Technical Notes

Removal of Reaction Solvent by Extractive Workup: Survey of Water and Solvent Co-extraction in Various Systems

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Abstract:
In some chemical processes, extractive workup is used to remove the solvent of reaction in an aqueous layer and to isolate the product in the organic layer. Most of the time some reaction solvent is co-extracted in the organic layer, along with some water. This has a non-negligible impact on subsequent operations (washing, crystallization), and we have thus determined those levels for ten reaction solvents and five extraction solvents in order to help the process chemist in the development of efficient isolation procedures.

Over the years, progress in organic chemistry has brought to the process chemist more and more synthetic methods, requiring sometimes specific solvents as reaction media. Among the solvents available for process chemists, dipolar aprotic solvents (DAS) are commonly used in substitution reactions (S_NAr, S_N1, S_N2) and potentially in all other reactions where an organic substrate and a mineral reagent have to be simultaneously dissolved.[1] Despite their exceptional effects on the reactivity of the dissolved species, the DAS present a main hurdle to their use: they are difficult to remove when one wants to isolate the product of the reaction. Indeed, DAS are characterized by high boiling points and are thus difficult to distill off. On the other hand, removal of a crystalline product by filtration is also difficult, given the high solvency of the DAS. The most common procedure is thus to remove the DAS by selective extraction of the reaction solvent with water and, simultaneously, of the product with a suitable water-immiscible extraction solvent. Unfortunately, the selectivity of extraction is usually not sufficient, and there will always be small amounts of DAS and water co-extracted in the extraction solvent. Those amounts depend on the nature of the species present in the extraction mixture. The equilibrium concentrations of water and DAS in the organic solvent layer give very useful information for the selection of the best extraction system. However, very little is known about those concentrations, and we have thus decided to build our own data set in order

Table 1. **Selected reaction solvents and extraction solvents**

#	reaction solvent	extraction solvent	aqueous solvent
1	DMSO	toluene	H_2O
2	DMF	AcOEt	$NaCl/H_2O$ (10 cg/g)
3	NMP	AcOiPr	
4	DMAc	1-chlorobutane	
5	TMU[a]	heptanes (isomers mix)	
6	DMI[b]		
7	THF		
8	1,4-dioxane		
9	diglyme		
10	acetonitrile		

[a] TMU = tetramethylurea. [b] DMI = 1,3-dimethylimidazolidin-2-one.

to support the development of workup procedures for future projects in our chemistry laboratories.

We have here surveyed ten reaction solvents (dipolar and less dipolar aprotic solvents) and five extraction solvents (Table 1). These solvents have been selected on the basis of the frequency of their use in process development, taking into account HSE and cost considerations. In the real world, the aqueous layer would contain dissolved salts, bases, or acids that are used during the reaction. In order to assess the effect of such solutes on the distribution of the DAS two aqueous systems were considered: water and a 10% solution of NaCl. On the other hand, the organic layer will contain organic solutes such as the reaction product itself. This might also affect distribution of the DAS. However, this is by essence a case-by-case phenomenon, and it will therefore not be evaluated in this study.

Results and Discussion

We have brought to thermodynamic equilibrium at 23 °C equal amounts by volume of water or NaCl/water (10 cg/g), the extraction solvent and the reaction solvent (Table 1). One hundred (10 × 5 × 2) ternary solvent systems have been prepared, and for each of them, the residual water content in the organic layer was determined by Karl Fischer titration, and the amount of reaction solvent in the organic layer, by gas chromatography[2] (GC) using a flame-ionization detector (FID). These values, combined with measurements of the

(1) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003. Loupy, A.; Haudrechy, A. *Effets de Milieu en Synthèse Organique*; Masson: Paris, 1996.

