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RESEARCH ARTICLE

Accelerating column chromatography: the bundled approach

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The use and construction of a novel apparatus for a variant of conventional column chromatography is described. Relative to a single large conventional column, a bundled apparatus facilitates scale-up by accelerating fraction collection. The bundled approach permits prior knowledge of total running time, total solvent volume, and product location.

Keywords: Organic synthesis; Column chromatography; Bundled apparatus

1. Introduction

Column chromatography is frequently employed to resolve mixtures of organic compounds. Traditionally, silica gel or alumina is slurry-packed and elution is gravity-driven. A pressurized variation, flash chromatography, has been widely applied to the purification of smaller organic samples [1].

Typically, synthetic research proceeds by conducting a series of small-scale exploratory reactions followed by larger-scale production runs. When reaction products have been purified by column chromatography, the columns need to be scaled up as work progresses. In the event that synthesis is intended to provide samples for biological testing in animals, multigram synthesis is unavoidable.

It has been our experience that larger chromatography columns take much longer to run. Three factors routinely contribute to the substantially increased time and effort. First, when scaling up, one is rarely certain which fractions will contain product. Hence, fractions, including some which contain nothing of interest, need to be examined (usually by TLC or spectroscopically). Secondly, if chromatographic resolution is maintained (requires constant height/diameter quotient) solvent flow rates slow appreciably as the amount of adsorbent is increased. Thirdly, larger columns elute product in larger solvent volumes, which require more time to concentrate. Thus, uncertainty about product location may lead to the evaporation of large fraction volumes which yield no product and waste significant amounts of time.

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In addition to those routine problems, some compounds exhibit metastability with respect to column chromatography. During our exploration of the Trithioorthoformate Reaction [2,3], we found that the key intermediate **1** could be purified by column chromatography but that isolated yields declined as column size increased. The next neutral ground-state intermediate, **2**, was never isolated but column fractions gave hydrolysis products presumed to be derived from it. More recently [4], we have described a new thioformaldehyde dication synthetic equivalent for the preparation of α-substituted disulfides. Purification of precursor **3** proved to be difficult [5]. Subsequently, efforts to purify **3** by chromatographic means using less polar solvents led to the observation that larger, slower columns provided smaller quantities of purified ester disulfide **3**. Because future research, employing our new reagent, was jeopardized by problematic column chromatography, a re-examination of the traditional technique was undertaken.

$$p\text{-}CH_3(C_6H_4)SCH_2SO_2O(C_6H_4)Cl\text{-}p$$

1

$$[p\text{-}CH_3(C_6H_4)S]_2CHSO_2O(C_6H_4)Cl\text{-}p$$

2

$$PhCO_2CH_2SSCH_3$$

3

2. Results and discussion

We began to develop this novel separation tool with an examination of solvent flow rates. If one had to make an n-fold increase in the amount of adsorbent in a single conventional column, solvent flow rates would decline. If, rather than an n-fold increase in the size of one column, n columns, packed with equal amounts of silica gel, were run simultaneously, initial solvent flow rates would be conserved even though solvent volumes collected would increase n-fold per unit time. Metastable product recoveries would not decline with increasing scale. We refer to a set of n simultaneously eluted chromatography columns as an n-bundle apparatus.

In the prototypes, each component column could hold 50 grams of silica gel. In running an n-bundle apparatus using 50-gram component columns, the first 50-mL portion of solvent from each component column was combined to give fraction 1, and so on.

Assuming that an initial 50-gram pilot column (50-mL fractions) has been run, one would know, in advance, which fractions from the n-bundle apparatus contain purified product. Hence, in principle, no irrelevant fractions need be evaporated. The pilot column would establish approximate elution time/fraction so that one would have a good idea of the total running time for the n-bundle apparatus. Furthermore, knowledge of the total required solvent volume for the n-bundle apparatus is particularly helpful when a mixed solvent system is employed for elution.

After acquiring experience with a 2-bundle followed by a 4-bundle apparatus, several design questions were settled. First, individually packed columns often run at similar but different rates. To ensure that each column delivered the same volume to each fraction, each column had a calibrated 50 mL receiving flask built into it. Secondly, to minimize the time required to initiate solvent flow in each column, the columns were arranged in a carousel fashion which could be easily rotated. Thirdly, as the number of columns in the n-bundle apparatus is increased, solvent is consumed much more quickly than a corresponding single conventional column would consume it, so that reservoirs, which provide simultaneous solvent feed to all component columns, are essential.

Exploratory work on the development of this technique examined the purification of the disulfide ester **3** with a 2-bundle, a 4-bundle, and finally a 6-bundle apparatus. Very shortly after construction of the 12-bundle apparatus (see figure 1) was complete, ongoing research required rapid chromatographic purification of the disulfide ester **4** [6,7], which was accomplished nicely with that apparatus. Both esters **3** and **4** were satisfactorily purified using a solvent system of 3:1 petroleum ether/chloroform. Results from both the 6-bundle and 12-bundle apparati *versus* conventional columns are presented in table 1.

