A solvent having switchable hydrophilicity†

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A new kind of switchable solvent, a switchable-hydrophilicity solvent, is hydrophobic and has very low miscibility with water when in air but is hydrophilic and has complete miscibility with water when under an atmosphere of CO_2. We report here the first example of such a solvent, N,N,N'-tributylpentanamidine. Solvents such as these could be used for the extraction of low-polarity organic products, such as vegetable oils, followed by the removal of the solvent from the product by carbonated water. Carbonated water is able to extract the solvent from the product because the CO_2 converts the solvent to its hydrophilic form. The solvent can then be separated from the carbonated water upon removal of the CO_2, because this removal triggers the conversion of the solvent back to its hydrophobic, water-immiscible form. Importantly, distillation is not required for removal of the solvent from the product.

Introduction

The removal of solvents by distillation is a common industrial practice but suffers from two disadvantages that result in environmental damage. First, distillation requires the use of a volatile solvent, which leads to significant vapour emission losses and the resulting contribution to smog formation; in Canada alone, 4 400 tonnes per year of hexane are emitted to the atmosphere, one third of that from oilseed processing.[1] Second, distillation requires a large input of energy. Therefore it would be desirable to find a new non-distillative route for the separation of solvents from products, so that volatile solvents would not have to be used.

Solvent removal from a hydrophobic product, without distillation, could be achieved if there were a solvent that could be reversibly switched from being hydrophobic to hydrophilic. Such a solvent could be termed a switchable-hydrophilicity solvent (SHS). Specifically, we have been looking for a solvent that exhibits the following desired phase behaviour with water: very little miscibility of the solvent with water in the absence of CO_2 but complete miscibility with water in the presence of CO_2 (Fig. 1).[2] CO_2 is preferred as the trigger for the switching process because it is non-toxic, benign, inexpensive and easily removed. Based upon our previous experience with amidine/CO_2 and guanidine/CO_2 chemistry,[3-6] we believed that there may be a liquid amidine or guanidine that would exhibit this phase behaviour. If such a solvent were found, then it could be used as a substitute for volatile solvents and be removed from organic products (such as oilseed oils), without distillation, by extraction of the solvent with carbonated water.

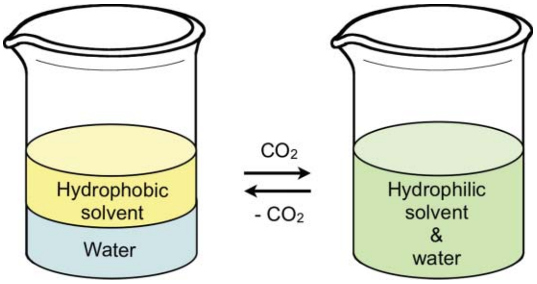
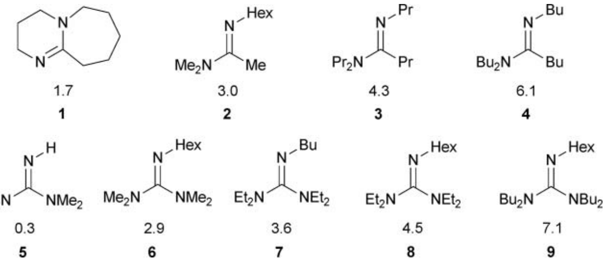


Fig. 1 The phase behaviour of a mixture of water and an SHS.

This paper describes the successful search for an SHS and preliminary tests of that solvent for the extraction of soy oil from soybean flakes.

Results and discussion

A series of amidines was tested for the desired phase behaviour: immiscibility with water under air and miscibility with water in the presence of 1 bar of CO_2. The compounds tested are shown in Scheme 1. Amidines **1** and **2** were unsatisfactory because they were soluble in water, even in the absence of CO_2. Two amidines with greater hydrophobicity (**3** and **4**) exhibited the desired phase behaviour.



Scheme 1 The amidines and guanidines mentioned in this study. The number in plain font is the predicted log K_{ow}, while the number in bold font is the compound number.

