Ionic Liquids as Solvents for the Knoevenagel Condensation: Understanding the Role of Solvent-Solute Interactions

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(A) Materials and methods

All reagents and solvents were purchased from Sigma-Aldrich and were dried and purified according to previously reported procedures.[1] Reichardt`s dye 30, *N*,*N*-diethyl-4-nitroaniline and 4-nitroaniline were used as received. ^{1}H (400 MHz) and ^{13}C (100 Hz) NMR spectra were recorded on a 400 MHz Bruker BioSpin GmbH spectrometer (δ in ppm, *J* in Hz). For neat ILs and their mixtures with molecular solutes ^{1}H NMR chemical shifts were referenced externally against the CH_3CN singlet. CH_3CN was introduced into the sample as a sealed capillary and was found to have a ^{1}H NMR shift of 2.797 ppm relative to the residual solvent peak of $CDCl_3$. In all ^{13}C NMR spectra, signals were referenced externally to DMSO-*d*$_6$. DMSO-*d*$_6$ was a lock solvent for all of the performed measurements. The IR spectra were recorded on a PerkinElmer FT-IR/FIR Frontier instrument (ν_{max} in cm^{-1}). The UV-Vis spectra of the dye solutions in ILs were measured on a PerkinElmer Lambda 25 spectrophotometer using Quartz SUPRASIL® UV/Vis Spectroscopy cells (1 mm or 10 mm). Kamlet-Taft linear solvation energy relationship (LSER) equations and fitting statistics between the Kamlet-Taft solvent descriptors of the ILs used in the Knoevenagel condensation and lnk_2 were obtained using multivariate regression that was performed with MS Excel 2007. The gas chromatography analyses were carried out on a YL6100 GC apparatus equipped with an Equity™-5 column (30 m × 0.25 mm × 0.25 μm) and a flame ionization detector (FID). Helium was exploited as a carrier gas (flow 1 mL/min) and the injector temperature was 300

°C. Temperature gradient 100 °C (hold 1 min) to 280 °C (hold 12 min) and a heating rate of 10 °C/min was applied.

(B) Experimental Procedures

(a) Synthesis of ionic liquids

ILs for the kinetic experiments and the investigation of IL interactions with molecular solutes were prepared according to previously reported procedures.[2–4] All ILs were treated with activated charcoal and filtrated through a pad of basic alumina (0.063-0.200 mm).[4a,5] In order to remove any remaining particles of charcoal and alumina, the solution of each IL in an appropriate solvent (MeOH or DCM) was filtered through a PTFE filter (0.45 μm). The filtrate was then concentrated by rotary evaporation and the pure IL was dried under vacuum (0.6 mbar, 65 °C, 12 h).

(b) Measurements of the Kamlet-Taft solvent descriptors of ionic liquids

The Kamlet-Taft solvent descriptors α, β and π^* were measured according to a previously reported procedure.[3]

(c) Kinetics of the Knoevenagel condensation in ionic liquids

The Knoevenagel condensation was performed in a thermostated reaction tube under argon atmosphere. All ILs were dried under vacuum (0.6 mbar, 65 °C, 12 h) prior to their exploitation. 4-(Dimethylamino)benzaldehyde (**1**) (120 mg, 0.80 mmol) was placed in the reaction tube that was further purged with argon for approximately 15 min. After addition of the appropriate IL (2.0 mL), the tube was equipped with a septum and the aldehyde **1** was dissolved in the IL by stirring at 80 °C temperature under argon atmosphere. Ethyl cyanoacetate (**2**) (91 mg, 0.80 mmol) was added with vigorous stirring. The start of the reaction (t = 0) was taken as the time of ethyl cyanoacetate (**2**) addition. Samples (80-100 μL each) were taken with a syringe after appropriate intervals of time and extracted with 1 mL of an EtOAc/brine mixture (3:1, v/v) at -10 °C. The EtOAc layer was separated and the brine layer was repeatedly extracted with EtOAc (9 × 1 mL) at -10 °C. An aliquot (60-100 μL) of a biphenyl standard solution in EtOAc was added to the combined extracts and the resulting mixture was concentrated to ~ 1 mL by rotary evaporation (100 mbar, 30 °C). The concentrations C_1 of 4-(dimethylamino)benzaldehyde (**1**) and C_2 of ethyl cyanoacetate (**2**) were calculated from the data obtained *via* gas chromatography according to the Equation S1 and Equation S2:

