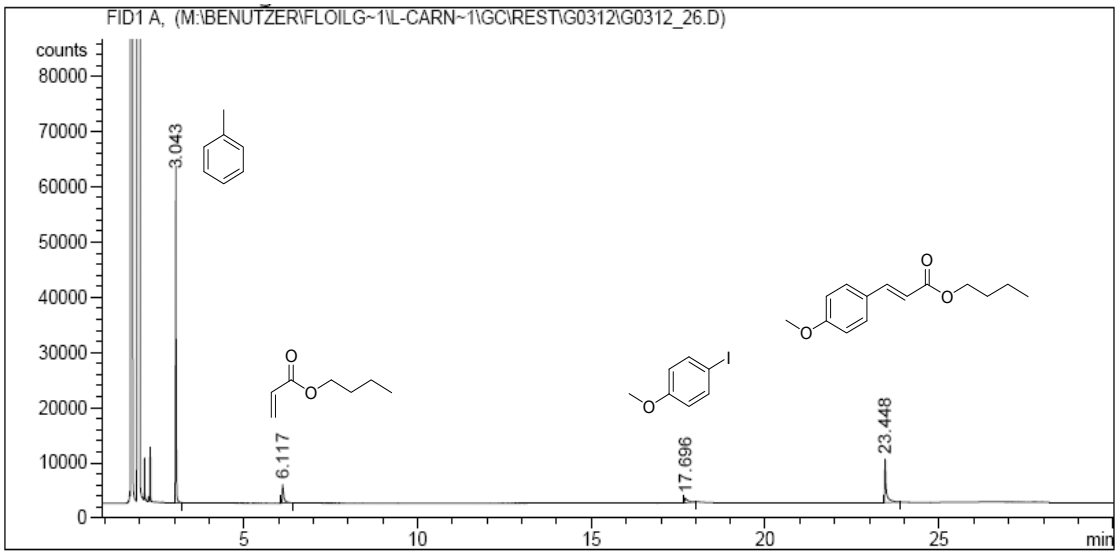


Fig. ES2.2 Chromatogram for the reaction of 4-iodoanisole with *n*-butyl acrylate sorbitol/urea (1:1, w/w).

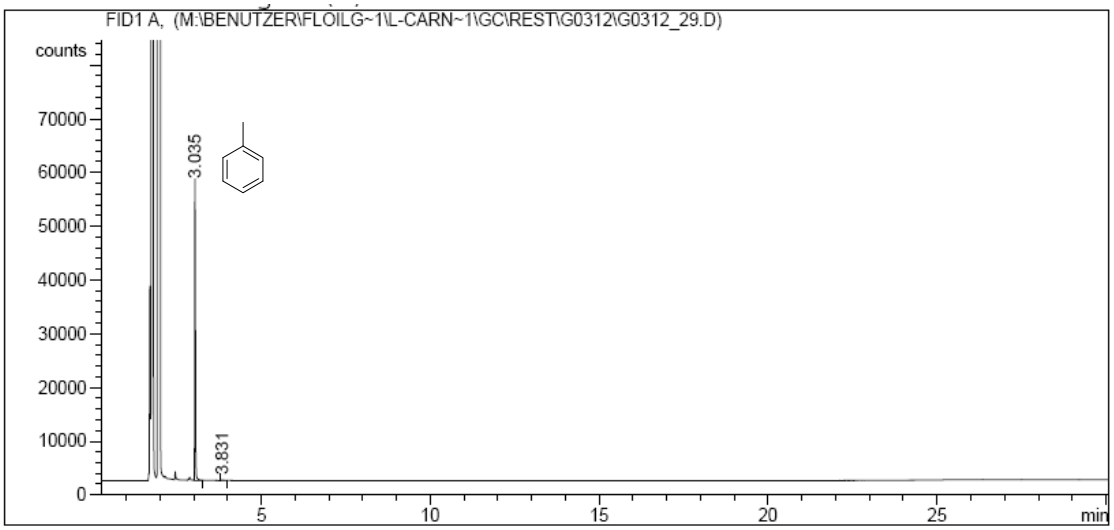


Fig. ES2.3 Chromatogram for the reaction of 1-bromo-4-iodo benzene with *n*-butyl acrylate after 3 recycling runs in sorbitol/urea (1:1, w/w) and aqueous work-up (melt was dissolved in water (50 mL) and subsequently extracted with EtOAc (3x20 mL), the combined organic phases were analysed for remaining substances).

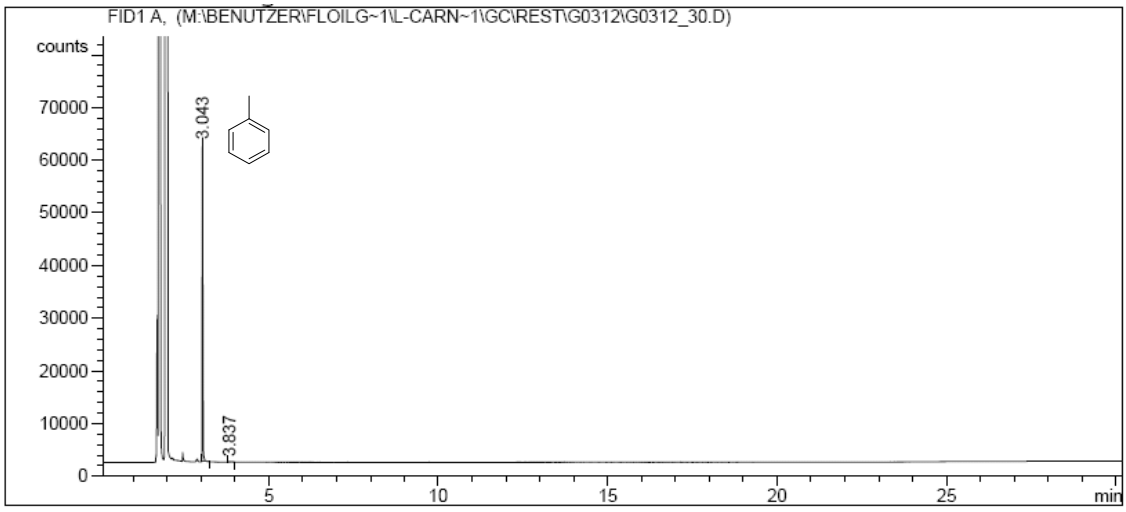


Fig. ES2.4 Chromatogram for the reaction of 4-iodoanisole with *n*-butyl acrylate after 3 recycling runs in sorbitol/urea (1:1, w/w) and aqueous work-up (melt was dissolved in water (50 mL) and subsequently extracted with EtOAc (3x20 mL), the combined organic phases were analysed for remaining substances).

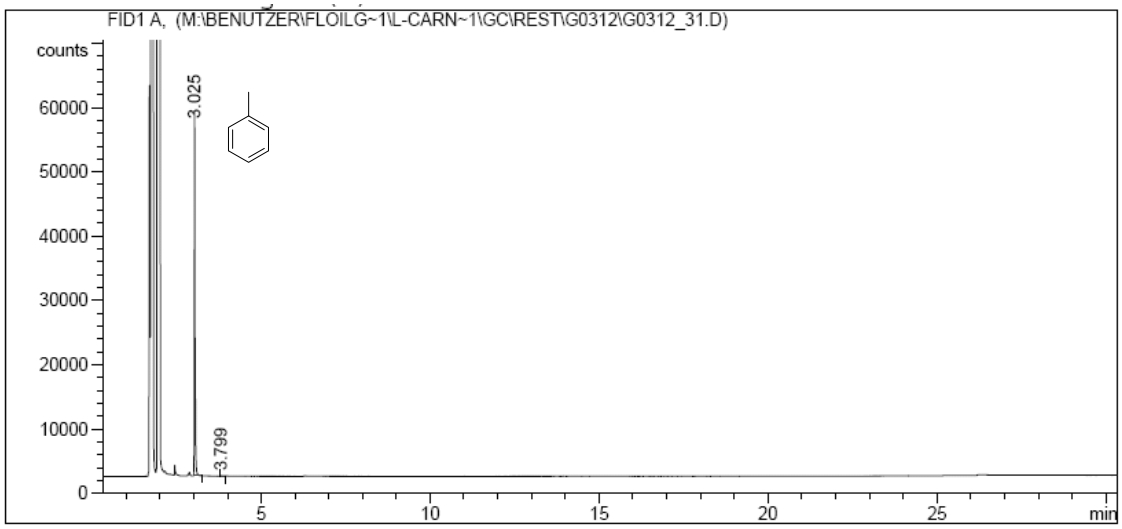


Fig. ES2.5 Chromatogram for the reaction of 4-iodoanisole with *n*-butyl acrylate in L-carnitine/urea after aqueous work-up with 3 mL EtOAc (aqueous phase was extracted with EtOAc (3x20 mL) and analysed).

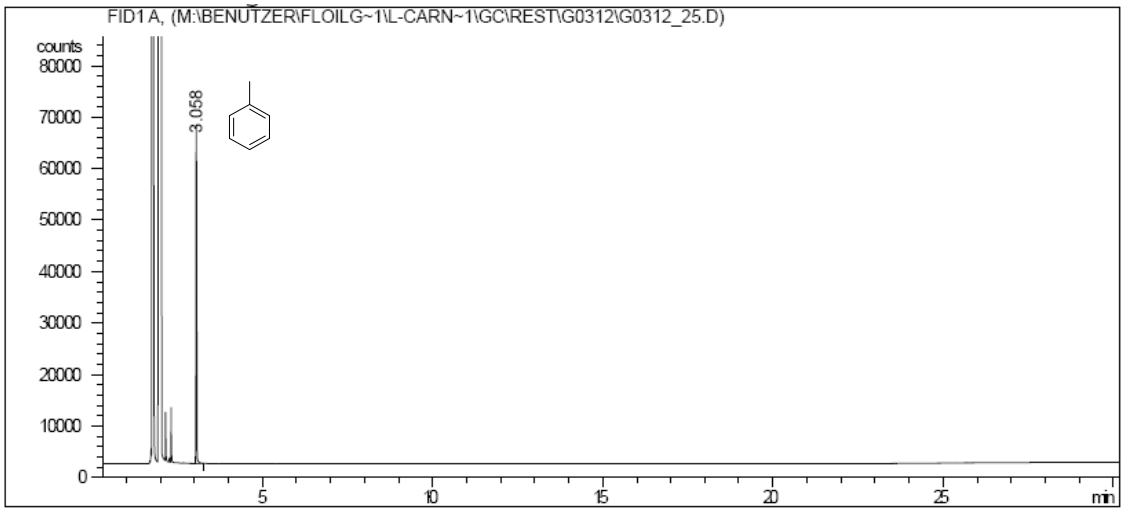


Fig. ES2.6 Chromatogram for the reaction of 4-iodoanisole with *n*-butyl acrylate in sorbitol/urea/NH_4Cl after aqueous work-up with 3 mL EtOAc (aqueous phase was extracted with EtOAc (3x20 mL) and analysed).

