

Acetone–Heptane as a Solvent System for Combining Chromatography on Silica Gel with Solvent Recycling

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Supporting Information

ABSTRACT: Solvents used in chromatographic purification of intermediates and products are a major source of waste and expense in synthetic research and synthetic processes. The ethyl acetate–hexane mixtures most commonly used for flash chromatography on silica gel are not readily separable by distillation due to their similar boiling points and azeotrope formation. Potential solvents for chromatography that are more amenable to separation and recovery by distillation were thus explored. Acetone–heptane mixtures were found to be convenient and sufficiently separable for routine use and recovery for organic separations. The greater eluotropic strength and especially the transparent short-wavelength UV window of acetone provide additional advantages over the commonly used ethyl acetate. The recycling of solvents from chromatography can greatly reduce the volume of waste generated by synthetic laboratories while also reducing operating costs.

KEYWORDS: Chromatography, Distillation, Recycling, Waste Reduction, Acetone, Heptane

flash chromatography



acetone + heptane
acetone-heptane mixture



fractional distillation

Recover
Redistill
Recycle

The reduction or elimination of waste from chemical processes is a central issue in green chemistry initiatives.^{1,2} Perhaps the largest waste stream from laboratories performing synthesis of organic compounds is the solvent used for purification of intermediates and products. These separations are most commonly performed on silica gel by flash column chromatography, in which pressure is used to increase the flow rate.^{3–5} While any of a number of solvents could be used, the common standard is hexane and ethyl acetate combined in a ratio to achieve the desired polarity or eluotropic strength.^{3,4} These mixtures are not readily amenable to recovery of individual solvents by distillation as the components have similar boiling points (69 °C for hexane vs 77 °C for ethyl acetate) and form an azeotrope of about 38% ethyl acetate.⁶ Efforts to separate and recover one or both of the solvents have been reported, including azeotropic distillation with an added entrainer and a process based on enzymatic hydrolysis of the ethyl acetate component.^{7,8} Such strategies, however, are not likely to be practical for routine laboratory use. A simpler solution is to distill and reuse the mixture, adding an additional quantity of one of the solvents as necessary to achieve the desired ratio for a given separation. While this approach has merit, it is somewhat inconvenient with the recent adoption of automated flash chromatography systems that perform gradient elution by the mixing of pure solvents. An evaluation of alternative solvent choices to facilitate separation and reuse of solvents from flash chromatography was thus undertaken.

EXPERIMENTAL SECTION

Automated flash chromatography was performed using acetone–heptane gradients, with primary detection at 210 nm. In purifying compounds exhibiting UV absorbance, eluent not detected at 210 nm was sent directly to waste. The eluent not collected in fractions, discarded fractions, and solvent collected from rotary evaporation of saved fractions were combined for solvent recovery. The recovered solvent mixture was distilled using an automated commercial solvent recycling unit that performs fractional distillation in 19 L batches with a claimed efficiency of 10 theoretical plates. For acetone–heptane mixtures, the solvent distilling from 55° to 77 °C was collected as the acetone fraction and the solvent distilling from 77° to 120 °C was collected as the heptane fraction. For recycling of acetone from glassware washing, the liquid distilling from 50° to 80 °C was collected. Samples from before and after recycling were analyzed by ¹H NMR in CDCl₃. Ratios of acetone to heptane were determined by comparing integration of the acetone peak to both the methylene multiplet and the methyl signal of heptane and were converted to mass percent. ¹H NMR analysis of a 1:1 heptane–acetone mixture was used to confirm the accuracy of this quantitation method under standard spectral acquisition parameters.

RESULTS AND DISCUSSION

The solvent system for chromatography on silica gel should consist of relatively nontoxic and inexpensive/readily available solvents. It should consist of one solvent of very low polarity such as a simple hydrocarbon and a second solvent with

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sufficient polarity for elution of most of the compounds routinely purified in a synthetic laboratory. The solvents should have boiling points that differ sufficiently for separation, while both should have sufficient volatility for ready removal from products by rotary evaporation. Our initial consideration was to replace ethyl acetate with a different polar solvent in combination with hexane. As shown in Table 1, several of the

Table 1. Azeotropes with Hydrocarbon Solvents

solvent A (b.p.)	solvent B	$\epsilon^{\circ}_{(\text{SiO}_2)(\text{B})}^a$	bp (B)	bp (azeotrope)	% B
hexane (69)	acetone	0.47–0.53	56	50	59
hexane	ethyl acetate	0.38–0.48	77	65	38
hexane	ethyl alcohol	–	78	59	21
hexane	isopropanol	0.60	82	63	23
hexane	<i>n</i> -propanol	–	97	66	4
hexane	diethyl ether	0.38–0.43	35	no azeotrope	–
hexane	CH ₂ Cl ₂	0.30–0.32	40	no azeotrope	–
heptane (98)	ethyl acetate	–	77	–	86.5
heptane (98)	acetone	–	56	55.8	89.5
octane (126)	acetone	–	56	no azeotrope	–