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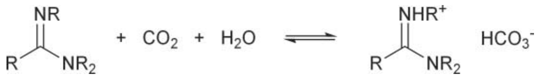
Protonation of the amidine by carbonic acid is the cause of the change in phase behaviour. In the presence of both CO_2 and water, amidines **3** and **4** are converted into water-soluble bicarbonate salts (eqn (1)). The $^{13}C\{^1H\}$ NMR spectrum of **4** in CO_2-saturated D_2O shows inequivalent butyl groups on the $–NBu_2$ nitrogen, and peaks at 160.1 (HCO_3^-) and 165.9 ppm (the sp^2 carbon of the protonated amidine). These peaks were assigned by comparison to the reported chemical shift of HCO_3^- in D_2O (160.8 ppm)[7] and because the peak at 165.9 ppm couples to the neighbouring methylene in the HMBC NMR spectrum. In contrast, the spectrum of **4** in $CDCl_3$ under air shows equivalent butyl groups on the $–NBu_2$ nitrogen and only a single peak far downfield, at 160.1 ppm, assigned to the C=N central carbon.



$$\mathrm{RC(=NR)NR_2} + CO_2 + H_2O \rightleftharpoons \mathrm{RC(=NHR^+)NR_2}\ HCO_3^- \qquad (1)$$

Similarly, the $^{13}C\{^1H\}$ NMR spectrum of **3** in CO_2-saturated D_2O shows inequivalent propyl groups on the $–NPr_2$ nitrogen, and peaks at 160.1 (HCO_3^-) and 165.9 ppm (the sp^2 carbon of the protonated amidine). In contrast, the spectrum of **3** in $CDCl_3$ under air shows equivalent propyl groups on the $–NPr_2$ nitrogen, and only a single peak far downfield at 160.1 ppm, assigned to the C=N central carbon.

Switching of amidine **4** to the bicarbonate was also monitored by ^1H NMR spectroscopy (Fig. 2). At first, **4** and D_2O were shaken together in a 1 : 2 v/v ratio at room temperature, giving a biphasic mixture. Aliquots of the two phases were removed, dissolved in CD_3OD and analyzed by ^1H NMR spectroscopy, showing that the upper phase was **4** with a small amount of water (Fig. 2a) and the lower phase contained water and a barely detectable trace of **4** (Fig. 2b). After CO_2 was bubbled through the biphasic mixture, the phases merged, and ^1H NMR spectroscopy showed both water and **4**, although the peaks of **4** were shifted slightly downfield because of protonation (Fig. 2c). Heating this homogeneous solution at 80 °C for 60 min caused a phase split, which persisted when the solution was cooled to room temperature. NMR spectra showed that the upper phase was **4** (Fig. 2d) while the lower phase still contained some of the bicarbonate salt of **4** (Fig. 2e). Therefore, the heat treatment largely reversed the reaction in eqn (1), but not completely. The amount of amidine that remained in the aqueous phase was calculated, with the help of an internal standard, to be 11% of the original amount. A comparison of the spectra in Fig. 2 clearly shows that the residual amidine in the water is in the form of the bicarbonate. Similar experiments with **3** showed that the conversion from biphasic to monophasic with CO_2 was facile but that the reverse process, restoring the biphasic mixture by heating, was rarely successful.