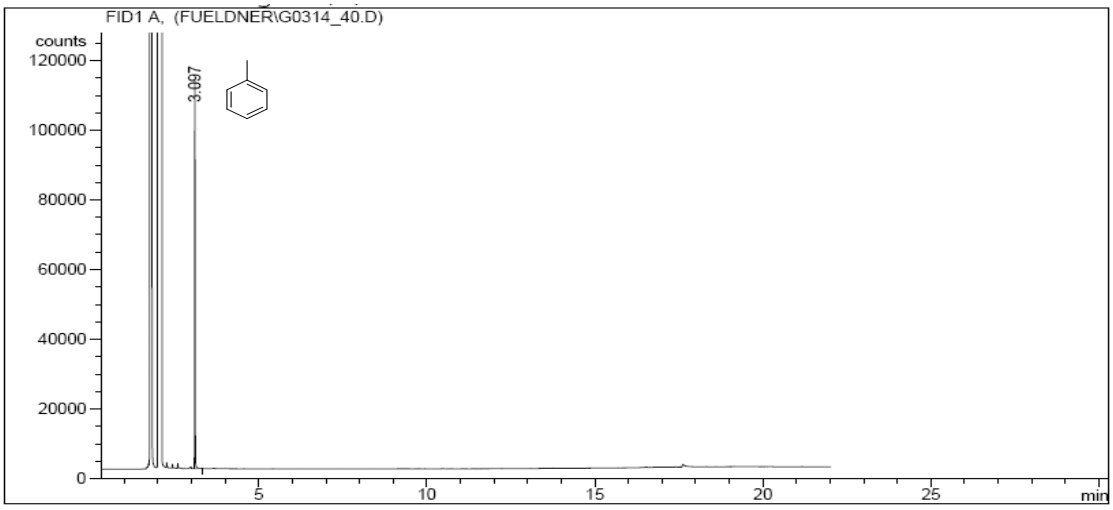


Fig. ES2.7 Chromatogram for the reaction of 4-iodoanisole with *n*-butyl acrylate in D-mannose/DMU after aqueous work-up with 3 mL EtOAc (aqueous phase was extracted with EtOAc (3x20 mL) and analysed).

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3. Efficient preparation of β-D-glycosyl and β-D-mannosyl ureas in carbohydrate melts*

* The investigations described in this chapter were carried out together with Christian Reil within his final thesis for his studies as a teacher.

Introduction

In the 21st century, the utilization of renewable raw material will gain significant importance in the industrial conversion of chemicals. This fact is a consequence of diminishing fossil fuel reserves which will urge to develop new methodologies to make use of sustainable sources for chemical production in the near future.[1] Since biomass is renewable, abundant and distributed widely in nature, it is a promising alternative for the sustainable supply of valuable intermediates and platform chemicals to chemical industry.[2]

Carbohydrates (more than 75 % by weight)[3] form the main part of biomass. They can be used directly for chemical conversion or after hydrolysis of poly- and oligosaccharides to monosaccharides like D-glucose and D-fructose. Substitution at the most reactive site in monosaccharides, the anomeric centre, gives access to the important and prominent group of the glycosides. O-,[4] S-,[5] C-[6] and N-glycosides[7] are examples for this group of C-1 substituted monosaccharides. A special representative of the N-glycosides is the stable class of glycosyl ureas, which are widely used. They can be applied in a mixture with phenol and water as an adhesive with excellent properties. This special formulation is important for the forest product industry which is interested in reducing the phenol content in adhesives for construction material and furniture due to its toxicity.[8] Glycosylthymines can be prepared from glycosyl ureas as described by Sano *et al*.[9] Another important application of glycosyl ureas is the use as lyophilization stabilizers for enzymes.[10] Recently, Shoji *et al.* introduced a glycosyl urea based lectin adsorbent with high and controllable adsorption capacity, which can be manufactured conveniently.[11]

The condensation product between aldoses and urea is obtained from acid catalysed reactions in water or water mixtures and was first described for D-glucose by Schoorl *et al*. as early as in 1900.[12] After minor modifications in the original procedure, the synthesis of glycosyl ureas was improved by Benn and Jones yielding 32% after 42 h with sulphuric acid as catalyst.[13] The best results so far were obtained by M. Sano *et al*. using the ion exchanger Amberlite IR-120 (H-form) to obtain β-D-glycosyl urea in 53% chemical yield after 4 d at 75-80 °C.[7] Higher yields could not be achieved

without significantly longer reaction times (7 to 14 d).[6]
The reported methods for the preparation of β-D-glycosyl and β-D-mannosyl ureas suffer from long reaction times, moderate chemical- and space-time yields. An ideal method for the conversion of biomass into platform chemicals, however, is the use of highly concentrated systems featuring high substrate concentration and high chemical yields. Such systems should allow efficient conversions with high space-time yield.

Here, we report the application of carbohydrate urea melts with diverse Brønsted and Lewis acids as catalyst in aldose concentrations as high as 3 mol/L. Using such carbohydrate melt systems, the reaction times are reduced, while the yields could be significantly increased compared to the reported systems (up to 78%). Apart from β-D-glycosyl urea, β-D-mannosyl urea was prepared in the highest yields (58-86%) so far reported in literature.

Results and discussion

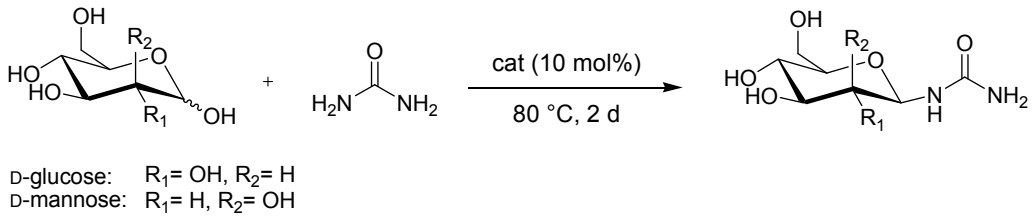
Formation of β-D-glycosyl urea in carbohydrate melt

The acid catalysed condensation of D-glucose with urea in aqueous media applying long reaction times was described both by Benn *at al.* and Sano *et al*. The stereochemistry at the anomeric centre was determined based on ^{1}H-NMR coupling constants of the two axial protons in C-1 and C-2 position by Helm to be the β-form.[6] Typically, the anomeric effect favours the α-configuration in sugars with electronegative substituents in C-1 position.[14] Here, nitrogen has a lower electronegativity compared to oxygen and halogens and thus contributes less to the anomeric stabilisation. Polar solvents are known to reduce the stabilisation at the anomeric centre. Both effects and the steric hindrance account for the preferred β-glycoside configuration.

In 1960, Benn *et al.* reported the glycosidic bond to be easily cleaved by hydrolysis of the glycosyl urea in sulphuric acid upon the addition of sodium nitrite within 4 h at 0 °C. The reaction could not be reproduced in our hands with

sulphuric acid but by using hydrochloric acid instead. The protection/deprotection methodology of the anomeric centre facilitates a selective oxidation of the primary hydroxyl group to form the precious and tedious to obtain glucuronic acid. Recently, the food industry showed increased interest in the efficient preparation of glucuronic acid which is usually obtained from cellulose in unsatisfactory yields.

First results for the condensation reaction were obtained for montmorillonite as catalyst in a D-glucose/urea/NH_4Cl melt (3:7:1, w/w/w). Montmorillonite, a phyllosilicate with Brønsted and Lewis acid character, was chosen as a catalyst because it is mild, non-toxic and could be recycled after the reaction since it is a heterogeneous catalyst. After 48 h reaction time at 80 °C, the reaction was analysed by ^{13}C-NMR showing high conversion and high selectivity. The resonance signal at the anomeric centre (92.3 ppm, d_6-DMSO) disappeared completely and the only carbonyl resonance signal detected at 158.0 ppm (d_6-DMSO) indicated the selective formation of only one isomer, presumably the β-anomer. The same sample was analysed by mass spectrometry to confirm that the urea was selectively mono glycosylated. A NOE-experiment additionally confirmed the β-configuration of the glycoside (Scheme 3.1).



Scheme 3.1 Acid catalysed formation of β-form condensation product in the melt.

After the initial experiment several other catalysts were tested. The product yield was determined by HPLC using isomalt as internal standard (Table 3.1).

catalyst	yield [%][a]
Amberlyst 15	78
$FeCl_3$	44
$ZnCl_2$	32
$CrCl_2$	21
$CrCl_3$	25
*p*TsOH	53
Montmorillonite	29

[a]Yields determined by HPLC

Table 3.1 Chemical yields for β-D-glycosyl urea preparation in carbohydrate melts.

After 48 h at 80 °C, the highest yield for the glycoside was 78% with Amberlyst 15 determined by HPLC. *p*TsOH and $FeCl_3$ yielded 53% and 44%, respectively. The finding of the ion exchanger giving the best results for condensation products here is interesting because in our earlier studies we found that heterogeneous catalysts showed a reduced performance compared to homogeneous ones. This finding was attributed to the increased viscosity in the melts compared to conventional solvents.[19f]

Formation of β-D-mannosyl urea in carbohydrate melts

After the successful conversion of D-glucose, the more stable epimer D-mannose was tried to show the general applicability of acid catalysed condensation with urea in high concentration carbohydrate melts for different sugars. Jones reported an inefficient procedure in water with sulphuric acid as catalyst and reaction times of up to 7 days. The yield of β-D-mannosyl urea after 7 days was 12% after recrystallization from MeOH.[15] β-Configuration at the anomeric centre was established by optical rotation of the derivatives after

periodate reaction which was compared to the value of derivatives of β-D-glycosyl urea.

In an initial study, a melt consisting of a D-mannose/urea/NH_4Cl melt (3:7:1, w/w/w) was stirred with Amberlyst 15 as catalyst and the purified product was analysed by NMR and mass spectrometry. ^{13}C-NMR and NOE experiments confirmed the expected β-anomer as the reaction product and the mass spectrometric analysis indicated that selective mono condensation took place. Again, the electronegativity of the nitrogen and the bulkiness of the urea moiety are supposed to be the reason for the observed stereochemistry.

Table 3.2 shows the HPLC results of the condensation reaction with diverse catalysts after 48 h reaction time at 80 °C.

catalyst	yield [%][a]
Amberlyst 15	58
$FeCl_3$	78
$ZnCl_2$	71
$CrCl_2$	61
$CrCl_3$	62
*p*TsOH	86
Montmorillonite	29

[a]Yields determined by HPLC

Table 3.2 Acidic β-D-mannosyl urea formation in carbohydrate urea melts.

Best yields of the condensation product were obtained with *p*TsOH (86%). Amberlyst 15, the best catalyst for glucose condensation, yielded only 58% in the case of mannose. Here, $ZnCl_2$ (78%) gave better results than Amberlyst 15, which is an interesting observation because in earlier studies we found that $ZnCl_2$ showed little to no activity for the acid catalysed dehydration of carbohydrates to form 5-hydroxymethylfurfural (HMF) in melt systems. [16]

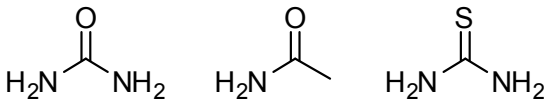
With 48 h for both β-D-mannosyl and β-D-glycosyl urea the reaction times could be significantly reduced compared to literature. A further reduction of the

reaction time (22 and 15 h) for mannose was investigated but ^{13}C-NMR spectroscopy indicated incomplete conversion. After 48 h, the missing resonance signal of the anomeric centre of β-D-mannose indicated complete consumption of the starting material. D-Mannose was chosen for the optimisation study, because it gave better yields compared to D-glucose.

A fructose/urea melt was reacted under acidic conditions (Amberlyst 15) at 80 °C for 24 h and formed a mixture of condensation products which could not be separated. We assume that the fructose/urea condensation products are present in the furanose and pyranose as well as in the α- and β-form.

After the successful condensation of D-glucose and D-mannose with urea, different nucleophiles with similar structures to urea were tested as melt components to form diverse glycosides. Mixtures of sugar and additive compound with the lowest melting point (eutectic point) were determined and in a subsequent experiment, the acid catalysed condensation was investigated in the melt.
Thiourea formed clear melts with both D-glucose (3:6:1 w/w/w, glucose:thiourea:NH_4Cl) and D-mannose (3:6:1 w/w/w, mannose:thiourea: NH_4Cl) at 80 °C, could however not be condensed to form glycosides after 24 h. Prolonged reaction times (72 h) lead to the decomposition of the carbohydrates.
Acetamide has a functional group similar to urea and was tested as melt component in binary mixtures with D-glucose (5:5 w/w) and D-mannose (4:6 w/w). Both catalysts montmorillonite and Amberlyst 15 could not catalyse the condensation after 24 h at 80 °C and the starting material was found unchanged.