^aEluotropic strengths on silica compiled in ref 9. The value for hexane is 0.00–0.01.

obvious solvent choices also form azeotropes with hexane.⁶ In fact, most esters, ketones, and alcohols form azeotropes with most hydrocarbon solvents. Ethyl ether is reported to not form an azeotrope with hexane, though its eluotropic strength on silica gel is less than that of ethyl acetate.^{9,10} Recycling of any ethers, however, is discouraged by at least one manufacturer of solvent recycling units due to the potential explosion hazard from peroxide formation.¹¹ The current analysis was thus performed with the assumption that ethers should be avoided. It would appear that dichloromethane–hexane mixtures might be separable by distillation given the 29° difference in boiling points and the absence of an azeotrope, but the relatively low eluotropic strength of dichloromethane would be expected to greatly limit its general applicability.^{9,10}

From this analysis, we anticipated and later observed that a significant quantity of the higher boiling solvent will inevitably distill with the lower boiling component, a point of certainty if the solvent pair forms an azeotrope. By choosing a pair of solvents with sufficiently different boiling points and a temperature cutoff sufficiently near the boiling point of the higher boiling solvent, the higher boiling fraction is likely to be much more pure. As a small amount of nonpolar diluent in a polar solvent has only a modest effect on its eluting power¹² and the more polar solvent in near pure form is not necessary for elution in most cases, it seemed that some contamination of the polar solvent by the nonpolar partner would be acceptable. In contrast, if the nonpolar solvent contained a significant amount of the more polar solvent, the baseline eluotropic strength of the gradient would be greatly affected, which would be a problem in purification of products of low polarity. Thus, it is preferred that the solvents be chosen such that the polar solvent is the lower boiling of the pair and thereby is the solvent that will have the major contamination by the other after distillation.

With options of mixtures of polar solvents with hexane seemingly limited, alternatives to hexane were considered for

the nonpolar component. Heptane also forms an azeotrope with ethyl acetate, but the azeotropic mixture contains only 13.5% heptane and the boiling points differ by 21°. A mixture of 5 L each of ethyl acetate and heptane was subjected to fractional distillation, with the cutoff between fractions set at 88 °C. Most of the mixture was collected as the lower boiling fraction below the 88 °C cutoff, with only about 1.5 L of higher boiling fraction obtained. The two fractions were analyzed by ¹H NMR. The high boiling heptane fraction contained 10% ethyl acetate (by mass), while the lower boiling ethyl acetate fraction contained about 40% heptane. The low volume of the heptane fraction was especially problematic. The volume could be increased by lowering the temperature cutoff but would result in a quantity of ethyl acetate in the heptane fraction even greater than the already somewhat high 10%. The ethyl acetate–heptane mixture was thus not pursued further.

Acetone–heptane mixtures were explored, the two having boiling points that differ by 42° and forming an azeotrope of 10.5% heptane. A 10 L quantity of a 1:1 mixture of acetone and heptane was subjected to fractional distillation, with 77 °C as the cutoff between fractions. The low boiling acetone fraction (7 L) contained 31% heptane, while the high boiling heptane fraction (3 L) contained 2.7% acetone. These percentages seemed acceptable on the basis of the analysis above. The acetone–heptane mixture was thus adopted as the solvent system of choice, and we began to use it routinely for flash chromatography. In our experience, the recovered solvent typically contains about 30% acetone and upon distillation consistently gives heptane fractions containing <5% acetone, with acetone fractions containing 30–40% heptane. While the percentage of acetone in the heptane fraction is fairly consistent, the heptane percentage in the acetone fraction increases somewhat with a decreasing percentage of acetone in the starting mixture. When traces of ethyl acetate have entered the solvent stream, its concentration in the low-boiling fraction is about 50% greater than in the high-boiling fraction. ¹H NMR spectra of a representative sample of recovered solvent containing ethyl acetate and of the acetone and heptane fractions from fractional distillation are provided in the Supporting Information.

The adoption of acetone–heptane solvent mixtures for chromatography requires some adjustment of solvent ratios relative to the commonly used ethyl acetate–hydrocarbon mixtures due to the greater eluotropic strength of acetone.^{9,10,12} For TLC analysis that mirrors the preparative chromatography, we generally use acetone–pentane mixtures to avoid selective evaporation of acetone from the TLC chamber and resulting changes in polarity. Programming of the elution gradient also requires some consideration of the heptane dilution of the acetone and possibly of the acetone contamination of the heptane for gradients starting at very low acetone. An advantage of the greater eluotropic strength of acetone relative to ethyl acetate is that it compensates for the dilution effect of heptane in the recovered acetone.^{9,10,12}