(2) Method derived from: Jacobs, P.; Dewé, W.; Flament, A.; Gibella, M.; Ceccato, A. *J. Pharm. Biomed. Anal.* **2006**, *40*, 294−304.
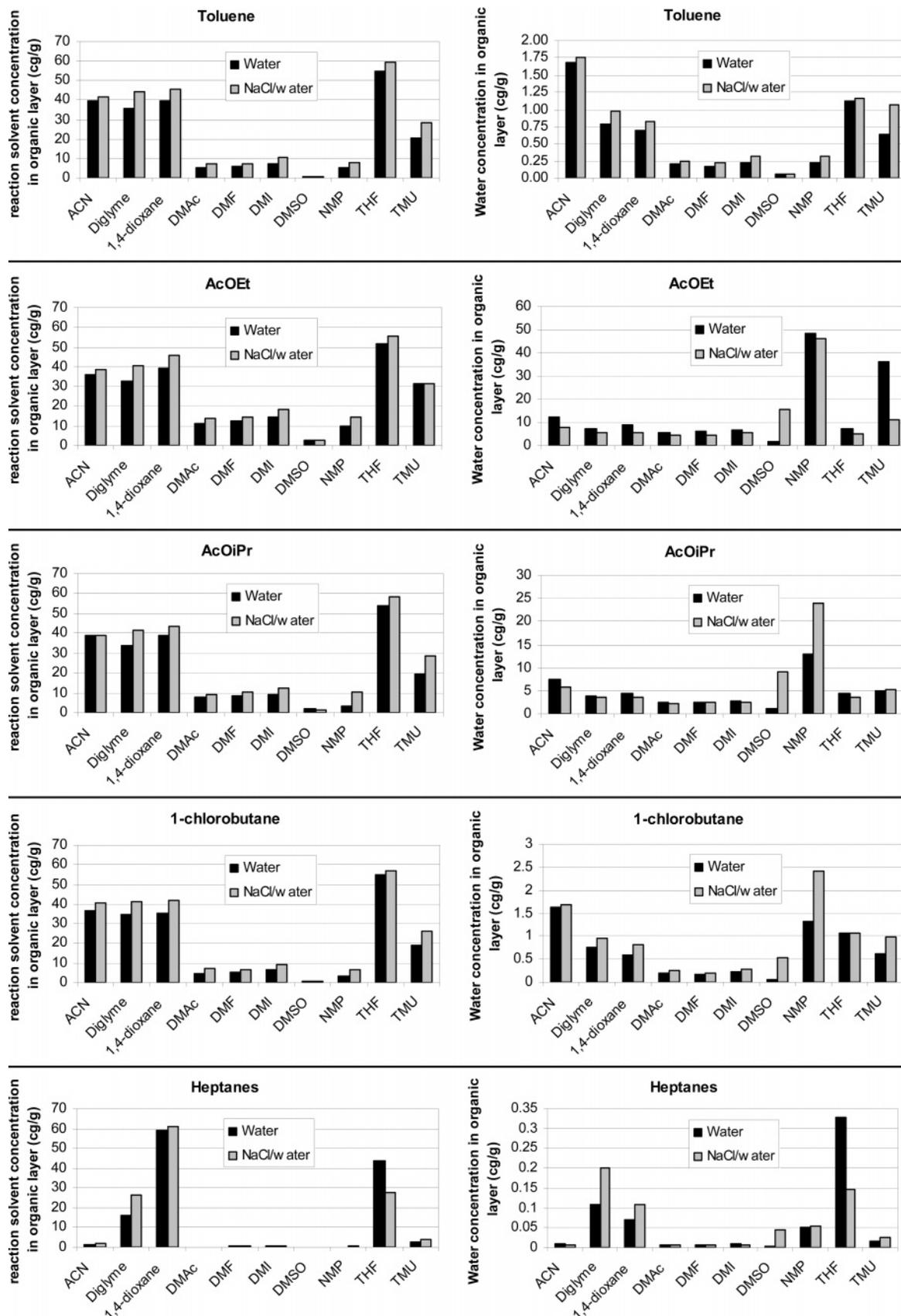
Figure 1. Concentrations of extracted water and reaction solvent in the organic layers (in cg/g), ordered by extraction solvent.