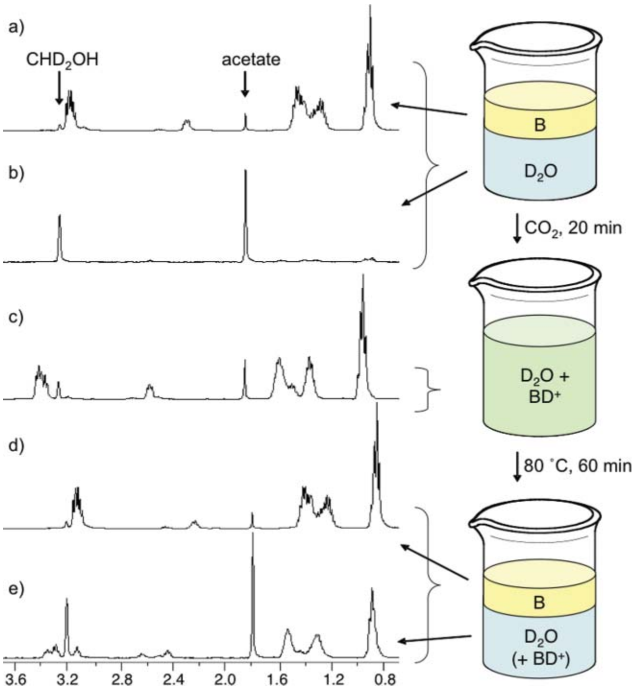


Fig. 2 The switchability of **4** in D_2O monitored by ^1H NMR spectroscopy of aliquots withdrawn from observed phases and dissolved in methanol-d_4 with sodium acetate internal standard. B = compound **4**. BD^+ = bicarbonate salt of **4**.

Conversion of the aqueous solution of the bicarbonate salt of **4** to the biphasic mixture of water and **4** could also be achieved without heating. Bubbling air slowly through the solution at room temperature for 5 h caused the mixture to split into the two phases.

Several guanidines were also tested for the desired phase behaviour (Scheme 1). Guanidine **5** was unsatisfactory because it was miscible with water in the absence of CO_2. Guanidines **6–8** were progressively less miscible with water. To determine the degree of miscibility of these partially-miscible guanidines, ^1H NMR spectra of saturated solutions in D_2O were measured. 2-Hexyl-1,1,3,3-tetramethylguanidine (**6**), 2-butyl-1,1,3,3-tetraethylguanidine (**7**) and 2-hexyl-1,1,3,3-tetraethylguanidine (**8**) dissolved in D_2O to the extent of 84, 38 and 13 mg mL^{-1}, respectively. All three of these liquid guanidines became completely miscible with water (with a water : guanidine ratio of 1 : 1 by volume) when treated with CO_2. Again, the miscibility is due to the formation of bicarbonate salts. Guanidine **7**, for example, showed peaks at 161.2 (guanidinium cation) and 160.1 (HCO_3^-) in its $^{13}C\{^1H\}$ NMR spectrum in D_2O after exposure to CO_2. The HCl salt of **7** also had a peak at 161.2 ppm, but no peak at 160.1 ppm. Guanidine **9** was abandoned because the crude guanidine was immiscible with water before and after exposure to CO_2.

Removal of the CO_2 from aqueous guanidinium bicarbonate solutions was not successful. For example, 1.0 g of **7** was mixed with 10 mL of distilled water and treated with bubbling CO_2 for 2 h. Then, the solution was put on a glass frit and argon passed up through the frit and the solution, for 18 h; no phase splitting was observed. A portion of this aqueous solution was then evaporated in a rotary evaporator at 33 °C and the residue then redissolved in D_2O. $^{13}C\{^1H\}$ NMR spectroscopy confirmed that the peaks at 161.2 and 160.1 ppm were both still present. Treating another portion of the aqueous solution with 2 M NaOH caused the guanidine to separate from the water as an organic liquid layer. ESI-MS confirmed that the layer consisted of compound **7**. Thus, the conversion of the guanidinium bicarbonate salt back to the neutral guanidine by flushing with a non-acidic gas is too difficult. The same observation was made with guanidines **6** and **8**. Further work with guanidines was therefore abandoned.

Thus, only five compounds (amidines **3** and **4**, and guanidines **6–8**) switched from water-immiscible to water-miscible, and the switching of only one of these (compound **4**) could be reliably reversed. In order to develop a method for predicting which amidines and guanidines might exhibit this phase behaviour, the log K_{ow} values (where K_{ow} is the octanol/water partition coefficient, a quantitative measure of the hydrophobicity) of each structure was predicted using standard algorithms (see the Experimental methods section). The results (Scheme 1) suggest that, for the desired phase behaviour, the log K_{ow} value should be approximately in the range 3 to 7. From this limited data set, it is clear that for the switching to be reversible, the solvent must be an amidine rather than a guanidine and that the log K_{ow} value should be closer to 7 than 3. Our further work continued with compound **4** exclusively.