In comparing acetone–heptane to the traditional ethyl acetate–hexane mixtures, the cost of acetone is generally less than that of ethyl acetate, though the approximate 3-fold greater cost of heptane relative to hexane results in an approximately 2-fold greater overall initial solvent cost. Acetone absorbs strongly at 254 nm, the wavelength routinely used for detection in ethyl acetate mixtures, and is often stated as having a UV cutoff of 300 nm. However, acetone has a window of minimal absorbance from about 205 to 220 nm. We routinely

detect at 210 nm, with the second wavelength of a dual-wavelength detection system set at 310 nm, just above the acetone absorbance. This has the advantage that 210 nm provides detection of a greater range of organic functionality and simpler chromophores relative to detection at 254 nm. This does prevent use of a 254 nm fixed wavelength detector. Use of acetone in purification of primary or secondary amines may be precluded due to imine or enamine formation, a problem not encountered with ethyl acetate.¹³ Evaporation of solvent from collected fractions requires a slightly higher bath temperature relative to ethyl acetate–hexane mixtures, especially for fractions containing minimal acetone, but is not problematic with a reasonably efficient evaporator. Heptane is also considered a more environmentally friendly solvent than hexane due to its lower toxicity and lower volatility and is recommended as a replacement for hexane and pentane, even without recycling considerations.¹⁴ Acetone is a preferred solvent on the basis of its environmental friendliness, though ethyl acetate is as well.¹⁴ Recycling of acetone–heptane mixtures is as simple and convenient as recycling of ethyl acetate–hexane mixtures, with the added advantages of component separation.

2,2,4-Trimethylpentane (isooctane) has an essentially identical boiling point and cost relative to heptane and thus could be an alternative to heptane in conjunction with acetone, with no obvious advantages or disadvantages. Octane in conjunction with acetone could be an alternative if a more complete separation of solvents is important or if a less efficient distillation system is to be used. The disadvantage of octane would be the greater difficulty in solvent evaporation from purified products. Octane is also much more expensive than heptane from sources we have found.

Some representative known compounds that have been purified using the acetone–heptane solvent system are shown in Figure 1.^{15–18} Also shown for each is the percent acetone in

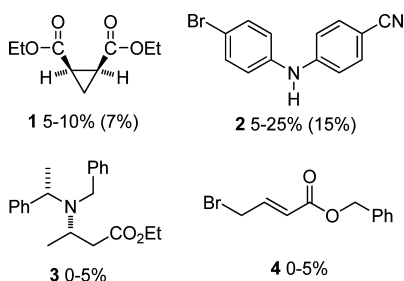


Figure 1. Representative compounds purified using recycled acetone and heptane and the percent acetone in the solvent gradient. Numbers in parentheses are the approximate percent acetone at the point of elution.

the solvent gradient for elution of each compound. Compound 1 is an example of a compound that was detected at 210 nm but could not have been detected by UV absorbance in an ethyl acetate mixture as solvent.

We also perform recycling of acetone used for rinsing of glassware.¹⁹ Solvent boiling below 80 °C is collected to maximize recovery. The collected product contains small amounts of other volatile organic solvents and water but is acceptable for cleaning purposes. The wash acetone stream is kept separate from the chromatography stream for two reasons. First, the generally substantial quantities of water in the wash acetone waste would be expected to distill with the heptane if

mixed with the chromatography mixture, thus probably necessitating an added drying step. Second, the substantial fraction of heptane in the acetone recovered from chromatography makes it poorly suited for glassware cleaning due to its lesser effectiveness in dissolving water and other polar substances and the rather slow evaporation of final traces of heptane.

The startup costs of recycling using a commercial system are substantial due to the instrument cost of about \$30,000. Operating costs of solvent recycling are minimal. On the basis of the 10 A/120 V rating of the recycling unit used in this work, a 3 h process for recycling 19 L of solvent uses at most 3.6 KWH of electricity for a total power cost of less than \$1.00. The system used in this work employs air cooling and thus requires no water hookup and occupies about 2.5 ft × 2.5 ft of floor space. The solvent recovered from one 19 L batch of acetone–heptane mixture saves about \$150 in solvent purchase, in addition to savings in disposal costs. Solvent has been reused for at least 12 cycles without any problem. Total recovery is generally >95% in distillation of acetone–heptane mixtures, though there is always some loss from less than complete recovery of the solvent mixture after chromatography. Recovered wash acetone in our experience contains typically about 30% of higher boiling material, primarily water, which is not collected in the distillate.

The acetone–heptane mixture is a convenient and effective solvent system for integrating solvent recycling with flash chromatography. Along with recycling of acetone from glassware cleaning, this can eliminate a major source of waste and operating expense in synthetic laboratories and processes.

■ ASSOCIATED CONTENT

📄 Supporting Information

¹H NMR spectra of a representative crude sample and of the acetone and heptane fractions from fractional distillation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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📄 Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Nuria Protopopescu, a voice for environmental concerns in science and everyday life.

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