A possible explanation why the three amides show different reactivity can be given on the basis of basicity/nucleophilicity trends for the three melt components. In Fig. 3.1, the pK_b values are given for urea, acetamide and thiourea.[17]



pK_b	13.8	14.5	15.0

Fig. 3.1 pK_b values for urea, acetamide and thiourea.

According to the reported pK_b values, urea is a stronger base in comparison to acetamide and thiourea. Although basicity and nucleophilicity do not necessarily have to match, correlations are often found: Malik *et al.* [18] reported the nucleophilic reactivity towards an imine for some nucleophiles following the order OH^- > urea > thiourea > acetate. In this case, the nucleophilicity and basicity differences of urea and thiourea are matching. The higher nucleophilicity of urea compared to acetamide and thiourea is a possible explanation for the reactivity in sugar melts.

N-Glycosides from pyrazole (5:5 w/w) or piperidine (suspension) could be formed from D-glucose with Amberlyst 15 at 80 °C (24 h). The reactions lead to many side products after 24 h reaction time. Aromatic products in the organic phase indicate Maillard reactions, which are likely to occur in the presence of amines.

Conclusion

Low melting carbohydrate mixtures represent a promising possibility to convert biomass into important platform chemicals like urea glycosides without the need of protecting groups. The melts are non-toxic, based on cheap bulk renewables, possess high sugar contents (up to 50%, facilitating a high space-time yield) and a negligible low vapour pressure.[19] Ternary sugar/urea/NH_4Cl melts were prepared and reacted for 2 d at 80 °C with different Brønsted and Lewis acids as catalysts. The configuration at the anomeric centre was determined by NOE experiments and the yields were obtained by HPLC analysis.

For β-D-glycosyl ureas highest yields were obtained with Amberlyst 15 (78%), an easy to recover heterogeneous catalyst. β-D-Mannosyl ureas were prepared

similarly giving even better results: Using *p*TsOH as catalyst, mannosyl urea was obtained in 86%.

Both reaction time and chemical yields could be significantly improved for β-D-glucosyl and β-D-mannosyl urea compared to procedures in literature so far. For mannosyl urea, the reaction time was reduced from 7 to 2 d while the yield was increased from 12 to 86%. High chemical yields, a high space-time yield and the use of heterogeneous catalysts facilitate larger scale syntheses using this methodology.

To synthesise different glycosides, related nucleophiles were investigated as melt components. Thiourea and acetamide could not be converted with D-glucose or D-mannose. Here, the different reactivities were attributed to the basicity differences of the amides. Pyrazole and piperidine lead to an unselective formation of aromatic products from glucose under acidic conditions.

The described methodology may allow for the efficient preparation of *N*-glycosyl-*N'*-substituted ureas which are of interest as N-linked-glycopeptide mimics,[20] polyvalent glycoconjugates[21] or ureido surfactants.[22] Investigations in this direction are in progress.

Further, protection of the anomeric centre by glycosyl urea formation in the melt and deprotection using hydrochloric acid and sodium nitrite may be developed into a convenient method for temporary protection of the anomeric center. This may be of interest for the selective oxidation of the primary hydroxyl group allowing a selective preparation of glucuronic acid.

Experimental Section

Typical procedure for the preparation of β-D-glycosyl urea:

D-Glucose (0.60 g, 3.30 mmol), urea (1.40 g, 26.7 mmol) and NH_4Cl (0.20 g, 3.74 mmol) were molten in a 50 mL reaction flask at 80 °C until a clear melt was formed. Amberlyst (0.20 g) was added and the reaction was stirred for 2 d at that temperature. After the reaction was finished, water was added to the still

warm melt and the catalyst was filtered off. After the removal of the water, the brownish solid was recrystallised from MeOH twice to give pure β-D-glycosyl urea as white crystals (0.47 g, 64%).

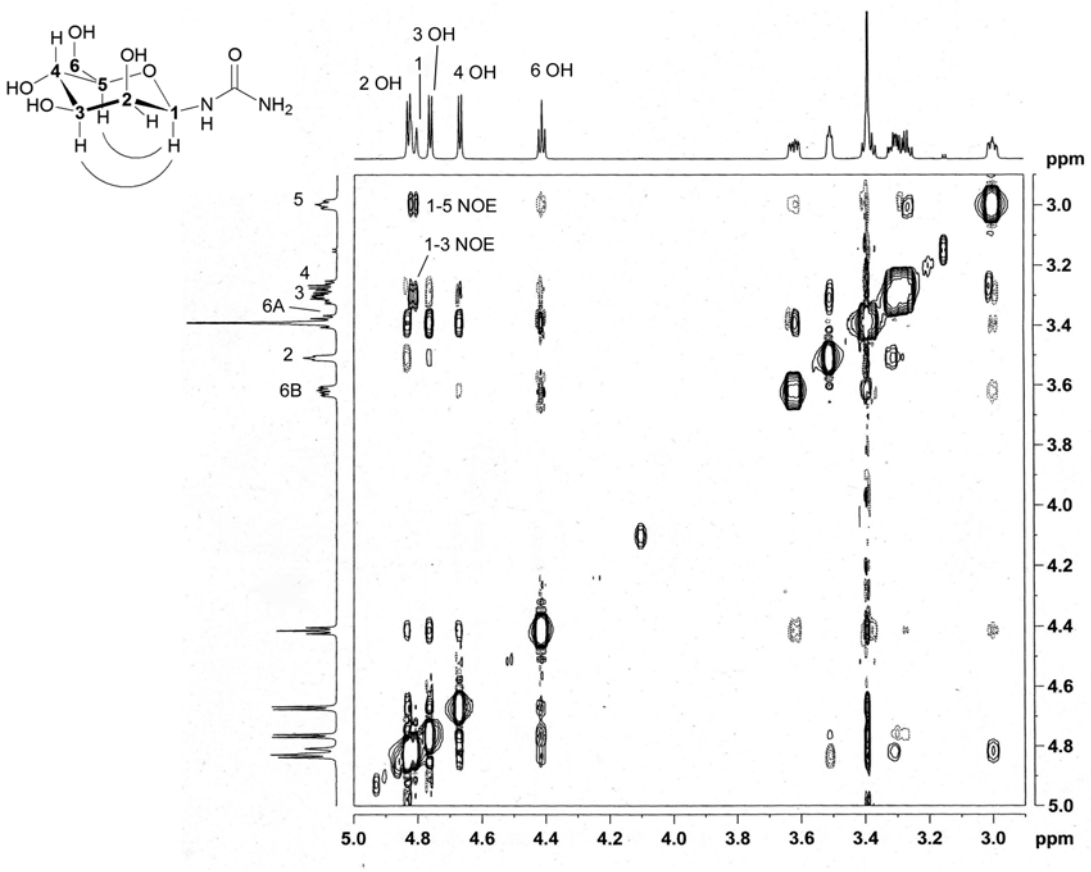
β-D-Mannosyl urea:

D-Mannose (0.60 g, 3.30 mmol), urea (1.40 g, 26.7 mmol) and NH_4Cl (0.2 g, 3.74 mmol) were molten in a 50 mL reaction flask at 80 °C until a clear melt was formed. *p*TsOH (57 mg) was added and the reaction was stirred for 2 d at that temperature. After the reaction was finished water was added to the still warm melt and the catalyst was filtered off. After the removal of the water, the brownish solid was twice recrystallized from EtOH to give pure β-D-mannosyl urea as a white powder (0.53 g, 72%).

^{1}H-NMR (600 MHz, DMSO-d6): δ [ppm] = 2.97-3.03 (m, 1 H), 3.24-3.34 (m, 2 H), 3.36-3.43 (m, 1 H), 3.50-3.52 (m, 1 H), 3.59-3.65 (m, 1 H), 4.41 (t, *J* = 6,0 Hz, 1 OH), 4.67 d (d, *J* = 5,0 Hz, 1 OH), 4.76 (d, *J* = 5,4 Hz, 1 OH), 4.80 (m, 1 H), 4.83 (d, *J* = 5,4 Hz, 1 OH), 5.84 (s, NH_2), 6.47 (s, NH); **^{13}C-NMR (150 MHz, DMSO-d6):** δ [ppm] = 61.41, 66.88, 71.22, 74.39, 78.30, 78.46, 157.53; **FT-IR (ATR):** *v* [cm^{-1}] = 3334, 3244, 2942, 2358, 1663, 1614, 1528, 1446, 1411, 1377, 1200, 1140, 1076, 1047, 1024, 958, 863, 801,614, 539: **MP:** 178 °C; **LSI-MS (glycerol):** m/z (%) = 223.1 (100) [MH^+], 315.3 (43) [MH^+ + glycerol]; **LSI-MS:** calcd.: 223.0930, found: 223.0933.

NOE spectrum for β-D-mannosyl urea:

The C-1/C-5 and C-1/C-3 NOE contacts in the β-conformation are clearly observed.



HPLC measurements:

The HPLC measurements were conducted with a LabID 86/Phenomenex Luna 3 NH_2 100 A, 150 x 2.00 mm column and run with ACN/H_2O/ 80:20 as eluent. The column temperature was 40 °C, the injection volume 0.2 µL, while a flow rate of 0.5 mL/min and isomaltose as internal standard was used. The system was run with ChemStation for LC 3D Systems Rev. B.03.02 as software.

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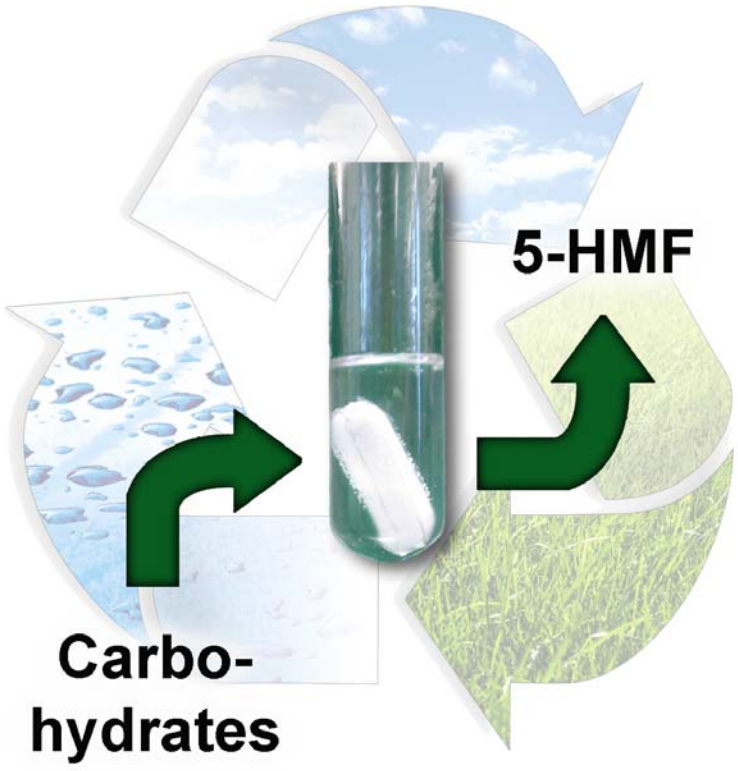
4. Conversion of carbohydrates into 5-hydroxymethylfurfural in highly concentrated low melting mixtures*

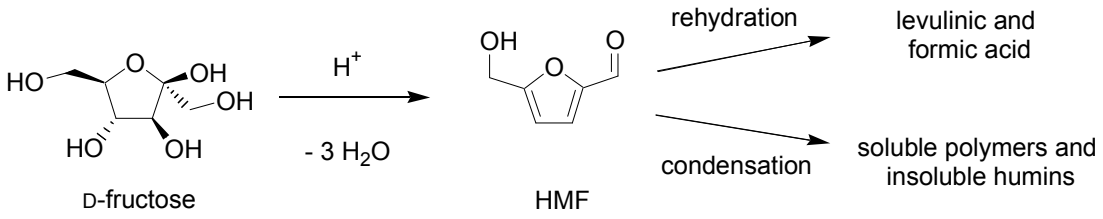


* F. Ilgen, D. Ott, D. Kralisch, C. Reil, A. Palmberger, B. König submitted for *Green Chem.*. Denise Ott evaluated the ecological performance of the carbohydrate melts. Florian Ilgen supervised and carried out the experiments together with Christian Reil and Agnes Palmberger within their final thesis for their studies as a teacher.

