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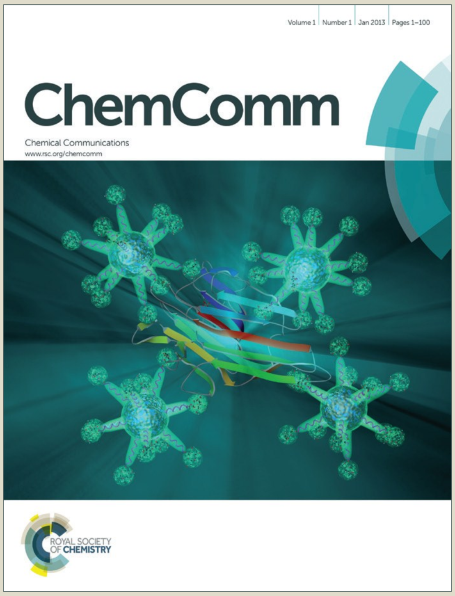

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A novel green approach for the chemical modification of silica particles based on deep eutectic solvents

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Tongnian Gu, Mingliang Zhang, Jia Chen, and Hongdeng Qiu*

Deep eutectic solvents (DESs), as a novel class of green solvents, was successfully applied as an eco-friendly and sustainable reaction media for fast surface modification of spherical porous silica, resulting in stationary phases for high-performance liquid chromatography. The new reaction media was advantageous over organic solvents in many aspects, such as high dispersibility of silica spheres and non-volatility.

In the last three decades, the concept "green-chemistry" has demonstrated significant vitality in chemistry. Within the framework of green chemistry, solvents occupy a place of strategical importance.[1] To be qualified as a green medium, the solvent has to meet different environment-friendly criteria, such as availability, non-toxicity, biodegradability, recyclability, inflammability, and low price.[2] There is a urgent require to replace hazardous and harmful non-green solvents of any kind with green and sustainable solvents. Nowadays, deep eutectic solvents (DESs) introduced by Abbott's group,[3] are widely hailed as a new generation of designable solvents, and promising green and sustainable media for multiple applications and alternatives to traditional organic solvents.[4]

DESs possess physicochemical properties similar to those of ionic liquids (ILs). They are conveniently obtained via the complexion of quaternary ammonium salts with hydrogen-bond donors. DESs are less expensive, more synthetically accessible (from bulk commodity chemicals using solvent/waste-free processes), non-volatile, nontoxic, recyclable, sustainable, biodegradable and biocompatible, which make them promising alternative to ILs, particularly room-temperature ILs (RTILs). Obviously, the excellent properties of DESs were highlighted by their widespread applications in many branches of chemistry. Up to now, DESs as green and sustainable media have attracted considerable attention in the fields of catalysis, electrochemistry, material chemistry, biochemistry, biology and organic synthesis.[5] Recently, bio-based DESs have excelled as suitable media for DNA/RNA and biotransformations.[6] Owing to their outstanding electrochemical nature, DESs can be tailor-made to realize applications of significance in electrochemistry.[7] Furthermore, they can be used as extraction media to achieve the green separation,[8] previously effective extraction of polar aromatic compounds from model oil was conducted in our laboratory.[9]

The typical reviews focused on DESs are regarded as benign and eco-friendly media alternatives to traditional organic solvents for synthesis of nanoscale and functional materials,[10] organic synthesis,[4a] and polymer synthesis.[4b] Recently, DESs have been applied to synthesis of porous carbons,[11] sustainable catalytic processes[12] and catalytic-free synthesis of quinazoline derivatives;[13] chemoselective addition of organolithium and grignard reagents to ketones in air;[14] and synthesis of novel lidocaine-releasing poly elastomers.[15] Besides, an efficient and green protocol based on DESs was proposed for the regioselective and chemoselective reduction of epoxides and carbonyl compounds with good to excellent yields.[16] However, in the analysis field, there are few available green solvents to substitute toxic solvents such as toluene, acetonitrile, dichloromethane, chloroform, methanol, and so on, for surface modification of silica by silylation.

