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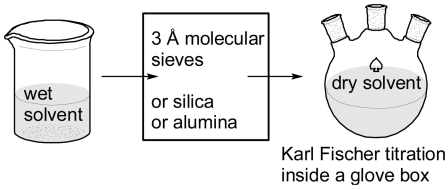
Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants

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Various commonly used organic solvents were dried with several different drying agents. A glovebox-bound coulometric Karl Fischer apparatus with a two-compartment measuring cell was used to determine the efficiency of the drying process. Recommendations are made relating to optimum drying agents/conditions that can be used to rapidly and reliably generate solvents with low residual water content by means of commonly available materials found in most synthesis laboratories. The practical method provides for safer handling and drying of solvents than methods calling for the use of reactive metals, metal hydrides, or solvent distillation.

Introduction

Laboratories involved with synthesis require efficient methods with which to dry organic solvents. Typically, prescribed methods[1] are taken from the literature where little or no quantitative analysis accompanies the recommended drying method. Frequently, such methods call for the use of highly reactive metals (such as sodium) or metal hydrides, which increases the risk of fires or explosions in the laboratory. This situation is aggravated by hot solvents that are present during the distillation process that removes the solvent from the desiccant. While many laboratories employ relatively expensive commercially available drying trains that use filled cartridges to dry solvents (these systems appear to be largely based on the pioneering work of Grubbs[2] in this context), a large number of laboratories do not have access to such facilities. Accordingly, users of the published drying methods rely upon procedures that generally have little or no quantified basis of application and generate samples of unknown water content. In a rather elegant exception, Burfield and co-workers published a series of papers[3] some three decades ago in which the efficacy of several drying agents was investigated making use of tritiated water-doped solvents. The drying process was followed by scintillation readings, and several shortcomings were noted in "standard" drying practices. Despite this rather extensive analysis, many of the methods identified as inept are still in use today.

In altogether a different context, we required solvents that were reliably dried to levels of water in the sub-10 ppm range in order to test some principles of Lewis acid catalysis.[4] Since even the notable work of Burfield did not give the information needed to prepare super dry solvents required for our earlier study, we investigated the drying of several solvents as followed by coulometric Karl Fischer titrations. The titrator instrument was housed inside a glovebox for ultimate analytical sensitivity and instrument stability. While several other methods[3,5]

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have been developed for water determination in solvents, advances to the design and sensitivity of particularly coulometric Karl Fischer titrators since Burfield's day now allow accurate measurements of water in organic solvents at the ppm level.[6] The objective of the present study was not to comprehensively cover a wide cross section of drying agents (Burfield and co-workers have already adequately performed this task, highlighting problem areas in the process, particularly in their seminal paper on the topic[3b]) but to generate sufficient data to allow a practical, safe, and easy-to-reproduce approach to drying several common solvents to be recommended for everyday use.

Results and Discussion

For this study, tetrahydrofuran (THF), toluene, dichloromethane (DCM), acetonitrile, methanol, and ethanol were employed. Initially, the water content of the "wet" solvents (i.e., as obtained from commercial sources as analytical reagent-grade or HPLC-grade solvents) was measured. Accordingly, samples of about 3.0 mL (the exact amount added was accurately determined by weighing the filled syringe on a three decimal balance inside the glovebox and also the empty syringe after injecting the sample into the cell and calculating the difference) were injected into the anode compartment of the measuring cell of the Karl Fischer apparatus ($n = 6$ per sample). Where moisture content was very low for acetonitrile (see below, Table 4), larger sample sizes (of 10.0 mL) were employed as a countercheck to ensure accuracy. However, this approach results in very inefficient use of the Hydranal solution used for the Karl Fischer titration and also of rapid filling of the anode compartment of the measuring cell. It was therefore not followed as a matter of course since the accuracy was found to be the same for the different sample sizes. Samples of solvents removed directly from the bottles as received were analyzed: these data are used as a measure against which to judge the success of a given drying agent for a selected solvent. When the solvents were dried, drying was performed in triplicate. Each dried sample was analyzed six times to provide statistically acceptable precision data.