volumes of the layers and the densities of the organic layers, gave us access to the distribution constants (pK_d) of water or reaction solvent, which are indeed distributed between

the organic layer and an aqueous layer consisting of water, reaction solvent, and in some cases, significant amounts of extraction solvent. The results are shown in Figure 1. A
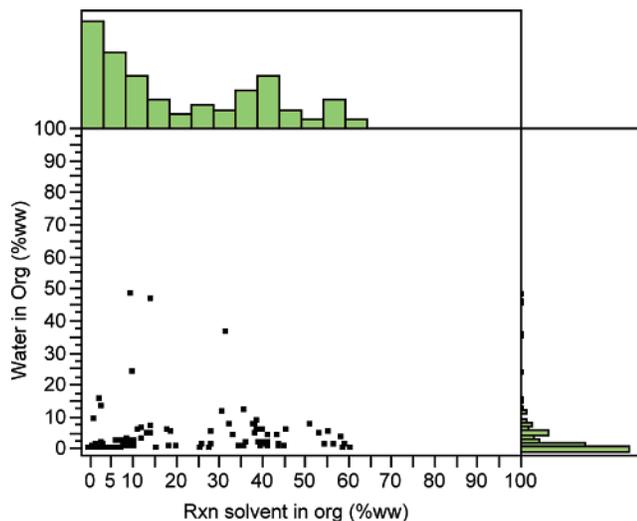
Figure 2. Distribution of results.

complete table with all results is available as Supporting Information. In addition, we provide below a general characterization of the data set and some comments.

Distribution of Data. The first characteristic of our data set is the high concentrations of water and reaction solvent found in some extraction layers (Figure 2). Indeed, in some cases, up to 60 cg/g of reaction solvent can be extracted. In other cases, we observed up to 50 cg/g of co-extracted water. This means that the major constituent of the upper organic layer can be water and/or the reaction solvent, and not the extraction solvent itself. The workup method envisaged here is thus not general. The second characteristic is the absence of correlation between the concentrations of water and those of the reaction solvent: a high concentration of reaction solvent does not necessarily mean a high concentration of water, and reversely.

In contrast, there is a correlation between the pK_d of water and the pK_d of the reaction solvents. As shown in Figure 3, there are two categories of reaction solvents: the ethers and the non-ethers (more polar solvents). Ethers display pK_d's of water that do not vary a lot with the pK_d's of the reaction solvent, and non-ethers display pK_d's of water that increase with pK_d's of the reaction solvent. Interestingly, for a given pK_d of the reaction solvent, the pK_d of water depends on the extraction solvent. This leads us to classify the extraction solvents into three categories following their affinity for water: the esters (AcOEt, AcOiPr), then toluene and 1-chlorobutane, and finally, the heptanes.

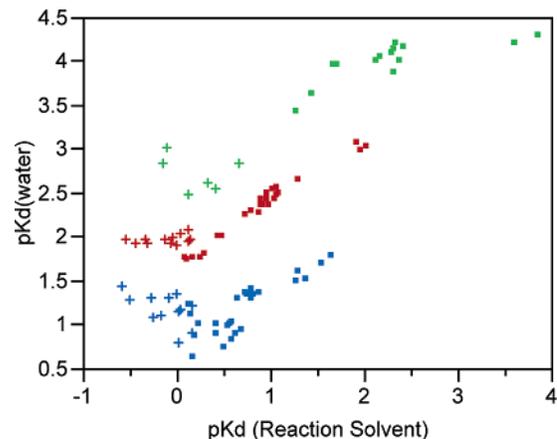Even though this workup method is not general, it is still useful for cases where it is efficient. Table 2 displays the combinations of reaction and extraction solvents that satisfy or not the threshold values of 10 cg/g of water and 10 cg/g of reaction solvent in the organic layer. Ethereal solvents do not fulfill the criteria because of the reaction solvent threshold (Figure 4). For ethereal solvents such as THF and 1,4-dioxane, this is not a problem, provided the product of reaction is not volatile. In contrast, diglyme is very prob-

(3) Mosaic Plot: width of a column is proportional to presence of the extraction solvent in the data set. Relative height of the rectangle in the extreme right scale reflects the presence of each reaction solvent in the data set.

Figure 3. Bivariate plot of distribution constants (pK_d) of water and reaction solvents between both layers. Reaction solvents are ordered by shape, and extraction solvents, by color. (+) Ethereal solvents. (dots) Other reaction solvents. (Blue) AcOEt and AcOiPr. (Red) Toluene and 1-chlorobutane. (Green) Heptanes.