Introduction

Declining fossil fuel reserves steadily increase the need to develop sustainable sources for chemical production in the near future.[1] Hence, the utilisation of biomass for the industrial production of chemicals is required to address the need for commodities.[2] Renewable and vastly abundant biomass is a promising alternative for the sustainable supply of precious intermediates and platform chemicals to the chemical industry.[3]

With more than 75%, carbohydrates are the largest part of all biomass[4] and therefore of particular interest for conversion into fine chemicals. Amongst many possible biomass-derived chemicals, 5-hydroxylmethylfurfural (HMF) is considered to have the potential to be a sustainable substitute for petroleum-based building blocks.[5] Intermediates like 2,5-furandicarboxylic acid, 2,5-dihydroxymethylfuran, 2,5-bis(hydroxymethyl)tetrahydrofuran and dimethyl-furan are derived from HMF by oxidation, hydrogenation, hydrogenolysis or aldol condensation.[6] The most convenient and efficient method in terms of chemical yield for the preparation of HMF is the acid catalysed dehydration of D-fructose. For fructose conversion traditionally highly polar organic solvents, namely DMSO,[7] DMF[8] and sub-critical or high-temperature water[9] are used. High boiling solvents, however, require significant energy input during the separation process of HMF from the solvent. Further, HMF molecules, generated under aqueous acidic conditions partially rehydrate to the undesired side products levulinic and formic acid, which is a major challenge in the synthesis of HMF (Scheme 4.1). Another significant side reaction is the self-condensation of the reactive HMF to form both soluble polymers and insoluble humins.



Scheme 4.1 Acid catalysed dehydration of D-fructose to HMF and possible subsequent side reaction by rehydration to levulinic and formic acid and the self-condensation to soluble polymers and humins.

Due to the increased interest and demand for industrial application more efficient catalytic systems were recently developed. Biphasic systems are used to continuously or intermittently remove the produced HMF from the reactive phase and thus reduce the side reactions.[10] Róman-Leshkov *et al*. developed a system where DMSO and PVP (poly(1-vinyl-2-pyrrolidinone) were added to the aqueous phase in order to enhance the dehydration, while the extraction phase (methyl isobutyl ketone, MIBK) was modified with 2-butanol for better separation from the aqueous phase. At 89% fructose conversion, a maximum selectivity of 85% was achieved.[11] Excellent yields (92%) from D-fructose were obtained by Stark *et al*. with a biphasic reactor based on 1-butyl-3-methylimidazolium methylsulfonate and MTBE (methyl tert-butyl ether) as extracting reagent.[11] Comparable yields (90%) were obtained by Smith *et al*. using microwave heating of D-fructose in a 70:30 (w/w) acetone/DMSO mixture.[12] Xie *et al*. could show that a biphasic system consisting of EtOAc and choline chloride/citric acid/D-fructose melt can be used for the preparation of HMF at 80 °C in yields as high as 90%.[13] Recent reports focus on the formation of HMF from glucose rather than from fructose, since the former one is cheaper in production as it is obtained from the hydrolysis of cellulose. Zhao *et al.* demonstrated the use of metal chlorides reporting best results for $CrCl_2$ and $CrCl_3$ with $[C_2mim]Cl$ as solvent. HMF yields as high as 68% were obtained from glucose. The initial loading of glucose was 10 % by weight.[14] Recently, a new concept using N-heterocyclic carbene-metal (NHC/M) complexes in ionic liquids (ILs) was

introduced by Ying and co-workers. This new methodology enabled the group to obtain HMF in yields of 96% and 81% for fructose and glucose, respectively. The NHC/M/IL system is reported to be tolerant towards carbohydrate concentrations as high as 20 % by weight.[15]

The use of diluted solutions for the conversion of carbohydrates into HMF, however, limits the efficacy of the process.[16] A more desired approach would allow the conversion of highly concentrated liquids or neat substances to gain larger product amounts in a minimal volume and to avoid solvents and concentration steps. Such a solvent system tolerating diverse carbohydrates would make the HMF preparation more efficient and thus be a premise to meet the increasing demand for HMF and its derivatives.

Here, we report the use of highly concentrated carbohydrate melts (up to 50 % by weight) for the selective conversion of D-fructose, D-glucose and other di- and oligosaccharides into HMF. Different reaction conditions as well as homogeneous and heterogeneous catalysts were investigated.

In addition a preliminary ecological evaluation was performed for the preparation of HMF in a ChCl/D-fructose and compared to other representative solvents.

Results and discussion

The low melting carbohydrate/urea mixtures recently developed in our group[17] allows converting biomass derived renewables at high concentration into valuable intermediates. To obtain HMF, a D-fructose/*N,N`*-dimethyl urea (DMU) melt was tested for acid catalysed dehydration. In preliminary experiments $CrCl_2$ and $CrCl_3$ (10 mol% each) were used as catalysts, because they were reported to have very high activites in dehydration reactions. The reactions were conducted with 40 % by weight fructose over 2 h at 110 °C. Extraction of the still liquid melt with EtOAc gave HMF in only low yields of 6% and 2%, respectively. Catalysts like $FeCl_3$ and $AlCl_3$ gave similar results. The only catalyst which gave HMF in acceptable yield was Amberlyst 15, an ion-exchange resin (27%). Upon extraction, the organic phase was evaporated, weighted and analysed by NMR to find no side products beside HMF. In a further experiment, the usability of

urea derivatives as melt components was tested systematically. Urea, DMU and TMU (*N,N,N',N'*-tetramethyl urea) were used as components, reducing the inherent condensation ability by the introduction of methyl groups (Table 4.1). Both, urea and DMU showed the formation of difficult to interpret side products, probably due to urea-fructose condensation products. This is reflected in the low HMF yields.

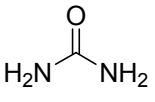
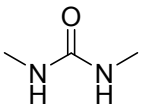
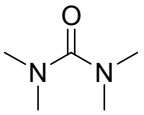
$FeCl_3$			
HMF	no prod.	8%	89%

Table 4.1 Acid catalysed dehydration of D-fructose to HMF using $FeCl_3$ (10 mol%) as catalyst and different melt components.

TMU based solution, in which a condensation of fructose and urea is not possible, gave HMF in 89% yield. However, TMU can not be considered as a suitable additive as its separation is energy intensive similar to the use of DMSO and its inherent toxicity.

Therefore, new melts had to be found meeting the requirements of having a high sugar content, low melting point, low viscosity, and low toxicity. Table 4.2 shows the results for mixtures of carbohydrates and sugar alcohols with melt additives expected to have melting point depressing properties. Glucosamine was tested, too, because it can be obtained from the second most abundant biopolymer chitin.

	urea	DMU	imidazole	4Me-imidazole	pyrazole	ChCl	guanidinium HCl	malonic acid
D-glucose	[b]	80 °C (3:7)	60 °C (4:6)	50 °C (2:8)	80 °C (5:5)	80 °C (4:6)	70 °C (4:6)	[b]
D-mannose	[b]	80 °C (4:6)	80 °C (4:6)	50 °C (2:8)	50 °C (4:6)	50 °C (4:6)	80 °C (4:6)	90 °C (5:5)
D-fructose	70 °C (6:4)	70 °C (4:6)	70 °C (5:5)	50 °C (2:8)	70 °C (5:5)	70 °C (4:6)	70 °C (4:6)	100 °C (7:3)
D-sorbitol	70 °C (5:5)	80 °C (4:6)	80 °C (3:7)	50 °C (2:8)	60 °C (3:7)	70 °C (4:6)	[a]	[c] 70 °C
sucrose	[a]	[b]	80 °C (7:3)	70 °C (4:6)	60 °C (4:6)	80 °C (5:5)	[b]	80 °C (6:4)
isomaltose	[b]	90 °C (4:6)	80 °C (4:6)	70 °C (3:7)	70 °C (5:5)	90 °C (4:6)	60 °C (4:6)	[a]
glucosamine	[b]	[b]	[a]	50 °C (3:7)	90 °C (1:9)	100 °C (1:9)	[b]	[b]

melting point of mixtures followed by weight fraction in parenthesis, [a] = not determined, [b] = no melt at 100 °C, [c] = decomposition

Table 4.2 Eutectic mixtures of carbohydrates and sugar alcohols with several H-bond donor and acceptor additives.

To obtain a mixture close to the eutectic point, the components were blended using compositions of 1:9, 2:8 etc. up to 9:1 (w/w) and the melting point was determined. The pH values of the eutectic mixtures were measured and the results are summarised in Fig. 4.2.

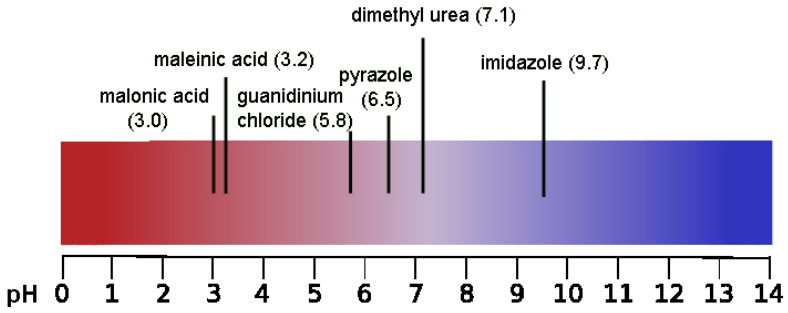


Fig. 4.2 pH values of different melt systems with fructose as carbohydrate component.

The low melting mixtures show different pH values, from acidic to basic, which can be used to establish the desired reaction conditions. In addition, the melts were tested for dehydration of fructose by Amberlyst 15 and $FeCl_3$ as catalysts. Neither imidazole- nor pyrazole-based melts gave conversion to HMF. In the case of malonic and maleinic acid only levulinic acid was found in the organic phase (23% and 26%) indicating conditions prone for rehydration of HMF due to the low pH value. Guanidinium chloride leads to a product mixture which was

difficult to analyse. Choline chloride is the only melt component which gave HMF in 25% and 40% for Amberlyst 15 and $FeCl_3$ as catalysts under the described conditions. For comparison a melt consisting of only fructose was investigated resulting in the exclusive formation of levulinic acid (20%). This shows the beneficial effect of the melt additives for the synthesis of HMF.