Tetrahydrofuran

THF is one of the mainstay solvents in synthesis laboratories. It is often predried over KOH pellets after which it is dried by heating under reflux over sodium wire in the presence of benzophenone as indicator.[1] Under these conditions, THF was found to be dried to approximately 43 ppm water content (Table 1). Matters significantly improve by simply allowing the solvent to stand over activated 3 Å molecular sieves (Table 1). Here, a 20% mass/volume (m/v) loading of the desiccant allows low ppm levels to be achieved after 48 h. Lower mass loadings also give good results but take significantly longer (about 5 days) to achieve single digit ppm levels of residual moisture. Several types of silica were assessed for their desiccating ability, including standard silica (70−230 mesh) typically employed in gravity column chromatography. Silica of some description is readily available in most synthesis laboratories making it an obvious target as a desiccant. There was essentially no correlation between pore size and drying efficiency with the various silicas used. A much stronger linear correlation was noted in respect of particle size, with finer particles given superior drying efficiencies in a given period of time (Figure 1; single passage of the solvent over a column of the silica, 10% m/v). While silica was reasonably good as a desiccant, neutral alumina was much better, rivaling the ultimate efficiency of molecular sieves after a single pass of the THF over a column of the activated alumina. For rapid drying, neutral alumina is the drying agent of choice, followed by storage over 3 Å molecular sieves if storage is necessary. Otherwise, simple storage over 3 Å molecular sieves provides THF with very low water content within 48−72 h. While THF may be polymerized to some extent upon standing with strongly Lewis/Brønsted acidic materials, this was not found to be problematic in the present instance given the short residence time of the THF on the alumina: samples of THF that had been passed over the alumina were evaporated to dryness with no significant residue remaining.

TABLE 1. Water Content in THF after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		107.8 ± 0.7
sodium/benzophenone[b]	48	43.4 ± 0.7
3 Å molecular sieves (10% m/v)	24	27.7 ± 1.0
3 Å molecular sieves (20% m/v)	24	14.7 ± 0.3
3 Å molecular sieves (20% m/v)	48	6.1 ± 0.2
3 Å molecular sieves (20% m/v)	72	4.1 ± 0.1
silica (28−200 mesh)[c,d]	*c*	56.2 ± 2.5
silica (35−60 mesh)[c,e]	*c*	105.7 ± 3.5
silica (60−100 mesh)[c,e]	*c*	89.4 ± 2.8
silica (70−230 mesh)[c,e]	*c*	82.5 ± 1.2
silica (100−200 mesh)[c,e]	*c*	74.6 ± 2.9
silica (200−425 mesh)[c,e]	*c*	59.5 ± 3.7
silica (100−200 mesh)[c,f]	*c*	69.0 ± 3.3
silica (200−425 mesh)[c,f]	*c*	60.8 ± 1.9
neutral alumina[c]	*c*	5.9 ± 0.4

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]THF was distilled from the desiccant once the indicator had turned a persistent blue color. [c]Solvent was passed over a column of the desiccant, 10% m/v, inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant. [d]Silica (pore size 22 Å). [e]Silica (pore size 60 Å). [f]Silica (pore size 100 Å).

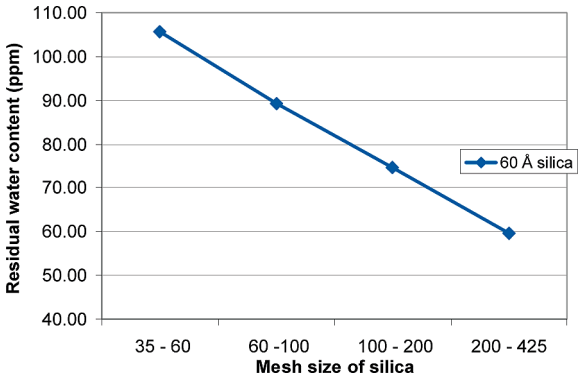


FIGURE 1. Linear dependency of the drying efficiency by columns of 60 Å silica (10% m/v) of THF with respect to silica particle size (data taken from Table 1).