This SHS (**4**) not only switches its hydrophilicity but also switches its polarity. While solvents of switchable polarity have been reported previously,[3,6,8-10] the increase in polarity upon exposure to CO_2 has always been moderate. Because compound **4**, in conjunction with an equal volume of water, forms an aqueous solution in the presence of CO_2, it has a polarity similar to that of water. The wavelength of maximum absorbance of Nile Red dye, which is used as a measure of polarity (Fig. 3), showed that the water/**4**/CO_2 single-phase mixture had a λ_{max} of 570 nm. In the absence of CO_2, the water is largely expelled from liquid **4**, meaning that the polarity of the solvent is that of the amidine with very little water dissolved therein (λ_{max} = 510 nm). As shown in Fig. 3, this results in a far larger polarity change than is observed in the previously reported switchable solvents. The new solvent also has the advantage over the some of the previously-reported switchable polarity solvents (B/ROH mixtures, where B is an amidine or guanidine) in that it is compatible with water: the B/ROH mixtures, if contaminated with water, give solid [BH][O_2COH] solid salts rather than [BH][O_2COR] ionic liquids upon treatment with CO_2.

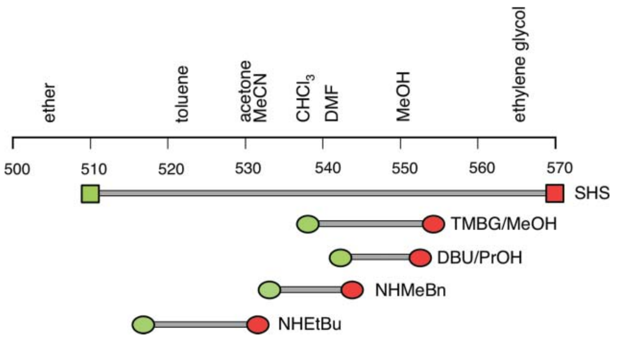


Fig. 3 The polarities of the low-polarity (green circle) and high-polarity (red circle) forms of selected switchable-polarity solvents, compared to the polarity of an equal volume mixture of liquid **4** and water in the presence of CO_2 (red square) and in the absence of CO_2 after the water has been largely expelled (green square). TMBG = 1,1,3,3-tetramethyl-2-butylguanidine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Bn = benzyl.

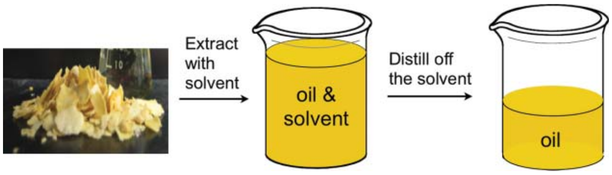


Fig. 4 The current industrial process for obtaining soybean oil involves extracting the oil from soybean flakes (flattened soybeans) with hexane and then removing the hexane by distillation. The process causes significant vapour emissions of hexane, which contribute to smog formation. Hexane is also a neurotoxin.[13]

Soybean processing is an industrial process that uses distillation to remove a volatile low-polarity solvent from a low-polarity product. In the process, soybeans are cracked, de-hulled and flattened into flakes or extruded into collets. Soybean oil is extracted with hexane, which is then removed by distillation to leave the pure oil (Fig. 4).[11,12] Because of the vapor emissions, neurotoxicity, and the risk of fire and explosion due to the large-scale use of hexane, the use of a non-volatile solvent (and therefore a non-distillative route for solvent removal) would be preferable. We performed a preliminary evaluation of an SHS for this application.