At first, we found improved dispersibility of solid particles in DESs, due to their high viscosity, which may be beneficial for silylation reactions. To explore this possibility, DESs were directly herein used as a novel green and recyclable media to synthesize the silica stationary phases by chemical modification. An eco-friendly and sustainable approach for the surface modification of silica stationary phases was successfully built, whereby an *N*-methyl-glucamine-functionalized silica stationary phase (Sil-*N*-Glu) for liquid chromatography was prepared. The glucose-based silica material showed satisfactory separation efficiency and outstanding selectivity for ginsenosides, nucleosides and sulfonamides.

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[a] *Key Laboratory of Chemistry of Northwestern Plant Resources and Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China. hdqiu@licp.cas.cn (H. Qiu)*

† Footnotes relating to the title and/or authors should appear here.
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First, DES was prepared according to the reference [9]. Choline chloride (ChCl) and urea were mixed together (ChCl with Urea in a 1:2 molar ratio) with magnetic agitation at 80 °C until clear, colorless and homogeneous liquid was formed.

Spherical porous silica (3 g) was dispersed ultrasonically into the freshly prepared DES, followed by the addition of silylation reagents (6 mmol), and then the solution was stirred at 60 °C for 24 h, the whole reaction was carried out in an atmosphere of nitrogen (Fig. 1). Modified silica was obtained by centrifugation at 8000 rpm min^{-1} for 10 min, subsequently washed with water and ethanol and dried at 60 °C under vacuum.

The different silylation reactions with various silane coupling reagents, including 3-chloropropyltrimethoxysilane (CPTMS), 3-mercaptopropyltriethoxysilane (MPTES), 3-trimethoxysilyl-propylmethacrylate (TMPMAS), 3-aminopropyltriethoxysilane (APTES) and 3-glycidoxypropyltrimethoxysilane (GPTMS), were performed using DES as reaction media. The carbon, hydrogen and nitrogen contents of the silanized silica support were summarized in Table 1. The silylation reagents were successfully immobilized on the surface of spherical porous silica. Irrespective to silane agents, good to satisfactory degrees of surface coverage were observed when the reaction proceeded in DESs as reaction solvent. It should be noted that octadecyltrichlorosilane stuck together in DESs. This may be ascribed to the high hydrophobicity of octadecyltrichlorosilane. The degrees of surface coverage of the modified silica support were calculated according to the following equation:[17]

$$\text{Coverage}\ (\mu\text{mol m}^{-2}) = \frac{X}{M_X \times n_X \times (100 - C - H - N) \times S} \times 10^6$$

where C (%), H (%), N (%), and X (%) represent the percentages of carbon, hydrogen, nitrogen, and the marked element, respectively. S is the specific surface area of the spherical porous silica (395 $m^2\ g^{-1}$). n_x is the number of the carbon, M_x is the molar mass of the marked element (X).Silylation is one of the most important methods for chemical modification and derivatization of silica materials, which constitutes the foundation for preparation of stationary phases for HPLC and gas chromatography. It is well-known that silylation reactions in heterogeneous conditions needs higher dispersibility of silica spheres so as to achieve a higher surface coverage. In our preliminary experiments, DESs was observed to maintain fine suspension of silica gels. Silica particles can be dispersed very well in DESs even after 24 hours, while precipitate quickly in toluene less than 5 minutes, as displayed in Fig. S1 (ESI).

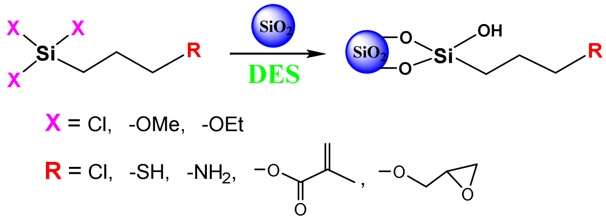

Fig. 1 Silylation reactions used DES as the reaction media.

Table 1 The results of elemental analysis and surface coverage of the different silylation reactions on silica.