$$C_1 = \frac{\gamma_{biphenyl} \cdot V_{biphenyl} \cdot \left(1.443 \cdot \frac{S_1}{S_{biphenyl}} - 0.067\right)}{149.20 \cdot V_{sample}} \qquad \text{(S1)}$$

$$C_2 = \frac{\gamma_{biphenyl}\cdot V_{biphenyl}\cdot\left(2.656\cdot\frac{S_2}{S_{biphenyl}}-0.007\right)}{113.13\cdot V_{sample}} \tag{S2}$$

where S_1, S_2 is the area (mV·s) of the peaks corresponding to 4-(dimethylamino)benzaldehyde (**1**) and ethyl cyanoacetate (**2**), $S_{biphenyl}$ – area (mV·s) of the peak corresponding to biphenyl, $\gamma_{biphenyl}$ – concentration of the biphenyl standard solution (g/L), $V_{biphenyl}$ – the volume (μL) of the biphenyl standard solution added to the sample and V_{sample} – the volume (μL) of the sample. The calibration curves, exploited in the method of standard addition, for 4-(dimethylamino)benzaldehyde (**1**) and ethyl cyanoacetate (**2**) are depicted in Fig. S1 and Fig. S2.

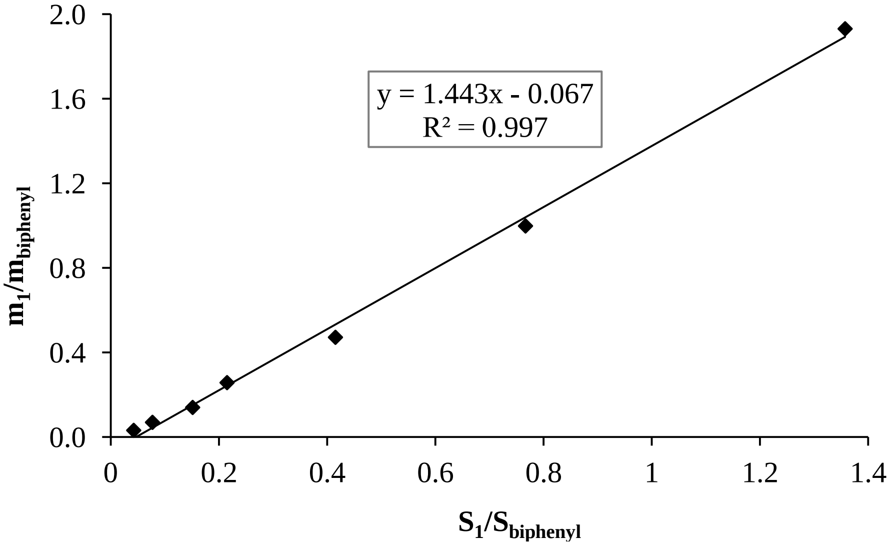

Fig. S1 The calibration curve for 4-(dimethylamino)benzaldehyde (**1**).