Switchable hydrophilicity solvents make it possible to extract soybean oil from soybeans, and then to separate the solvent from the extracted oil, without using a volatile organic compound. The proposed process is illustrated in Fig. 5. First, the oil would be extracted from the flakes using the SHS in its hydrophobic form. Then, the SHS would be extracted from the oil using carbonated water, which would convert the solvent to its hydrophilic form. Flushing air through the SHS/water mixture would then separate it into the two components, which would then be re-used. For practical purposes, if a portion of the SHS remained in the aqueous phase, this would not be considered a significant problem because the aqueous phase would be re-used. However, if a portion of the SHS remained in the oil, then that would be more problematic, because it would represent the loss of some SHS and the contamination of the product oil.

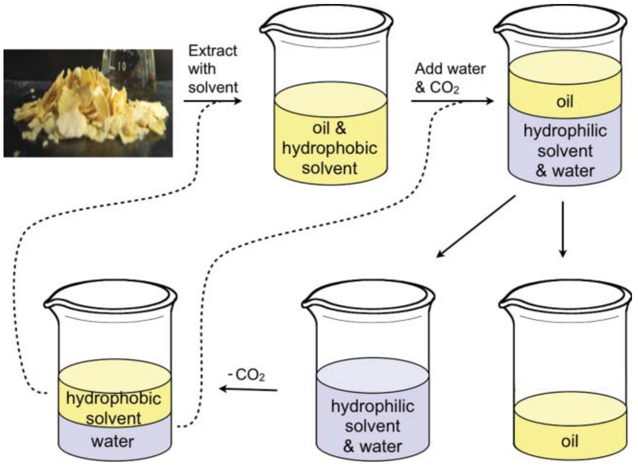


Fig. 5 The process by which an SHS can be used to extract soybean oil from soybean flakes without a distillation step. The dashed lines indicate the recycling of the solvent and the aqueous phase.

The ability of compound **4**, in its hydrophobic form, to extract soy oil from soybean flakes was compared to the ability of hexane. The solvent (500 mg) and flakes (100 mg) were stirred overnight and then filtered. The amount of extracted oil in the filtrate, determined by ^{1}H NMR spectroscopy, was the same (8.8 mg) for both solvents, within experimental error.

To confirm that switching of the solvent can help remove the solvent from soy oil, we added D_2O to a mixture of **4** and soybean oil (D_2O : **4** : oil 2 : 1 : 1 by volume). After thorough mixing, two liquid phases of equal volume were visible. ^1H NMR spectroscopy of each layer showed that the upper phase was primarily soybean oil and **4** (Fig. 6, centre spectrum), while the lower phase was primarily D_2O. CO_2 was bubbled through the system for 1.5 h, after which time the top layer appeared to halve in volume. ^1H NMR spectroscopy, using the peak for **4** at 3.17 ppm, showed that 96% of the amidine had been removed from the soybean oil (Fig. 6, lower spectrum). This was achieved with only one wash with carbonated water; higher levels of removal would be expected with further washes and/or treatment with silica. The removal of **4** from the water was then performed as described above, demonstrating that this switchable hydrophilicity solvent can be used for the extraction of soy oil, that it can be removed from the soy oil with carbonated water and that it can be recovered from the water for re-use. The soybean oil was not changed in colour by this overall process.

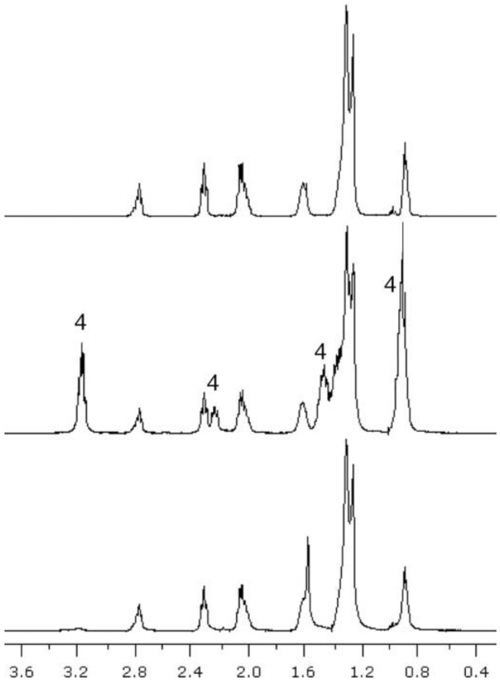


Fig. 6 ^1H NMR spectra ($CDCl_3$) of pure soybean oil (top), soybean oil and **4** (middle) and soybean oil after the removal of **4** by carbonated water (bottom). Peaks corresponding to compound **4** are indicated.