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TABLE 2. Water Content in Toluene after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		224.9 ± 1.3
Sodium/benzophenone[b]	48	31.4 ± 1.9
3 Å molecular sieves (10% m/v)	24	0.9 ± 0.3
silica (10% m/v)[c]	*c*	2.1 ± 0.2

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]Toluene was distilled from the desiccant once the indicator had turned a persistent blue color. [c]Solvent was passed over a column of silica (pore size 22 Å, 28−200 mesh) inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

TABLE 3. Water Content in DCM after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		22.4 ± 1.2
CaH_2[b]	24	12.9 ± 1.3
3 Å molecular sieves (10% m/v)	24	0.1 ± 0.1
silica (10% m/v)[c]	*c*	1.3 ± 0.3

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]Dichloromethane was distilled from the desiccant. [c]Solvent was passed over a column of silica (pore size 22 Å, 28−200 mesh) inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

Toluene

Toluene can be predried using $CaCl_2$, CaH_2, or $CaSO_4$ and is most commonly dried by heating over sodium with benzophenone as indicator.[1] Such treatment (Na/benzophenone) reduced the water content from 225 ppm to about 34 ppm in our hands (Table 2). Storage of the "wet" toluene over 3 Å molecular sieves for 24 h or simple passage thereof over a column of silica readily provided "super dry" toluene with a moisture content in the low single digit ppm range. Either of these methods may be conveniently used to rapidly provide dry toluene suitable for the most demanding of reactions.

Dichloromethane

Dichloromethane is relatively easy to dry. It is not particularly hygroscopic, and even commercially available material has a low water content. Heating DCM over CaH_2 appears to be the method of choice for drying this solvent,[1] conditions which provided samples with a moisture content of about 13 ppm (Table 3). In contrast, simple storage of the solvent over activated 3 Å molecular sieves or passage thereof over a column of activated silica provided significantly drier material with very low water content in the single digit ppm range.

Acetonitrile

Acetonitrile is a polar, aprotic solvent with high solvating ability. It has a high affinity for water and can be difficult to dry.[1] Burfield[3b] found that P_2O_5 was particularly efficient at removing water from acetonitrile, where a desiccant loading of 5% (w/v) with 24 h of static drying leaves a residual water content of 9 ppm. In our hands, as was found for THF as described above, treatment of acetonitrile with 3 Å molecular sieves or neutral alumina readily gave solvent with very low residual moisture content (Table 4). Again, passage over neutral alumina followed by storage over 3 Å molecular sieves is a highly desirable method to rapidly and confidently

TABLE 4. Water Content in Acetonitrile after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		142.0 ± 1.2
3 Å molecular sieves (5% m/v)	24	4.0 ± 0.7
	48	1.8 ± 0.5
	72	< dl[b,c]
3 Å molecular sieves (10% m/v)	24	0.5 ± 0.4 (0.7 ± 0.1)[d]
	48	< dl[b,c]
activated neutral alumina (10% m/v)[e]	—[e]	5.9 ± 0.4

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]For 2.6 and 8.7 g sample sizes (3.0 and 10.0 mL). [c] < dl = below detection limit of the Karl Fischer instrument. [d]10.0 mL sample sizes (instead of the customary 3.0 mL) of the solvent gave the results in parentheses. [e]Solvent was passed over a column of alumina inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

TABLE 5. Water Content in Methanol after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		175.1 ± 0.4
KOH powder (10% m/v)[b]	24	33.1 ± 0.9
Mg/I_2 (0.5 g Mg/L)[b]		53.6 ± 0.6
3 Å molecular sieves (5% m/v)	24	77.3 ± 0.7
	48	46.8 ± 0.6
	72	34.2 ± 0.4
	120	26.5 ± 1.1
3 Å molecular sieves (10% m/v)	24	40.6 ± 0.6
	48	29.4 ± 0.8
	72	20.1 ± 0.6
	120	18.2 ± 0.9
3 Å molecular sieves (20% m/v)	24	28.1 ± 0.4
	48	23.1 ± 0.6
	72	19.2 ± 0.6
	120	10.5 ± 0.9

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]Methanol was distilled from the desiccant once the magnesium had been consumed.

secure access to dry acetonitrile. The reliability of the method was checked by making use of a larger sample size, namely 10.0 mL of the solvent for samples dried over 3 Å molecular sieves (10% m/v) for 24 h, providing essentially identical results to those derived from the smaller (3.0 mL) sample sizes.