As choline chloride was found to be a suitable additive for melts with very high carbohydrate content, the melting point of mixtures was investigated more detailed with differential scanning calorimetry (DSC). The lowest melting point was found for the ratio 2:3 of fructose : choline chloride with a melting range of 79-82 °C (Fig. 4.3). The choline chloride melt component is water soluble and not extractable by organic solvents like EtOAc. Choline chloride is less expensive as most ionic liquids,[18] has a very low toxicity to humans[19] and the environment,[20] is non-flammable,[20] and can be considered as thermally stable.[21] Hence, these properties can make choline chloride a suitable media for this specific task.[22]

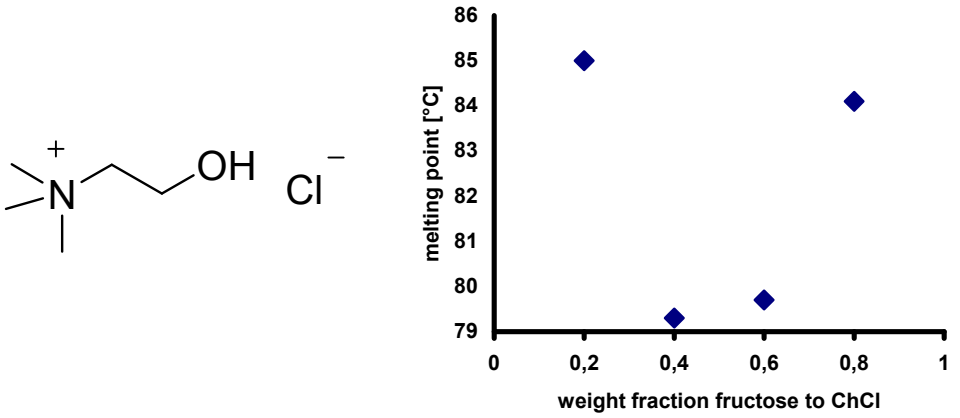


Fig. 4.3 Chemical structure of choline chloride and melting points determined by DSC of different fructose-ChCl-mixtures.

Heterogeneous catalysts can be easily recycled by filtration or centrifugation. Therefore the heterogeneous catalysts Amberlyst 15 and montmorillonite, a weakly acidic phyllosilicate, were selected for dehydration reactions of diverse carbohydrates in ChCl melts. An optimal catalyst loading of 50 mg per 1 g of melt was found and used for all carbohydrate conversions discussed in the following. For homogeneous catalysts 10 mol% were used.[9,23]

The reaction conditions for D-fructose conversion in ChCl using $FeCl_3$ (10 mol% based on sugar) as catalyst were optimised and found to be best for a short reaction time of 0.5 h at a reaction temperature of 100 °C. Longer reaction times or temperatures above 100 °C lead to the formation of significant amounts of humins as black insoluble solids. The high sugar concentration may lead to a high local HMF concentration which favours subsequent condensation reactions.

D-Glucose is of relevance for the preparation of 5-hydroxymethylfurfural, due to its higher abundance and lower price. For glucose conversion the same ratio of sugar to ChCl (4:6) was used and the reaction conditions were tested and found to give the highest HMF yields after 0.5 h at 110 °C.

To further expand the scope of monosaccharide starting materials, an eutectic mixture of D-glucosamine hydrochloride and ChCl (1:9 w/w) was developed with a melting point of 100 °C.[24] The dehydration of D-glucosamine to HMF in this mixture using Amberlyst 15 and $FeCl_3$ as catalysts was tested. However, even prolonged reaction times at 120 °C did not result in the formation of the desired product. The dehydration reaction of D-glucosamine to HMF was reported in pure AcOH by Zivanovic *et al*.[25]

Next, the more complex carbohydrates sucrose and inulin were used as starting materials for HMF synthesis in the melt. Sucrose is supposed to react around 18 times faster than glucose.[26] Inulin is an abundant polyfructan with an average of 100 fructose units per molecule. The direct conversion of both sucrose and inulin into HMF combines the hydrolysis step to monosaccharides and the elimination of water in one process, thus saving one reaction step in the synthesis.[27]

The formation of HMF, levulinic acid and humins was monitored for different reaction times (0.5 to 2 h) and temperatures (80 to 100 °C): The best HMF yields were found for sucrose at 100 °C and 1 h reaction time. Longer reaction times at this temperature led to the formation of insoluble humins (Fig. 4.4). Reactions at 110 °C gave in less than 0.5 h high amounts of humins. For inulin

the identical reaction conditions were used, but the use of *p*TsOH as catalyst gave the highest HMF yields (57%) from inulin (Table 4.3).

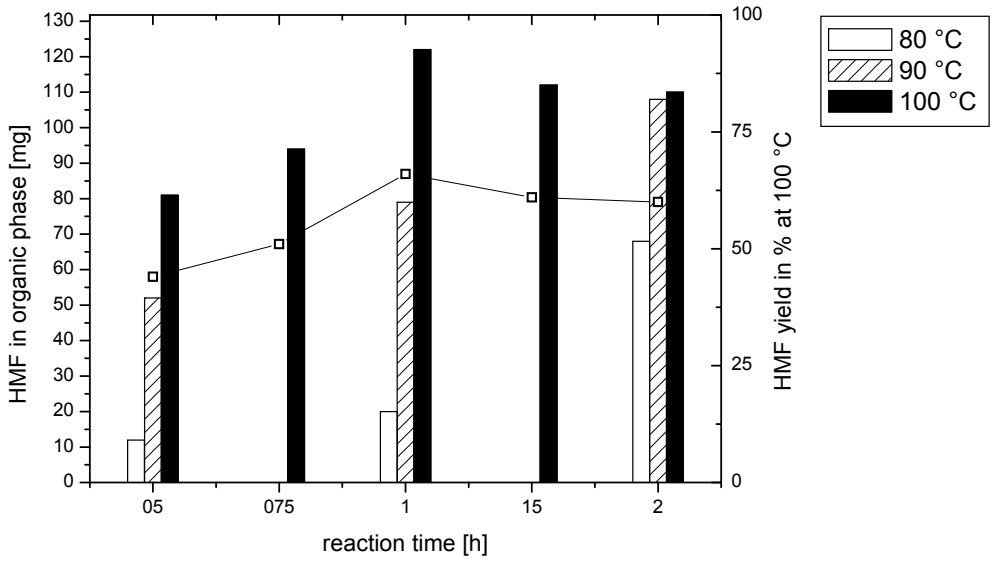


Fig. 4.4 HMF formation at 80, 90 and 100 °C from sucrose at different reaction times with $CrCl_2$ as catalyst (10 mol%). At 100 °C the HMF formation reached its maximum after 1 h, longer reaction times decreased the HMF content due to the preferential condensation of HMF and subsequent humin formation (black graph shows chemical yields of HMF at 100 °C).

Catalyst	Yield of HMF [%] from			
	D-fructose/ChCl (4:6)[a]	D-glucose/ChCl (4:6)[b]	sucrose/ChCl (5:5)[c]	inulin/ChCl (5:5)[d]
Amberlyst 15	40	9	27	54
$FeCl_3$	59	15	27	55
$ZnCl_2$	8	6	6	3
$CrCl_2$	40	45	42	36
$CrCl_3$	60	31	43	46
*p*TsOH	67	15	25	57
$Sc(OTf)_3$	55	9	28	44
montmorillonite	49	7	35	7

Reaction conditions: 10 mol% catalyst (montmorillonite: 50 mg, Amberlyst 15: 50 mg) [a] 400 mg fructose, 600 mg ChCl, 100 °C, 0.5 h, [b] 400 mg glucose 600 mg ChCl, 110 °C, 0.5 h, [c] 500 mg sucrose, 500 mg ChCl, 100 °C, 1h, [d] 500 mg inulin 500 mg ChCl, 90 °C, 1 h.

Table 4.3 Conversion of different carbohydrates into HMF using different reaction conditions and catalysts. Yields were determined by HPLC analysis.

Preliminary ecological evaluation of carbohydrate – ChCl melts for carbohydrate conversion

In a first ecological screening, we compared the environmental effects of selected solvent mixtures used for the conversion of carbohydrates to 5-hydroxymethylfurfural, as discussed in the introduction (water, DMF, DMSO, acetone/DMSO, EtOAc/ChCl/citric acid, $[C_2mim]Cl$, $[C_4mim]Cl$[28]), see Fig. 4.5. The assessment is mainly based on safety data sheets.[29] Concerning mobility, solvents with lower boiling points might enter the environment more likely, especially by working under higher reaction temperatures as in the case of the HMF formation. Therefore, especially the ionic liquids $[C_2mim]Cl$ and $[C_4mim]Cl$ as well as choline chloride and choline chloride/citric acid and water might be suitable media reducing the environmental impact into air due to their negligible low vapour pressure as well as the inherent low toxicological impact in the case of water, citric acid and choline chloride. Accordingly, the potential impact on

human health can be reduced. However, especially in the case of ionic liquids often not enough data for the assessment of the toxicological risks for human and ecosystems are currently available.

Taking into consideration the bioaccumulation potential, the selected solvents feature log K_{OW} values < 1, indicating that no bioaccumulation can be expected and the bioaccumulation potential can be stated as low, respectively. However, the persistence also influences the environmental fate and toxicity potential of the solvents. For determining the biodegradation properties, safety data sheets as well as the software BioWIN[30] was consulted. DMSO is not readily biodegradable, while for the studied ionic liquids only limited information is available, indicating that they are not readily biodegradable. Recently reported results indicate, that for imidazolium based ionic liquids with short alkyl (≤ 6) and short functionalised side chains no biological degradation can be expected, while ionic liquids consisting of imidazolium and pyridinium cations with octyl chains are biodegradable.[31,32] Therefore, the persistence of the ionic liquids in the environment was classified as “medium to high”. The factors of bioaccumulation and persistence influence the ecological effects and toxicity on aquatic organisms. Hence, the entry into the water pathway should be avoided, especially in the case of the ionic liquids where disposal strategies are still rare.[31,33]

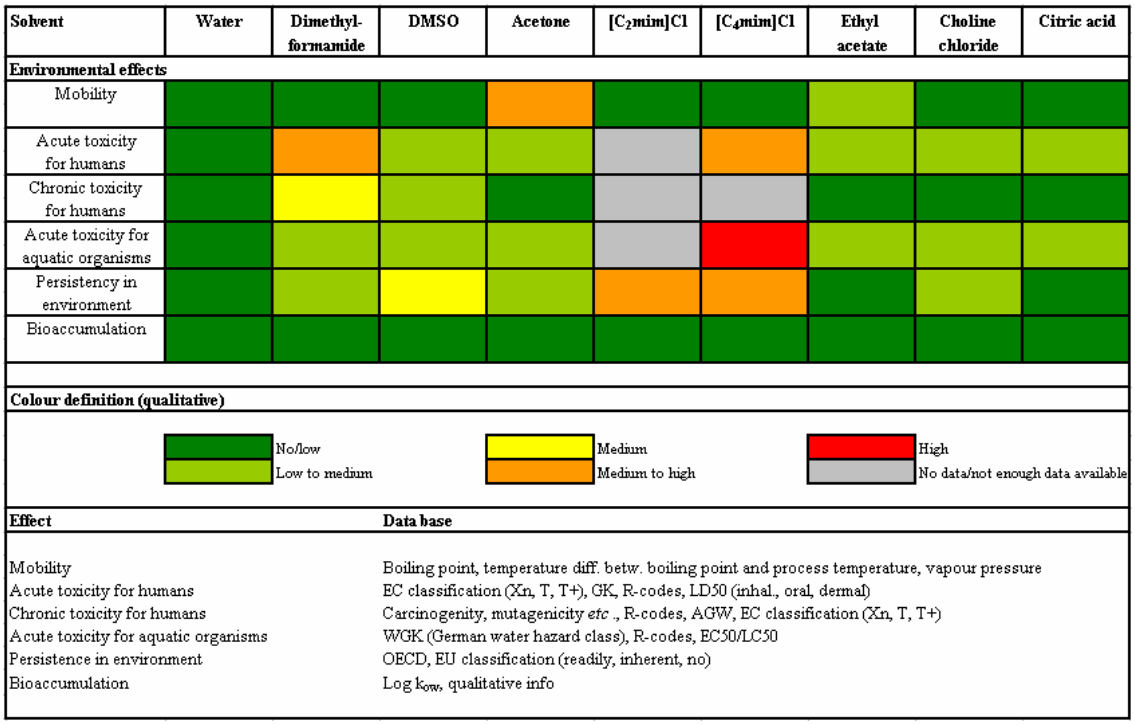


Fig. 4.5 Qualitative assessment of the environmental effects of selected solvent systems used in the conversion of carbohydrates to 5-hydroxymethylfurfural: water, DMF, acetone/DMSO, [C_2mim]Cl, [C_4mim]Cl, ethyl acetate/choline chloride/citric acid and choline chloride, respectively.