Table 2. Combinations of reaction and extraction solvents affording water and reaction solvent concentrations in organic layer both below 10 cg/g (√); (×) one or both of the measures are above 10 cg/g (mixtures with pure water as aqueous solvent)

	toluene	AcOEt	AcOiPr	1-chlorobutane	heptanes
DMSO	√	√	√	√	√
DMF	√	×	√	√	√
NMP	√	×	×	√	√
DMAc	√	×	√	√	√
TMU[a]	×	×	×	×	√
DMI[b]	√	×	√	√	√
THF	×	×	×	×	×
1,4-dioxane	×	×	×	×	×
diglyme	×	×	×	×	×
acetonitrile	×	×	×	×	√

[a] TMU = tetramethylurea. [b] DMI = 1,3-dimethylimidazolidin-2-one.
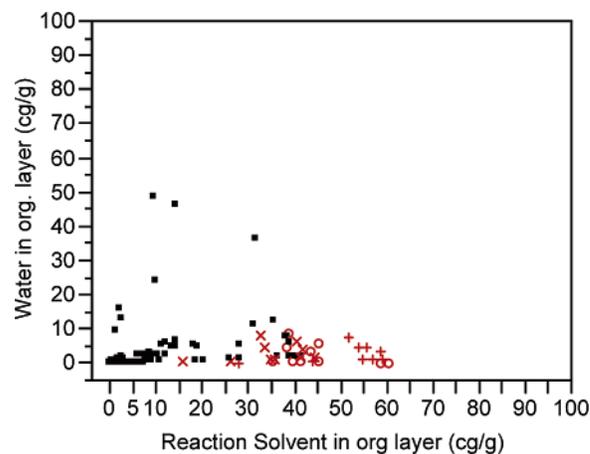
Figure 4. Distribution of results: detail of ether solvents: (+) THF; (○) 1,4-dioxane; (×) diglyme.

lematic, and a crystallization/filtration workup would be preferred. For the other reaction solvents, it is possible to find at least one solvent that would not co-extract more than 10% of solvent, even though ACN and TMU are borderline cases. The situation for extraction solvents can be summarized as following:

• 1-chlorobutane and toluene can be used with each dipolar aprotic solvent, except TMU;

• ethyl acetate can be used only with DMSO;

• isopropyl acetate can be used with each dipolar aprotic solvent, except TMU and NMP;

• heptane mixtures can be used with each dipolar aprotic solvent and acetonitrile (ACN).

Solvent Classification. We fitted a linear first-order model on our data set in order to classify the investigated solvents in terms of their ability to afford low concentrations of co-extracted water and reaction solvent. Interaction (synergetic effect) between extraction and reaction solvents was found to be significant and thus was added to the model.[4]

The amount of co-extracted water is not affected by the salt content in the aqueous layer, but it is influenced by the reaction and the extraction solvents. NMP induces very high levels of water as compared to the other reaction solvents. Reaction solvents cause increases of water concentrations in the organic layers as follows: DMAc, DMF, DMI < diglyme, THF, 1,4-dioxane < DMSO < ACN < TMU ≪ NMP. Not surprisingly, the extraction solvents cause increases of water concentrations in organic layers as follows: heptanes, toluene, 1-chlorobutane < AcOiPr ≪ AcOEt. Noticeable synergetic effects have been emphasized: the combination of NMP and AcOEt should be avoided, as it results in an additional increase of 25 cg/g of co-extracted water as compared to what would have been expected on the basis of the sum of average effects of each of those solvents separately. In contrast, the combination of NMP with toluene results in a concentration of water which is 10 cg/g below the expectations. Other deviations to the average behavior of solvents due to specific combinations of reaction and extraction solvents are less significant.

The amount of co-extracted reaction solvent is slightly increased by the salt content in the aqueous layer. However, this effect is small when compared to the effects of extraction and reaction solvents. DMSO is the reaction solvent which has the lowest affinity for the organic layer. Concentrations of co-extracted reaction solvents in organic layer increase as follows: DMSO < NMP, DMAc, DMF, DMI, TMU < ACN < diglyme < 1,4-dioxane < THF. Heptanes almost do not extract any reaction solvent at all, followed by 1-chlorobutane, then by toluene and AcOiPr with the same selectivities, ethyl acetate affording the highest reaction solvent content. Important synergetic effects are observed for heptanes. Extracted levels are lower than expected with ACN, but higher than expected with 1,4-dioxane. Other deviations to the average behavior of solvents due to specific combinations of reaction and extraction solvents are less significant.