$CH_3O_2CCH_2SSCH_3$

4

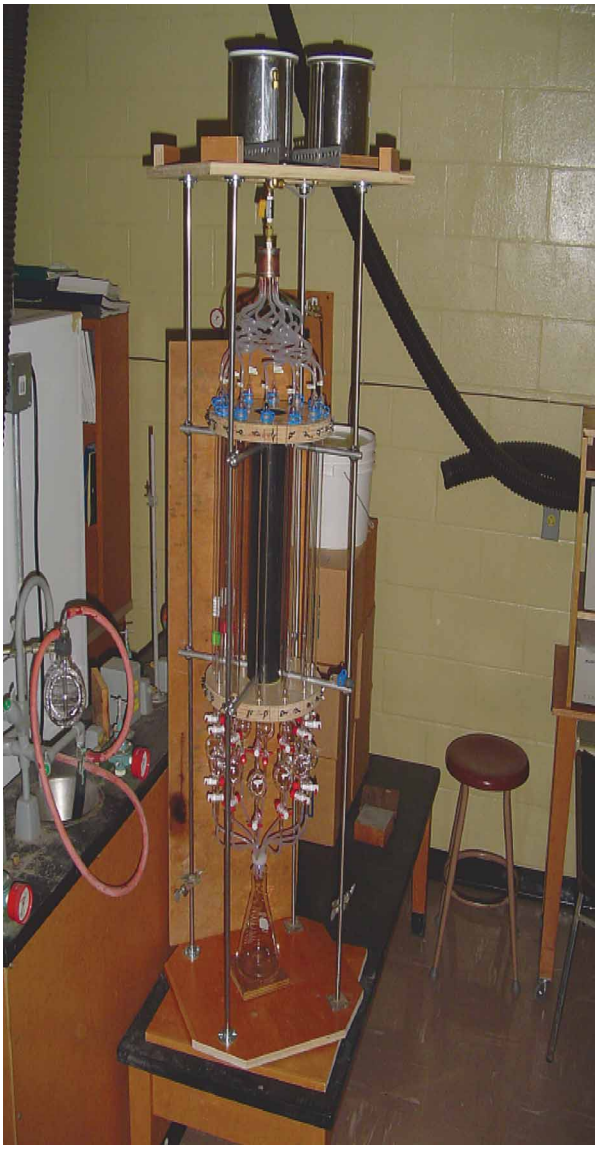

Figure 1. A 12-bundle apparatus.

Table 1. *n*-Bundle apparati *versus* conventional single columns

Weight of silica gel (g) (fraction volume (mL[a]))	Time (min) for single fraction collection	
	Conventional column[b] (h/d quotient)	*n*-Bundle[c]
300 (300)	11.8 (14.4)	4.4 ($n = 6$)
600 (600)	15.8 (17.1)	5.0 ($n = 12$)

[a]3:1 Petroleum ether/chloroform was employed for elution.
[b]Each conventional column was equipped with a 2-mm stopcock. The solvent flow rate without adsorbent in the column was 1.6 min/600 mL, establishing that the stopcocks were not rate-limiting.
[c]Individual component columns had an h/d quotient of 16.2.

From the data in table 1 it is clear that as sample size and n increase, the n-bundle technique offers increasing efficiency for fraction collection.

Because each component column delivers its 50-mL contribution separately, the bundled apparatus can be used for smaller amounts of material. As an example, one could use four component columns of a 12-bundle apparatus to purify a two-gram sample. Furthermore, if a few columns are already committed to the purification of one sample, the remaining component columns could still be used to purify a completely different sample. Of course, that would be most convenient if separate samples were purified with the same solvent system.

Flash chromatography [1] is widely employed for the routine purification of smaller samples. In principle, the application of a pressurized n-bundle apparatus would permit one to apply flash chromatography to the purification of multigram samples as well. Collecting a standard volume/fraction from each component column prevents complications from modest differences in flow rates which may arise from internal pressure differences between component columns.

3. Experimental

The sample was dissolved in chloroform ($n \times 20$ mL) and stirred to obtain a homogeneous solution. The solution was divided into n portions (20 mL each) with a buret. Each portion was concentrated.

Dry silica gel (60–200 μm; product R10040B, Silicycle, Quebec, Canada) for column chromatography (50 g) was measured by volume (93 mL) and poured into petroleum ether (150 mL). Swirling produced an immediate slurry, which was loaded into a component column and the excess of solvent was drained off. After the loading of every component column with silica gel, one portion of sample was applied to each component column. Three aliquots (15 mL each) of the eluting solvent were added sequentially and each was drained before the next was added. Each column was topped up with eluting solvent and connected to the solvent reservoir. The ground-glass joint pair at the top of each column was secured with a Keck® clip of appropriate size.

Thereafter, columns were run simultaneously to produce the required number of fractions to elute the desired product completely. Elution was completed in less than four hours for the 12-bundle apparatus (6-g sample, 31×600 mL).

Upon elution of the target compound, the solvent was completely drained from the 12-bundle apparatus and the glass wool plug removed from the top of each column. The entire apparatus was inverted and a bucket placed under the columns. Overnight, the silica gel fell into the

bucket. The last glass wool plug was removed from each column. The 12-bundle apparatus was re-inverted and each column rinsed with acetone.

Schematic diagrams showing how to assemble a 12-bundle apparatus are available from the corresponding author.

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