Concerning EHS issues of the solvents considered for the ecological evaluation, the solvent systems choline chloride/citric acid and water as well as the herein investigated low melting mixture choline chloride/fructose feature preferable properties making them more suitable media for a “greener” reaction process. However, a conclusive statement requires a more holistic examination, including e.g. the performance, energy requirements, auxiliary materials, catalysts as well as costs under consideration of upstream and downstream chains. For instance, the work up of the conversions we report here uses, similar to the procedure by Hu *et al.*,[10] ethyl acetate to extract the product phase from choline chloride, resulting in an additional solvent demand and exposure risks as well as time and energy consuming distillation steps. In contrast, the use of high boiling solvents like DMSO, water and DMF might also have the drawback of high energy consumption or the use of additional solvents during the separation process. We previously discussed the ecological performance of

[C_6mim][BF_4] and citric acid/DMU (40/60 w/w) in the Diels-Alder reaction of cyclopentadiene with methyl acrylate in comparison to molecular solvents. At this we could show, that the development of efficient recycling strategies should be addressed for further work, and the use of multiphase reaction systems might be beneficial concerning ecological as well as economic issues.[17]

Conclusion

Low melting carbohydrate mixtures are suitable to convert carbohydrates into 5-hydroxymethylfurfural. The melts are non-toxic, based on bulk renewables, have high sugar contents (up to 50 % by weight) and a negligible low vapour pressure. In an optimisation study choline chloride was found to be the most suitable melt additive since it is chemically inert under the reaction conditions used. For fructose an eutectic point at 4:6 (fructose:ChCl, w/w) with a melting region of 79-82 °C (DSC) was determined. This melt has a pH-value of 5.9. A reaction time of 1 h at 100 °C gave best results for HMF using $CrCl_2$ (10 mol% based on sugar). Apart from D-fructose, D-glucose, sucrose and inulin were tested with different catalysts at individually optimised conditions. The best HMF yields from the carbohydrate-ChCl systems were 67% for D-fructose (*p*TsOH, 100 °C, 0.5 h), 45% for D-glucose ($CrCl_2$, 110 °C, 1 h), 43% for sucrose ($CrCl_3$, 100 °C, 1 h) and 57% for inulin (*p*TsOH, 90 °C, 1 h), respectively.

In a screening study, a comparison of the environmental impact of different conventional and alternative solvents for the conversion of carbohydrates into HMF indicates advantages of the melt systems in terms of low toxicity and reduced mobility. However, these investigations have to be extended by a more holistic ecological as well as economic evaluation under consideration of upstream and downstream chains to provide a final comparison. At the moment, investigations are extended to optimise the reaction performance, to study the possibility of recycling the reaction medium and to facilitate the product separation. Then, a more accurate statement especially concerning ecological improvements will be possible. In addition, the use of heterogeneous catalysts, like Amberlyst 15 and montmorillonite for the conversion of biomass, or the

possibility of biphasic reaction systems while the catalyst remains in the solvent phase, should be addressed in further research.
Summarising the results, we have used highly concentrated melt systems consisting of up to 50 % by weight of carbohydrates, corresponding to carbohydrate concentrations of 2.9 to 3.1 mol/L, for the conversion of the carbohydrate content into HMF in the presence of catalysts. The reported conditions with short reaction times at high concentrations allow for high space-time yields, which may be of interest for the development of efficient continuous processes for carbohydrate conversion to HMF.

Experimental Section

General:

All chemicals for synthesis were used as received without further purification. For DSC measurements the compounds were dried under vacuum at 90 °C for 5 h. The dried compounds were kept under nitrogen and transferred to a glove box. HMF was purchased from Sigma Aldrich and stored under nitrogen at 4 °C.

Preparation of the melts:

Unless otherwise stated, the constituents of the melts were ground with a mortar and pestle, filled into a resealable vial equipped with a stirring bar and placed into an oil bath. Upon formation of the melt, the catalysts were loaded under nitrogen (unless otherwise stated) before the vial was sealed.

NMR spectroscopy:

NMR spectra were recorded on a Bruker Avance 300 (^{1}H: 300.1 MHz, ^{13}C: 75.7 MHz, T = 300 K). The spectra are referenced against the internal NMR-solvent standard and chemical shifts are reported in ppm.

Determination of the pH value:

For the measurements a 691 pH-meter from Metrohm was used which was calibrated with pH 4.0 and 7.0 buffer solutions prior to use. Determination of the pH value is conducted by measuring a solution of 100 mg melt in distilled water (0.9 mL). The pH value reported represents the average of three independent measurements.

Melting point and DSC measurements:

The melting points were determined in a first approximation with a Büchi SMP 20. More exact measurements were conducted by differential scanning calorimetry. The pre-dried samples were blended, transferred to aluminium pots and sealed in a glove box. Two heating cycles were recorded with a temperature range of -15 to 100 °C within 5 minutes time.

Synthesis of 5-hydroxymethylfurfural (HMF):

D-Fructose (0.40 g, 2.20 mmol) and choline chloride (0.60 g, 4.30 mmol) were molten in a 50 mL reaction flask at 100 °C until a clear melt was formed. Amberlyst 15 (50 mg) was added and the reaction was stirred for 0.5 h. Afterwards water (20 mL) was added and the mixture was extracted with ethyl acetate (3x50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to give HMF (166 mg, 40%). The ^{1}H and ^{13}C NMR-spectroscopic data complied with the literature.[34]

HPLC measurements:

The HPLC measurements were conducted with a LabID 86/Phenomenex Luna 3u HILIC 200 A, 150x2.00 mm column and run with ACN/H_2O/100 mM NH_4OAc: 90:5:5 as eluent. The column temperature was 40 °C, the injection volume 0.1 µL, while a flow rate of 0.3 mL/min and both sucrose (for glucose and fructose) and acetanilide (for sucrose and inulin) as internal standard were used. For monitoring and evaluation of the chromatographic results the program ChemStation for LC 3D Systems Rev. B.03.02 was used.

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For the bioaccumulation a bioconcentration factor (BCF) of 0.59 was found indicating that no bioaccumulation is to be expected. OECD SIDS Initial Assessment Report for SIAM 19, 2004.

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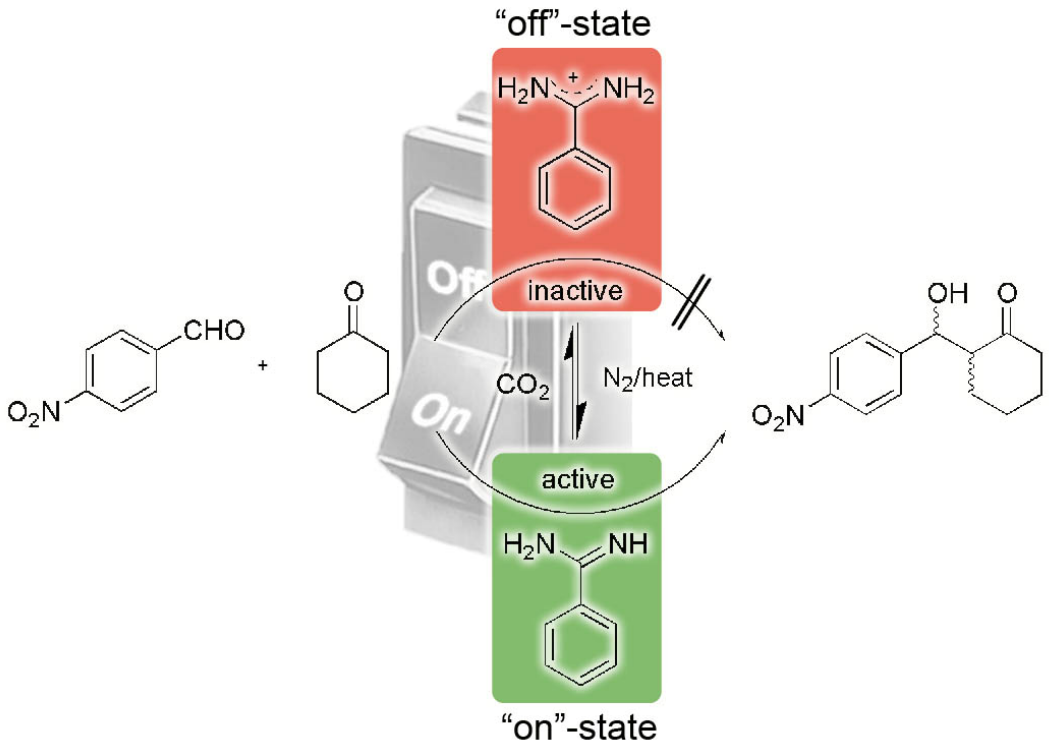
5. Reversible regulation of a benzamidine catalysed aldol Reaction by CO_2*



Preface

In nature complex transformations to process chemical information have to be regulated to guarantee a reliable functionality and to avoid malfunctions. The modulation of catalytic activity is fundamental for cellular function and a common feature of biological receptors and enzymes. Especially for those involved in metabolic pathways.[5b] In organic chemistry, however, catalytic activity is rarely regulated, although the ability to understand and regulate functions at a molecular level is a key requirement for the development of "smart" devices and materials.[1] Here, we present a system using CO_2 as orthogonal switching signal to reversibly regulate the activity of benzamidine. For the first time CO_2 is used to directly control the catalytic properties of an

* F. Ilgen, B. König submitted for *Chem. Commun.*

amidine base during a classical chemical transformation, the aldol reaction. With this work the reversibility of modulation and orthogonality of the external stimuli CO_2 and N_2 to regulate catalytic transformations should be demonstrated. The proposed system is thus envisioned to be an example for a chemical transistor or a system which can be used for signal amplification.

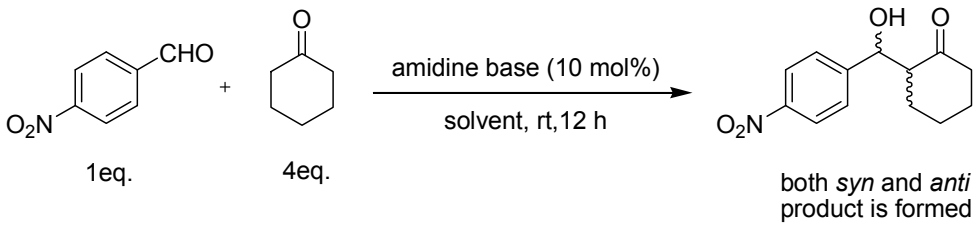
Introduction

Regulation of function on the molecular level by external signals is essential for the design of smart devices and materials.[1] The modulation of reactivity is also a common feature of biological receptors and enzymes and natural models inspired chemists to develop chemical analogous of reduced complexity.[2] Apart from physical stimuli like light, magnetic and electric signals, chemical triggers namely pH value, radicals, ions, or gases have been applied for the regulation of chemical functions,[3] reactivity[4] or catalytic activity.[5] Gases are particularly advantageous because of their quick diffusion. During the past decade especially CO_2 attracted interest as signal since it can bind reversibly to amines and amidines to form carbamates. These carbamates can easily be removed by bubbling N_2 or Ar through the solution and/or apply heat. CO_2-controlled molecular switches were used in applications like switchable surfactants,[6] sequestering and consecutive separation,[7] recovery of a homogeneous catalyst,[8] and reversible fixation and release systems for temporary storage.[9]
Aldol reactions typically require catalysis and amidines, such are DBU (diazabicyclo[5.4.0]undecene) and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) are widely used as basic catalysts.[10] The related benzamidine has been described as catalyst for different reactions, but to the best of our knowledge has never been used as aldol catalyst.[11] However, benzamidine is particular suitable to reversibly interact with CO_2.
We describe here the reversible inactivation of a benzamidine catalyst during an aldol reaction using CO_2/N_2 cycles and report optimised reaction conditions to quantitatively control the reaction progress at atmospheric pressure.