In conclusion, we have built a data set of concentrations of co-extracted water and of ten reaction solvents in five extraction solvents. The average order of efficiency of extraction and reaction solvents has been defined, and deviations from the additivity of effects, both in positive and negative directions, have been emphasized. The data set and its characterization will guide the process chemist in the development of suitable extractive workup procedures, along with the specificity of his process: constraints on acceptable co-extraction levels and compatibility of solvents. Further work could be directed towards evaluating additional extraction solvents as well as evaluating the effect of organic solutes in various concentrations and washings of organic layers with water.

Experimental Section

The chromatographic experiments were carried out using a factor Four VF 624 MS column (60 m × 0.32 mm i.d.) coated with 1.8 μm thickness film of 6% cyanopropylphenyl and 94% dimethylpolysiloxane from Varian Inc. (Palo Alto, CA, U.S.A.). The GC was operated under the following conditions: carrier gas was helium; the inlet pressure was set to 10.0 psi; the injector and detector temperatures were set to 280 and 320 °C, respectively. A 1.0 μL volume was injected using the split mode (ratio 1:10). The column temperature was programmed at 70 °C for 10 min, and then raised to 120 °C at a rate of 40 °C/min. The 120 °C temperature was kept constant for 8 min and then was raised to 300 °C at a rate of 20 °C/min. GC determinations were performed using an external calibration. For each experiment and for each solvent, a standard calibration curve was established and was used to perform the assay of the solvent of interest.

Experimental Procedure. Into a 25-mL graduated cylinder with a stirring magnet was placed 8 mL of the aqueous layer, the total volume was measured, and the volume of the magnet was deducted. The reaction solvent (8 mL) and the extraction solvent (8 mL) were added under stirring. After thermostatization to 23 °C (45 min in bath with stirring), stirring was stopped, and volumes of both layers (V_{aq}, V_{org}) were measured. The organic layer was sampled for GC assay (A_{rs}), Karl Fischer analysis (A_w), and determination of density (ρ_{org}). Calculations are performed as follows:

NOMENCLATURE

Symbols (units)

m	mass (g)
V	volume (mL)
A	assay result (GC or KF) - (cg/g)
C	concentration (cg/mL)
r	density (g/mL)

Subscripts

tot	refers to the three species together
w	refers to water
NaCl	refers to NaCl/water
es	refers to extraction solvent
rs	refers to reaction solvent
org	refers to organic (upper) layer
aq	refers to aqueous (lower) layer

water	NaCl/water (10 cg/g)
$m_{tot} = \rho_w V_w + \rho_{es} V_{es} + \rho_{rs} V_{rs}$	$m_{tot} = \rho_{NaCl} V_{NaCl} + \rho_{es} V_{es} + \rho_{rs} V_{rs}$
$m_w = \rho_w V_w$	$m_w = \rho_{NaCl} V_{NaCl}(1 - 0.1)$

(4) See Supporting Information for numerical data and statistical properties of the models.

$$m_{\text{org}} = \rho_{\text{org}} V_{\text{org}}$$

$$m_{\text{aq}} = m_{\text{tot}} - m_{\text{org}}$$

$$\rho_{\text{aq}} = m_{\text{aq}}/V_{\text{aq}}$$

$$C_{\text{rs,org}} = A_{\text{rs}}/\rho_{\text{org}}$$

$$C_{\text{rs,aq}} = [(\rho_{\text{rs}}V_{\text{rs}}) - (m_{\text{org}}A_{\text{rs}})]/V_{\text{aq}}$$

$$C_{\text{w,org}} = A_{\text{w}}/\rho_{\text{org}}$$

$$C_{\text{water,aq}} = (m_{\text{w}} - m_{\text{aq}}A_{\text{w}})/V_{\text{aq}}$$

$$pK_{\text{d}}(\text{reaction solvent}) = -\log(C_{\text{rs,org}}/C_{\text{rs,aq}})$$

$$pK_{\text{d}}(\text{water}) = -\log(C_{\text{w,org}}/C_{\text{w,aq}})$$

Supporting Information Available

Complete data table and first-order regressions results. This material is available free of charge via the Internet at http://pubs.acs.org.