Precursors	C (%)	N (%)	H (%)	Coverage (μmol m^{-2})
CPTMS	6.30	0.00	1.268	4.79
MPTES	2.54	0.00	0.919	1.85
TMPMAS	10.84	0.00	1.583	3.73
APTES	4.81	1.86	1.685	3.66
GPTMS	7.48	0.00	1.524	2.89

Based on the finding of silylation reactions can be easily and well performed in DESs, we tried to synthesize a new stationary phase in this new solvent. The preparation of *N*-methyl-glucamine-modified silica (Sil-*N*-Glu) was performed as followed: 6 mmol of 3-glycidoxypropyltrimethoxysilane and equivalent *N*-methyl-glucamine was dissolved in 20 mL of the DESs, the solution was heated at 60 °C for 24 h, and then silica spheres (3 g) was added under stirring and the slurry was heated for another 24 h in N_2. Sil-*N*-Glu was gained by the aforementioned isolation method. After characterizations using elemental analysis, thermogravimetric analysis (Fig. S2, ESI), and IR spectroscopy analysis (Fig. S3, ESI), the modified silica particles were packed into the stainless steel column (150 × 4.6 mm i.d.) for high-performance liquid chromatography (HPLC) evaluation. The ring opening reaction of epoxyethane utilizing DESs as reaction solvents was also reported by Najmadin Azizi and co-workers.[16]

The results proved that DESs can be used as an eco-friendly and sustainable reaction media to synthesize the chemically modified silica gel stationary phases. From the elemental analysis results, the C (%), H (%), and N (%) of the Sil-*N*-Glu was 9.64, 1.74, and 0.81, respectively. The amount of glucamine moieties was 1.67 μmol m^{-2}. The other characterizations including thermogravimetric analysis and infrared spectra also demonstrated that the synthesis of silane and the grafting of silane on the silica was successfully performed in DES (Fig. S2 and Fig. S3 in ESI).

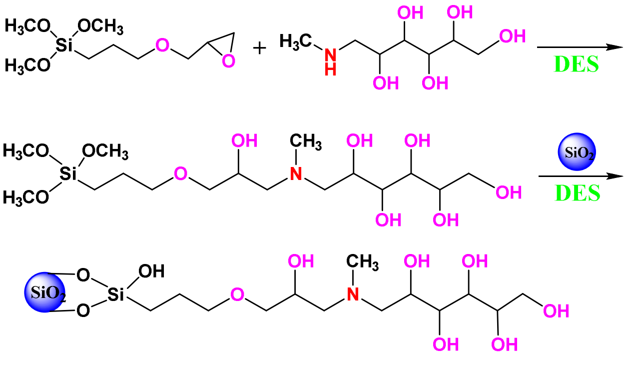

Fig. 2 Synthetic strategy for the glucamine-modified spherical silica stationary phase.

Table 2 The results of elemental analysis and surface coverage of Sil-*N*-Glu with toluene, methanol, fresh DESs and the reused DESs as reaction media, respectively.

Solvents	C (%)	N (%)	H (%)	Coverage (μmol m^{-2})
Toluene	10.90	0.81	2.115	1.69
Methanol	9.36	0.67	1.812	1.37
DESs (fresh)	9.64	0.81	1.738	1.67
Recycled Ⅰ	8.85	0.78	1.754	1.59
Recycled Ⅱ	8.82	0.72	1.694	1.47
Recycled Ⅲ	8.72	0.76	1.726	1.55