Results and discussion

The aldol reaction is a well studied C-C bond-forming reaction with miscellaneous applications.[12] The reaction is catalysed by bases[13] or acids,[14] metal-[15] or organocatalysts.[16] Amines and amidines are widely used as basic catalysts and they are known to react with CO_2 to be either protonated by H_2CO_3 or carbamoylated depending on the basicity, steric hindrance,

conjugation and induction effects, and the solvent. This step can be inverted upon brief bubbling of N_2, Ar or simple air through the solution. Increasing the temperature (40-60 °C) typically accelerates the release of CO_2.
We investigated the effect of CO_2 on the reaction progress of the aldol addition of 4-nitrobenzaldehyde and cyclohexanone in different solvents using several amidine bases (Scheme 5.1).



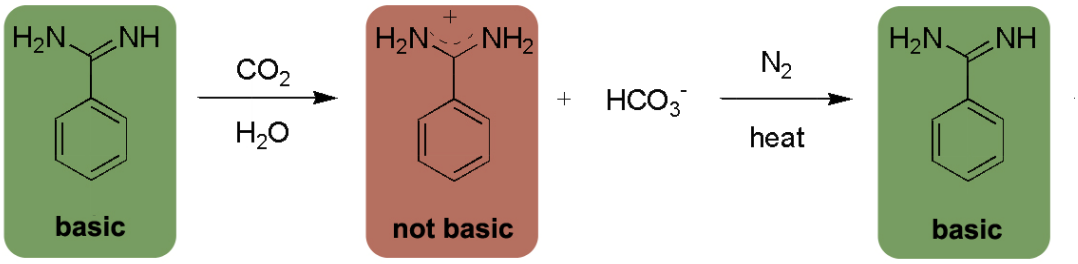
Scheme 5.1 Amidine catalysed aldol addition of 4-nitrobenzaldehyde and cyclohexanone.

DBU is reversibly protonated upon CO_2 saturation[6,8] and 10 mol% of the base were used to catalyse the above aldol reaction in different solvent systems. For the formation of a protonated base, the presence of water, an alcohol or an amine is required. “Wet” DMSO (>700 ppm water), water, ACN, methanol, and ethanol were tested as solvents for the aldol reaction and the reversible protection of the amidine base. The aldol reaction proceeded cleanly in wet DMSO and stops after CO_2 saturation of the solution. However, removal of the CO_2 amidine inactivation by nitrogen to reawaken the conversion of the aldol addition was not possible. Alcohols (MeOH, EtOH) as solvent showed very good reversibility of the base inactivation, but led to the formation of hemiacetals which hamper kinetic monitoring of the reaction. In water and ACN the reaction did either not proceed or the reversibility of the base inactivation by CO_2 was limited. A solvent mixture of ACN : H_2O, 1:1 (v/v) gave a clean conversion of the aldol reaction and allowed reversible inactivation of the amidine base by CO_2. Unfortunately, phase separation occurred during the course of reaction, causing problems studying the spectroscopic monitoring of the conversion. A stable homogeneous solvent system was obtained after reducing the water content to ACN : H_2O 9:1 (v/v).

Next, different bases were tested since DBU catalysed reactions lead to undesired side products, such as aldol condensation and twofold addition to the cyclohexanone. Piperidine and the amidine bases mono-, di-, and triboc guanidine, as well as benzamidine were used. Piperidine and benzamidine catalysed the reaction at a convenient rate and could be reversibly inactivated by CO_2. Benzamidine was chosen for a kinetic study due to the faster completion of the aldol addition.

Benzamidine is reversibly protonated, and not carbamoylated, if CO_2 is bubbled into the solution as confirmed by ^{13}C-NMR measurements. The amidine carbon of the free base form shows a resonance signal at 166.8 ppm in ACN : H_2O, 9:1 (v/v) which is shifted to 167.7 ppm upon introduction of CO_2. In addition, a new resonance signal at 161.5 ppm is detected which was assigned to bicarbonate and does not match a carbamate resonance. In the same solvent mixture benzamidine hydrochloride showed a signal at 167.7 ppm for the amidine carbon, reinforcing the statement. Pure $NaHCO_3$ in D_2O gives a resonance at 160.5 ppm. [17] When $NaHCO_3$ was added to the protonated/carbamoylated species in question in D_2O no further signal but an increase of intensity for the signal at 160.4 ppm was detected, supporting the protonated species.

Benzamidine as a base is reversibly inactivated by bubbling CO_2 through the solution, while the introduction of N_2 restores its basic character (Scheme 5.2).



Scheme 5.2 Reversible inactivation of a benzamidine base using CO_2 and N_2.

The reaction was monitored by ^{1}H-NMR, following the resonance signals of the benzylic protons of the addition product as probes. The conversion of the

reaction is described by the ratio of the product integrals in relation to the starting material.

All components except the cyclohexanone were dissolved in the ACN : H_2O (9:1, v/v) solvent mixture and placed in the NMR tube. This solution was saturated by CO_2 gas introduced by a long cannula into the solution at room temperature for 5 minutes. Cyclohexanone was added and CO_2 introduction continued for another 5 minutes. A ^{1}H-NMR spectrum was recorded to analyse the composition of the reaction mixture before conversion. The reaction was then started by initial heating to 60 °C for 20 s and then bubbling N_2 through the NMR tube for 10 min. After 10 min in the “base-on”-state, a ^{1}H-NMR spectrum was recorded to monitor the progress of the reaction by integrating the benzylic proton resonance signals as the sum of the *syn* and the *anti* isomer and the aldehyde proton. Since no side product formation was observed, the ratio of benzylic to aldehyde proton resonance signals was used to monitor the course of the aldol addition. The reaction progress was determined five times every 10 min. Then the reaction was stopped by introducing CO_2 gas and after another 10 min in the “base-off”-state a proton NMR spectrum was recorded showing that no further conversion occured. The sample was stored for 150 min without additional product formation. Another “base-on”-state proved that a reversible and repeated switching of the reaction progress by CO_2/N_2 is possible. A very long “base-off”-period of 18 h demonstrates the effective silencing of the benzamidine base with little background reaction: An increase of the product/starting material ratio of only 11%, which corresponds to 0.6% per h, is observed. Fig. 5.1 illustrates the developing ratios of product and starting material during indicated “base-on”- and “base-off”-states.

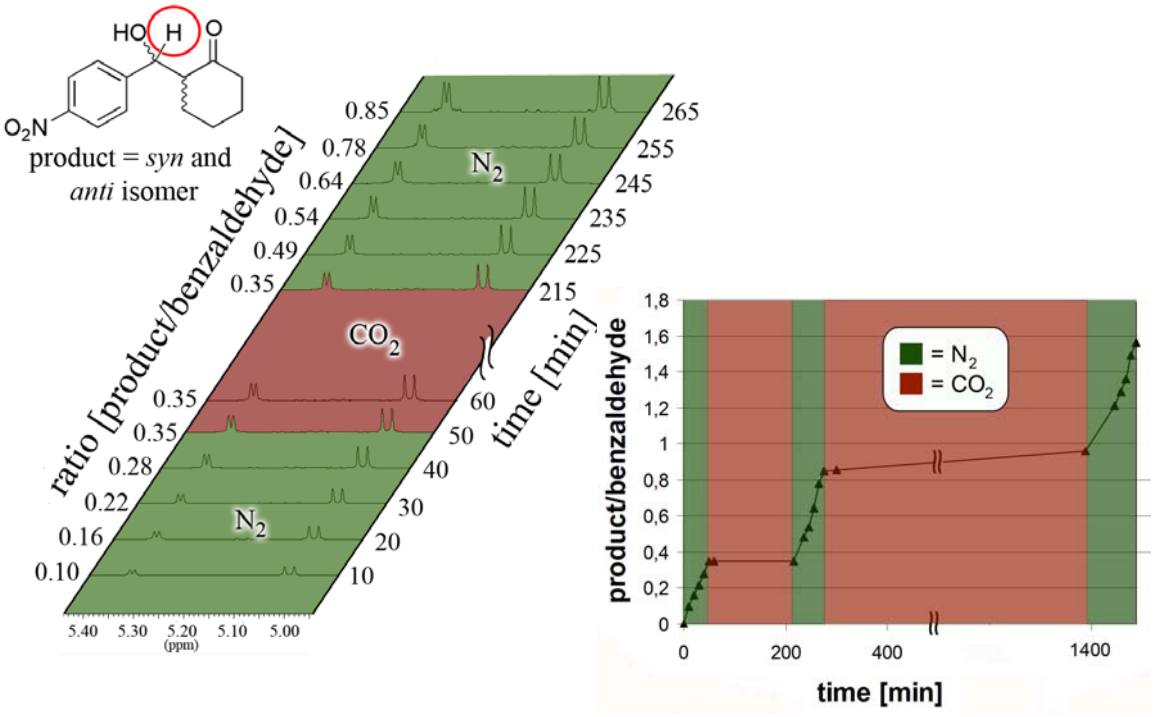


Fig. 5.1 ^{1}H-NMR monitored CO_2/N_2 regulated aldol reaction. Left: Developing resonance signals of *syn*- and *anti*-benzylic protons during the N_2 and CO_2 cycles between 5.0 and 5.4 ppm. Right: Product to starting material ratio plotted against the overall reaction time. Activation and inactivation cycles are indicated by green and red areas. The slopes (product formed/time) during the on-states are $2.2*10^{-11}$ mol/s, $2.3*10^{-11}$ mol/s and $2.2*10^{-11}$ mol/s, respectively, indicating no significant loss in catalytic activity.

In a final activation step the amidine base was deprotonated again to verify the completion of the aldol reaction after several “base-on” and “base-off”-cycles. The observed reaction rate after “on” and “off” phases is comparable to the unprotected benzamidine. After an overall reaction time of 20 h and 10 min (actual reaction time resulting from subtraction of deactivation phases is 210 min) a product yield of 62% was reached. The yield of the uninterrupted reaction under otherwise identical reaction conditions (210 min) was determined to be 63%.

Conclusion

We have shown that the catalytic activity of a benzamidine base is reversibly switched on and off during an aldol reaction using N_2/CO_2 cycles controlling the reaction progress. During the CO_2 cycles the base is reversibly protonated and not carbamoylated. The reaction progresses during “base on” periods with the same rate as observed in uninterrupted reactions.
The experiments demonstrate that the application of gases as chemical input signal can control an aldol reaction without affecting the converted compounds. Such orthogonal chemical control mimics allosteric regulation and may find applications in analytical signal amplification or chemical processing of information.

Experimental Section

Benzamidine was obtained from benzamidine HCl following the procedure of Tobin.[18]
4-Nitrobenzaldehyde (37.8 mg, 0.25 mmol) and benzamidine (6.0 mg, 0.05 mmol, 25 mol%) were dissolved in H_2O (0.07 mL) and d_3-ACN (0.63 mL). The solution was transferred into an NMR tube and the reaction mixture was saturated with CO_2 gas for 10 min using a long cannula. After 5 min, cyclohexanone (0.1 mL, 1.0 mmol) was added to the solution. A ^{1}H-NMR spectrum was recorded to analyse the reaction mixture without conversion. To start the reaction, N_2 was bubbled through the solution for 10 min after initially heating the mixture to 60 °C for 20 sec. To stop the reaction again a CO_2 flow was applied like described above. NMR spectra of the reaction mixture were recorded after each cycle to monitor the reaction progress.[19]

During the reaction in the NMR tube with d_3-ACN:D_2O of 9:1 (v/v) as solvent the expected benzylic signals (*syn* and *anti* doublets at about 5.0 and 5.3 ppm) turned more complex, losing the doublet character with increasing reaction time

(Fig. ES5.1). Exchanging D_2O by H_2O suppressed the D/H exchange at the *alpha* position to the carbonyl.