For the soybean application, where the solid materials (the flakes after the oil has been extracted) are used rather than discarded, the removal of residual solvent from the solid materials is also important. For other applications, the solid materials would not be used. We have not yet addressed this issue in our research. Another area of future research is a comparison of the energy cost for this process compared to that for a conventional distillation-based process.

Persistence, bioaccumulation and stability of a solvent are significant practical concerns. For industrial application, especially for repeated re-use, the solvent must be stable. Alkylamidines have been shown to be stable in acidic aqueous solution[14] because hydroxide attack on the amidinium cation is the primary mechanism for hydrolytic degradation.[15] Therefore, we anticipate no significant degradation of the amidine while it is dissolved in CO_2-saturated water. Because it separates out of the water once the CO_2 has been removed, hydrolysis of the amidine at that stage is also not anticipated to be a problem, although small losses are inevitable. If this technology were to be adopted industrially, mechanisms for monitoring amide levels and for removing amide would be necessary.

If the amidine is stable and has a very high log K_{ow} value, then persistence and bioaccumulation in the environment are serious concerns. Fortunately, if some of the amidine were to escape into surface waters, then it would hydrolytically degrade because the pH of surface water (typically 6.0 to 8.5)[16] is typically much higher than the pH of CO_2-saturated water (3.9). The two amide products that would form from hydrolysis of compound **4** are *N*-butyl pentanamide (predicted log $K_{ow} = 2.3$) and *N*,*N*-dibutyl pentanamide (3.9). Neither of these amides are sufficiently hydrophobic to pose serious bioaccumulation risks.

Experimental methods

General

Chemicals were used as received, except as noted. Compounds **1** and **5** were obtained commercially. The synthesis and characterization of the other amidines and guanidines are described in the ESI material.† Compressed gasses were obtained from Praxair: 4.0 grade CO_2 (99.99%) and 5.0 grade Ar (99.999%).

TLC was carried out on aluminium-backed silica gel 60 F_{524} from ELD. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were collected at 300 K on a Brucker AV-400 spectrometer at 400.3 and 100.7 MHz, respectively. IR spectra were collected on a Nicolet Avatar 360 FT-IR E.S.P. instrument between potassium bromide plates.

Prediction of log K_{ow} values

log K_{ow} values were predicted using ALOGPS 2.1 software,[17–19] which calculates the log K_{ow} value for a given structure using nine different algorithms and then averages these values.

Measuring the miscibility of guanidines in water

To determine the miscibility of guanidines in water, ^1H NMR experiments were performed. The guanidine (0.5 mL) and heavy water (0.75 mL) were stirred vigorously together for 30 min. The two phases were separated and 200 µL of the aqueous solution, 10 µL of 1,4-dioxane and approximately 200 µL of additional D_2O were injected into an NMR tube. Solubilities were calculated from the ^1H NMR spectrum by comparing the signal of the terminal methyl group of the alkyl chain located at the 2-position of the guanidine with the singlet signal of the 1,4-dioxane protons at δ 3.75.

Evaluating the switching of guanidines

CO_2 at 1 bar was bubbled through a stirred mixture of guanidine (0.5 mL) and D_2O (0.75 mL) using a cannula. For testing the reversion to the hydrophobic form, argon was bubbled through the solution with vigorous stirring using a cannula. As this method did not cause a phase split, the method was revised to introduce the argon from below the solution *via* a glass frit, again without a phase split being observed.

Evaluating the switching of amidine 4

A methanol-d_4 solution was prepared containing a sodium acetate internal standard (48.8 mM) for use as the NMR solvent.