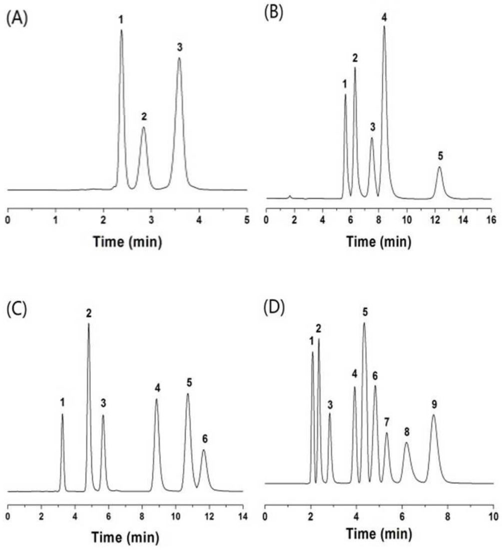

Fig. 3 Separations of three group mixtures with Sil-*N*-Glu columns, mixtures (A) containing three ginsenosides: (1) Rg1, (2) Re, (3) Rb1, mobile phase: CH_3CN/Water (7:3, v/v); (B) five flavonoid glycosides: (1) salicin, (2) arbutin, (3) aurantiamarin, (4) naringin, (5) amygdalin, mobile phase: CH_3CN/Water (9:1, v/v); (C) six nucleosides: (1) thymidine, (2) uridine, (3) adenosine, (4) inosine, (5) cytidine, (6) guanosine, mobile phase: 85% CH_3CN: 15% 20mmol NH_4AC solution; (D) nine sulfonamide drugs: (1) sulfanilamide, (2) sulfapyridine, (3) sulfamethazine, (4) sulfamerazine, (5) sulfathiazole, (6) sulfadimoxine, (7) sulfadiazine, (8) sulfadimethoxine, (9) sulfisoxazole, mobile phase: 20% CH_3CN : 80% 20mmol NH_4AC solution. Other chromatographic conditions: flow-rate=1.0 ml min^{-1}, T=30℃.

To get insight into the excellence of DESs as the reaction solvent for facile surface modification of silica gel, a comparative experiment was carried out to unfold the difference among surface coverages of the silica gel modified in toluene, methanol and DESs under their optimum reaction condition (particularly, the temperature for traditional organic solvents was under reflux condition), respectively. As shown in Table 2, the experiment demonstrated that the DESs resulted in surface coverage comparable to those resulted from traditional organic solvents, such as toluene, methanol. The recyclability of reaction media is a crucial factor for cost-saving and green chemistry. Investigation into the effectiveness of the recycled DESs indicated that DESs could be reused at least three times without significant impact on the surface coverage, as shown in Table 2.

The modified silica particles were packed into the column (150 × 4.5 mm i.d.) and the Sil-*N*-Glu column performance was evaluated. The relevant parameters such as theoretical plate number, peak tailing factor were determined by eluting uracil and cytosine in mobile phase composed of 85% CH_3CN in water at 30℃, the column pressure was 25 bar in 1.0 ml min^{-1} flow-rate. The theoretical plate number for two samples was 48000 and 49000, respectively, and the peak tailing factor was 1.14 and 1.05. Moreover, In order to exemplify sufficiently the chromatographic performance of the Sil-*N*-Glu column, the Van-deemter plots for different compounds and for the silica particles using the supports synthesized with conventional solvents (Toluene) and DESs were comparatively given in the Fig. S4 (ESI). The Sil-*N*-Glu column was applied for the separation of three ginsenosides (Rg1, Re and Rb1), five flavonoid glycosides and six nucleosides in hydrophilic interaction chromatography, and nine sulfonamide drugs in hydrophobic chromatography with a low concentration of acetonitrile within eight minutes. The chromatograms with satisfactory separation efficiency for the chosen set of samples were shown in Fig. 3. The structures of sulfoamide compounds were listed as shown in Fig. S5 (ESI). Besides, the comparison of separation properties for the silica stationary phase (Sil-*N*-Glu) using DESs and conventional solvents (Toluene) as reaction media was given in the Fig. S6 (ESI). The results demonstrated the advantages of proposed modified method.

Conclusions

In summary, an effective green synthetic method based on DESs as a new reaction media was developed for the chemical modification of silica materials. The solvent can be readily formed by mixing the raw materials. Fine dispersibility of solid particles was guaranteed due to the appropriate viscosity of DESs. Above all, the experiments proved that DESs are a new kind of suitable solvents for silylation reaction, as an alternative to the traditional volatile solvents. Notably, not only is DESs relatively inexpensive, eco-friendly, and then nonvolatile, non-flammable, making their storage convenient, but also able to be recycled without compromising the results. However, hydrophobic chlorosilane was inapplicable in this DESs, probably due to the insolubility of the lipophilic chain. In a word, DESs are a new generation of designable solvents, which enables them to be green reaction solvents for the surface modification of silica stationary phases. This new strategy is also hopeful to be used for the preparation of new functionalized solid materials in other research fields such as solid absorbents, recycling catalysts, and solid-state electrochemistry etc.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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