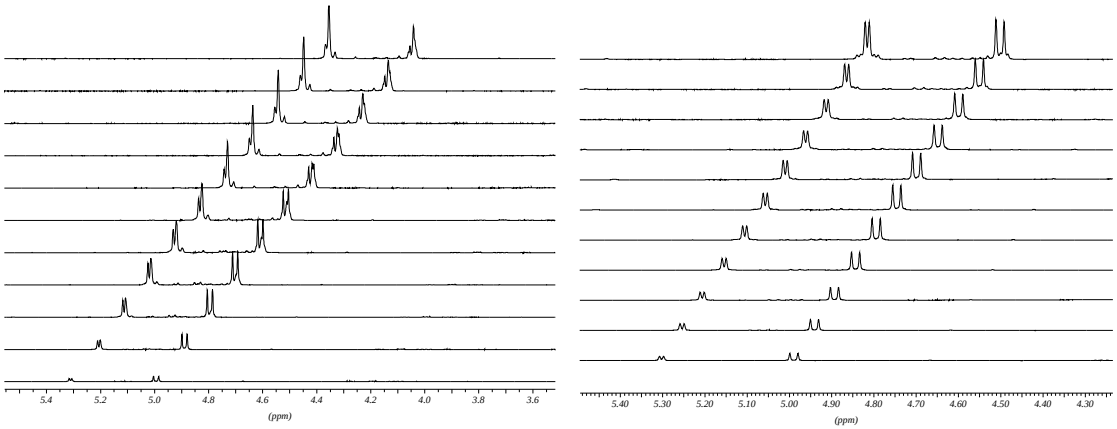


Fig. ES5.1 ^{1}H-NMR stack plot of aldol addition with 10 % D_2O (left) and 10 % H_2O (right).

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[17] $NaHCO_3$ was not soluble enough in an ACN/H_2O (9:1) mixture to detect a

signal in the ^{13}C NMR spectrum. For this reason the addition of $NaHCO_3$ to the protonated species was done in D_2O where $NaHCO_3$ shows high solubility.

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[19] The loss of ACN upon heating/bubbling was compensated by addition of new ACN.

6. Summary

The present dissertation discusses low melting carbohydrate mixtures as possible alternative solvent. In the first chapter performances and ecological (dis)advantages are investigated. A citric acid/DMU melt system is compared to other alternative and conventional solvents for a Diels-Alder cycloaddition as model reaction. In this comparison the melts showed a very low (eco)toxicity and could even outrank [C_6mim][BF_4] as solvent in a PROMETHEE procedure considering the EF, EHF(AcT), EHF(ChT), EHF(WmE) and CF.

In the second chapter, a new L-carnitine melt was compared to the established carbohydrate melts in terms of polarity and performance for diverse transition metal-catalysed reactions. For the Sonogashira and Heck cross-coupling reactions the carbohydrate melts gave better results while the 1,3-diplolar Cu-catalysed cycloaddition gave the best yields in the new L-carnitine melt. Price, chemical performance and thermal stability make the established carbohydrate melts a more favourable reaction medium compared to L-carnitine based melts.

It was shown that the highly concentrated melt systems (up to 50 % by weight) can be used for the efficient conversion of the carbohydrate part (Chapter 3). β-D-Glycosyl and mannosyl urea were prepared in this solvent by an acid-catalysed condensation reaction with urea.

Different melts were tested to obtain value added products like 5-hydroxymethylfurfural (Chapter 4). Here, choline chloride was found to be the best melt component for the preparation of HMF. Apart form the monosaccharides D-fructose and D-glucose, the di- and oligosaccharides sucrose and inulin could be converted using Lewis and Brønsted acids as catalysts demonstrating the applicability of the melt for diverse carbohydrates as starting material. The use of high molarities (2.9-3.1 mol/L) and short reaction times (0.5 to 1 h) allows for high space-time yields.

In an additional project (Chapter 5), the reversible regulation of a basic catalyst using the orthogonal switching stimuli CO_2 and N_2 was demonstrated. An aldol reaction was used as indication reaction and ^{1}H-NMR spectroscopy for the monitoring.

7. Zusammenfassung

Im Zuge dieser Dissertation werden niedrig schmelzende Kohlenhydratmischungen als mögliches alternatives Lösungsmittel diskutiert. Im ersten Kapitel werden sowohl chemische Ausbeuten, als auch ökologische Vor- und Nachteile einer Zitronensäure/DMU-Schmelze untersucht und mit anderen alternativen und konventionellen Lösungsmitteln in einer Diels-Alder-Cycloaddition als Testreaktion verglichen. Hierbei zeigte die Schmelze eine sehr geringe (Öko-)Toxizität und konnte im direkten Vergleich unter Berücksichtigung der EF, EHF(AcT), EHF(ChT), EHF(WmE) und CF in einer PROMETHEE Rechnung gegenüber $[C_6mim][BF_4]$ ein besseres Ergebnis erzielen.

Im zweiten Kapitel wurde eine neue L-Carnitin-Schmelze mit gängigen Kohlenhydratschmelzen bezüglich Polarität und chemische Ausbeuten bei Übergangsmetall-katalysierten Reaktionen verglichen. Sowohl bei der Sonogashira-, als auch der Heck-Kreuzkupplung konnten für die Kohlenhydratschmelzen bessere Ergebnisse erzielt werden, während Cu-katalysierte 1,3-dipolar Cycloadditionen in der L-Carnitin-Schmelze mit höheren Ausbeuten verliefen. Sowohl Preis, Ausbeuten, als auch thermische Stabilität sprechen im Vergleich mit L-Carnitin-Schmelzen für die Verwendung von Kohlenhydratschmelzen.

Die Schmelzen weisen eine sehr hohe Zuckerkonzentration auf (bis zu 50 Gew-%) und eignen sich aus diesem Grund zur effizienten Konversion des Kohlenhydratanteils (Kapitel 3). Durch Säure-katalysierte Kondensation mit Harnstoff konnten β-D-Glycosyl- und Mannosylharnstoffe hergestellt werden.

Unterschiedliche Schmelzen wurden untersucht, um wertgesteigerte Produkte wie 5-Hydroxymethylfurfural herzustellen (Kapitel 4). Hierbei erwies sich Cholinchlorid als beste Schmelzkomponente. Neben den Monosacchariden D-Fructose und D-Glucose konnten auch die Di- und Oligosaccharide Saccharose und Inulin erfolgreich durch die Verwendung von Lewis- und Brønsted- Säuren als Katalysatoren umgesetzt werden. Bei einer Reaktionsführung mit sehr hoher Molarität (2,9-3,1 mol/L Kohlenhydrat/Schmelzvolumen) und kurzen Reaktionszeiten (0,5-1 h) lassen sich hohe Raum-Zeit-Ausbeuten erzielen.

In einem zusätzlichen Projekt (Kapitel 5) wurde die reversible Regulierung eines basischen Katalysators durch die Verwendung der orthogonalen Signale CO_2 und N_2 demonstriert. Hierbei wurde der Verlauf einer Aldol-Reaktion mittels ^{1}H-NMR Spektroskopie als Monitoring angezeigt.

8. Abbreviations

Ac	Acetyl-
ACN	Acetonitrile
$AcNMe_2$	Dimethylacetamide
AGW	Arbeitsplatzgrenzwert (Threshold limit value)
BASIL	Biphasic acid scavenging using ionic liquids
*t*BuOH	*tert*-Butanol
c	speed of the light
CED	Cumulative energy demand
CF	Cost factor
ChCl	Choline chloride
$[C_4mim]Br$	1-Butyl-3-methylimidazolium bromide
$[C_4mim]Cl$	1-Butyl-3-methylimidazolium chloride
$[C_2mim]Cl$	1-Ethyl-3-methylimidazolium chloride
$[C_6mim][BF_4]$	1-Hexyl-3-methylimidazolium tetrafluoroborate
$[C_6mim]Cl$	1-Hexyl-3-methylimidazolium chloride
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMU	*N,N'*-Dimethyl urea
EC_{50}	Half maximal effective concentration
ECO	Ecological and economic optimisation
EF	Energy factor
EHF	Environmental and human health factor
EHF(AcT)	Environmental and human health factor regarding acute toxicity risks
EHF(ChT)	Environmental and human health factor regarding chronic toxicity risks
EHF(WmE)	Environmental and human health factor regarding risks resulting from water-mediated effects
EHS	Environment, health, safety
E_T	Transition energy
EtOAc	Ethyl acetate
EtOH	Ethanol

GC	Gas chromatography
GK	Giftklasse (Swiss poison class)
h	Planck's constant
HPLC	High performance liquid chromatography
IL	Ionic liquid
λ_{max}	maximal absorption wavelength
LC_{50}	Median lethal concentration
LCA	Life cycle assessment
LCC	Life cycle cost
LD_{50}	Median lethal dose
Log K_{OW}	Log octanol-water partitioning coefficient
MAK	Workplace treshold value (Maximale Arbeitsplatzkonzentration)
Me	Methyl-
MeOH	Methanol
N_A	Avogadro's constant
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
OECD	Biodegradability after 28 days (standardised test)
OTf	Triflate
PE	Petroleum ether
Ph	Phenyl
*p*TsOH	*Para*-toluene sulfonic acid
R&D	Research and development
RPoD	Remaining potential of danger
rt	Room-temperature
$scCO_2$	Supercritical carbon dioxide
$Sc(OTf)_3$	Scandium (III) triflate
SLCA	Simplified life cycle assessment
T_{dec}	Decomposition temperature
TGA	Thermogravimetric analysis
TMU	*N,N,N',N'*-Tetramethyl urea
UV-Vis	Ultra violet/visible
WGK	Wassergefährdungsklasse (German water hazard class)

w	Weight

9. Appendix

Poster presentations

G. Imperato, F. Ilgen and B. König, Sugar melts as new environmental-friendly solvent.
1st International IUPAC Conference on Green-Sustainable Chemistry, 10 -15. September **2006**, Dresden.

F. Ilgen, G. Imperato and B. König, Clean transition metal-catalysed reactions in sugar melts.
Green Solvents for Process; 8. - 11. Oktober **2006**, Friedrichshafen.

F. Ilgen, G. Imperato, and B. König, Non-toxic melts based on renewables – an alternative solvent.
Nachwachsende Rohstoffe für die Chemie; 28. - 29. März **2007**, Oldenburg.

F. Ilgen, C. Reil, and B. König, Conversion of carbohydrates into 5-hydroxymethylfurfural in carbohydrate melts.
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F. Ilgen, C. Reil, and B. König, Conversion of carbohydrates into 5-hydroxymethylfurfural in carbohydrate melts.
Green Chemistry for Environment and Health; 13. - 16. Oktober **2008**, München.

Oral presentations

F. Ilgen, and B. König, Low melting carbohydrate mixtures as alternative solvent for chemical reactions.
Green Chemistry for Environment and Health; 13. - 16. Oktober **2008**, München.

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Publications

1	*Green Chem.* **2008**, *11*, 1170-1182. “Evaluating the greenness of alternative reaction media“
2	*Green Chem*. DOI:10.1039/b816551c “Organic reactions in low melting mixtures based on carbohydrates and L-carnitine – A comparison”
3	*Tetrahedron Lett*. **2006**, *47*, 1941-1944 “Preparation of highly functionalized arylmagnesium reagents by the addition of magnesium phenylselenide to arynes”

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