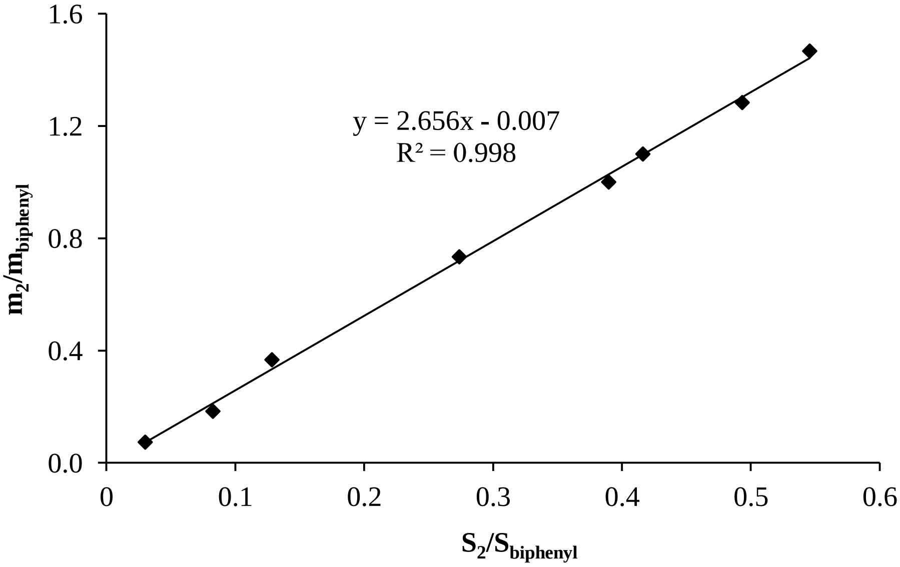

Fig. S1 The calibration curve for ethyl cyanoacetate (**2**).

(C) ^{1}H, ^{13}C NMR and FTIR spectroscopy data

Table S1 ^{1}H NMR chemical shift δ_H of benzaldehyde (C$\underline{H}$O) and IL (NC$\underline{H}$N, OC$\underline{H}_3$, O$\underline{H}$) protons, ^{13}C NMR chemical shift δ_C of benzaldehyde ($\underline{C}$=O) carbon and FTIR wavenumber ν of benzaldehyde C=O group[a]

Entry	Solvent	δ_H (C$\underline{H}$O)/ppm	δ_H (NC$\underline{H}$N)/ppm[b]	δ_H (OC$\underline{H}_3$)/ppm[b]	δ_H (O$\underline{H}$)/ppm[b]	δ_C ($\underline{C}$=O)/ppm	ν (C=O)/cm^{-1}
1	Neat	9.45	–	–	–	191.2	1696
2	HMDSO[c]	10.53	–	–	–	–	1712
3	$[C_6C_1im][Cl]$	10.28	10.61 (10.63)	–	–	192.9	1695
4	$[C_4C_1pyrr][Me_2PO_4]$	10.26	–	3.30 (3.31)	–	193.5	1695
5	$[C_6C_1im][Br]$	10.17	10.10 (10.23)	–	–	192.7	1695
6	$[C_4C_1im][Me_2PO_4]$	10.11	10.30 (10.25)	3.35 (3.31)	–	192.4	1697
7	$[C_4C_1pyrr][OTf]$	10.01	–	–	–	192.4	1695
8	$[C_4C_1im][MeSO_4]$	9.98	9.13 (8.43)	3.93 (3.53)	–	192.8	1697
9	$[(HO)^2C_2C_1im][Me_2PO_4]$	9.86	9.47 (9.47)	3.21 (3.22)	6.89 (6.86)	–	1697
10	$[C_4C_1pyrr][NTf_2]$	9.82	–	–	–	191.9	1697
11	$[((HO)^2C_2)_3C_1N][MeSO_4]$	9.81	–	3.54 (3.27)	4.52 (4.20)	193.4	1697
12	$[((HO)^2C_2)_3C_1N][OTf]$	9.76	–	–	4.14 (4.11)	193.5	1697

[a] Individual solutions ($\chi_{solute} = 0.17$) of benzaldehyde in a range of structurally divergent ILs were analyzed by ^{1}H, ^{13}C NMR and FTIR spectroscopy.