Methanol and Ethanol

Lower alcohols are typically dried by heating over iodine-activated magnesium with a magnesium loading of 0.5−5.0 g/L.[1] Several other desiccants, including KOH, BaO, and CaO,[1,3] have also been recommended. KOH and Mg/I_2 are found to provide methanol with a water content of 33 and 54 ppm, respectively (Table 5). Molecular sieves (3 Å) were efficient at drying this solvent only when present at a loading of 10% m/v or higher and when the solvent was left to stand over the sieves for a minimum period of 72 h. Optimum drying is obtained with storage of the methanol over 20% m/v 3 Å molecular sieves for 5 days, by which time the water content reduces to about 10 ppm.

Ethanol behaved similarly, requiring a minimum of 10% m/v of activated 3 Å molecular sieves before efficient drying is noted, optimally also after a period of 5 days over 10% or 20% m/v of the sieves, under nitrogen (Table 6). Powdered KOH proved a rather active desiccant for methanol, and ethanol and may be used in a predrying step prior to storage

TABLE 6. Water Content in Ethanol after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		1428.3 ± 3.8
KOH powder (10% m/v)[b]	24	26.4 ± 0.6
3 Å molecular sieves (5% m/v)	24	262.6 ± 2.0
	48	106.5 ± 0.7
	72	55.1 ± 0.9
	120	14.5 ± 0.4
3 Å molecular sieves (10% m/v)	24	186.1 ± 0.9
	48	69.5 ± 0.6
	72	36.9 ± 1.0
	120	12.3 ± 0.9
3 Å molecular sieves (20% m/v)	24	119.8 ± 0.7
	48	25.0 ± 0.7
	72	20.5 ± 0.5
	120	8.2 ± 0.4

[a]Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b]Ethanol was distilled from the desiccant.

over activated 3 Å molecular sieves to provide ultimate drying efficiency.

Conclusions

This work shows that the use of activated 3 Å molecular sieves, silica, or alumina readily and reliably provides dry solvents with residual moisture in the sub-10 ppm range. The method is practical, requires no special apparatus (apart from a column within which to house the silica or alumina and a two-necked flask for collecting the solvent under inert atmosphere using standard Schlenk techniques), and provides a safe method that does not make use of highly reactive materials such as sodium or metal hydrides. The developments here clearly indicate that laboratories currently making use of such methods could consider terminating such practices in favor of the safer methods detailed here which are, in the event, more efficient at drying solvents. **[CAUTION!** We did not test for the removal of peroxides from solvents such as tetrahydrofuran, so the usual precautions should be followed (such as testing for the presence of peroxides or performing a chemical quench of these reactive species[1]) with solvents for which the presence of peroxides may be an issue. For a discussion on the removal of peroxides, including the use of chemical and absorptive methods (with alumina and zeolites), the reader is advised to consult ref 7].

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Experimental Section

Analytical reagent- or HPLC-grade solvents were obtained from commercial sources and used as is or were dried using the various methods described herein. Desiccants (3 Å molecular sieves, various silicas, neutral alumina) were obtained from commercial suppliers and were predried at 300 °C for 24 h immediately before use. Solvents were dried either by allowing them to stand over the desiccant under nitrogen or by passing the solvent over a column of the desiccant as specified, inside the glovebox. Each solvent was dried in triplicate. Each dried solvent was analyzed six times, providing $n = 18$ per solvent per desiccant. A coulometric Karl Fischer titrator fitted with a diaphragm cell (this setup is preferred for low-level moisture determinations) was used inside a glovebox under nitrogen (< 1 ppm oxygen, < 1 ppm moisture). Each part of the cell (anode and cathode) was charged with the appropriate commercial solution (Hydranal) suited thereto. The titrator was primed by allowing it to equilibrate and stabilize, which removes all residual water from the measuring cell. The accuracy of the titrator was measured against a 100 ppm certified reference material and gave an average reading of 98.3 ± 0.6 ppm water for 4.0 mL sample sizes (the amount of sample added was accurately determined by weighing the filled syringe and the empty syringe after injection of the sample, using a three decimal balance inside the glovebox) of the reference material, well within acceptable accuracy and precision ranges.

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