Two 4 mL glass vials containing 1.0 mL D_2O and 0.5 mL **4** were prepared and shaken. A 50 µL sample was withdrawn from each layer of one vial and combined with 0.50 mL of the sodium acetate standard solution in each of two NMR tubes: the top layer (**4**) in tube A; the bottom layer (aqueous) in tube B.

CO_2 was bubbled through the unsampled vial until **4** had completely converted to the corresponding bicarbonate, as evidenced by the disappearance of the top layer. The pH of the solution was measured using pH paper to be approximately 8–9. A 50 µL sample was withdrawn from the aqueous solution and added to 0.50 mL of the sodium acetate standard solution in NMR tube C.

The 4.0 mL vial, from which sample C was withdrawn, was then heated at 80 °C for 1 h, stirred by a magnetic stirrer. Bubbles of CO_2 were observed escaping from the solution as a top layer, of hydrophobic amidine, appeared. After cooling the vial to room temperature, a 50 µL sample was withdrawn from each layer and combined with 0.50 mL of the sodium acetate standard in two NMR tubes: the top layer (**4**) in tube D; the bottom layer (aqueous) in tube E.

The NMR spectra of all five samples are shown in Fig. 3.

Nile red measurements

To measure the λ_{max} of the solvatochromic dye Nile Red dissolved in water-saturated **4**, 1 mL of **4** was added to a 1 dram vial containing 1 mL of distilled water. The contents were stirred at room temperature for 1 h under air. The top phase (water-saturated **4**) was pipetted into a quartz cuvette and 1 mg of Nile Red was added. The colour at this stage was bright orange-magenta ($\lambda_{max} = 510$ nm). Distilled water (1 mL) was then added to the cuvette and CO_2 slowly bubbled into the mixture for 1 h, after which the homogenous mixture turned purple ($\lambda_{max} =$ 570 nm).

Extraction of soybean oil from soybean flakes

Soy flakes (100 mg) were stirred for 18 h in a sealed 3 dram vial containing 500 mg solvent (either hexane or compound **4**). The mixture was filtered and 0.1 mL of the filtrate was analyzed by ^{1}H NMR spectroscopy with 0.1 mL ethanol as internal standard.

Separation of soybean oil from SHS

A 4 mL vial was prepared containing 1.0 mL D_2O, 0.5 mL **4** and 0.5 mL soybean oil. The vial was shaken thoroughly and allowed to settle, showing a 1.0 mL upper layer (primarily soybean oil and **4**) and a 1.0 mL lower layer, D_2O. ^{1}H NMR samples (50 µL) were withdrawn from each layer and mixed with methanol-d_4 (0.5 mL) containing a dioxane internal standard (51.5 mM). Another sample was withdrawn from the upper layer for analysis by ^{1}H NMR spectroscopy in $CDCl_3$, because soybean oil is not miscible with methanol. The same volume was discarded from the bottom layer to maintain the initial ratio.

CO_2 was bubbled through the system for 1.5 h, after which time the top layer appeared to have halved in volume. ^{1}H NMR spectra were again acquired for both layers in methanol-d_4 and for the top layer in $CDCl_3$.

A 1.0 mL portion of the bottom layer was withdrawn and transferred to a new 4.0 mL vial. A magnetic stirrer was added and the vial stirred at 80 °C for 1 h. Samples were withdrawn from both layers for ^{1}H NMR spectroscopy analysis in methanol-d_4 with reference to the dioxane internal standard.

Conclusions

A switchable-hydrophilicity solvent (SHS), meaning a solvent that can reversibly switch from having poor miscibility with water to having very good miscibility with water, has been identified. CO_2 at atmospheric pressure, is used to switch the solvent to its hydrophilic form, and air and/or heat can be used to switch it back again. This solvent can be used to extract and isolate organic materials, such as soybean oil, without the need for a distillation step. Because distillation is not required, there is no longer a need to use a volatile organic solvent.

Future work, already under way, includes a search for more examples, a more detailed phase behaviour study and thereby the development of solvent design principles for maximizing the quality of the separations.

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