[b] ^{1}H NMR shifts δ_H of the respective protons in neat ILs have been shown in parentheses. [c] Hexamethyldisiloxane was used as a solvent.

Table S2 ^{1}H NMR chemical shift δ_{H} of ethyl cyanoacetate (**2**) ($\mathrm{NCC\underline{H}_2C}$) and IL ($\mathrm{NC\underline{H}N}$, $\mathrm{OC\underline{H}_3}$, $\mathrm{O\underline{H}}$) protons, ^{13}C NMR chemical shift δ_{C} of ethyl cyanoacetate (**2**) ($\mathrm{\underline{C}{=}O}$) carbon and FTIR wavenumber ν of ethyl cyanoacetate (**2**) C≡N group[a]

Entry	Solvent	δ_H ($\mathrm{NCC\underline{H}_2C}$)/ppm	δ_H ($\mathrm{NC\underline{H}N}$)/ppm[b]	δ_H ($\mathrm{OC\underline{H}_3}$)/ppm[b]	δ_H ($\mathrm{O\underline{H}}$)/ppm[b]	δ_C ($\mathrm{\underline{C}{=}O}$)/ppm	ν (C≡N)/cm^{-1}
1	Neat	6.39	–	–	–	163.5	2265
2	HMDSO[c]	3.85	–	–	–	–	2265
3	$[C_4C_1pyrr][Me_2PO_4]$	4.63	–	3.33 (3.31)	–	164.6	2263
4	$[C_4C_1im][Me_2PO_4]$	4.52	10.21 (10.25)	3.37 (3.31)	–	164.3	2260
5	$[C_6C_1im][Cl]$	4.44	10.58 (10.63)	–	–	164.2	2258
6	$[C_6C_1im][Br]$	4.18	10.23 (10.23)	–	–	163.8	2262
7	$[C_4C_1im][MeSO_4]$	4.03	9.15 (8.43)	3.96 (3.53)	–	164.0	2262
8	$[(HO)^2C_2C_1im][Me_2PO_4]$	3.99	9.51 (9.47)	3.28 (3.22)	6.89 (6.86)	–	2256
9	$[C_4C_1pyrr][OTf]$	3.85	–	–	–	163.6	2262
10	$[((HO)^2C_2)_3C_1N][MeSO_4]$	3.77	–	3.55 (3.27)	4.52 (4.20)	164.0	2268
11	$[C_4C_1pyrr][NTf_2]$	3.65	–	–	–	163.2	2262
12	$[((HO)^2C_2)_3C_1N][OTf]$	3.64	–	–	4.13 (4.11)	163.9	2263

[a] Individual solutions ($\chi_{solute} = 0.17$) of ethyl cyanoacetate (**2**) in a range of structurally divergent ILs were analyzed by ^{1}H NMR, ^{13}C NMR and FTIR spectroscopy. [b] ^{1}H NMR shifts δ_H of the respective protons in neat ILs have been shown in parentheses. [c] Hexamethyldisiloxane was used as a solvent.

(D) References

1 W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Elsevier, Bodmin, 2003.

2 L. Crowhurst, N. Llewellyn Lancaster, J. M. Pérez Arlandis and T. Welton, *J. Am. Chem. Soc.*, 2004, **126**, 11549.

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

4 a) P. Nockemann, K. Binnemans and K. Driesen, *Chem. Phys. Lett.*, 2005, **415**, 131; b) E. Kuhlmann, S. Himmler, H. Giebelhaus and P. Wasserscheid, *Green Chem.*, 2007, **9**, 233; c) E. Priede, E. Bakis and A. Zicmanis, *Synlett*, 2014, **25**, 2447; d) L. Crowhurst, P. R. Mawdsley, J. M. Perez-Arlandis, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2003, **5**, 2790.

5 A. K. Burrell, R. E. Del Sesto, S. N. Baker, T. M. McCleskeya and G. A. Baker, *Green Chem.*, 2007, **9**, 449.