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FLASH CHROMATOGRAPHY
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FLASH CHROMATOGRAPHY: COMPETITION WITH THE PREP LC

In 1978, Still, Kahn and Mitra published a method which they designated "flash chromatography," J. Org. Chem., 43, 2923 (1978). In this technique, 40-63 μm silica is packed into a glass column fitted at the top with a joint to which a nitrogen tank line can be attached. The sample is layered on the top of the column and then solvent is flushed through the column at a rapid flow rate (as great as 50 ml/min).

Flash chromatography is claimed to be fast, cheap, and more efficient than other conventional means of silica gel chromatography. It does not, however, offer the kind of results obtainable with the PrepLC. In talking with customers some very negative comments about the PrepLC have been made in comparison to flash chromatography. Their comments can be summarized in three statements:

1) Flash chromatography is a technique that is easier to use than the PrepLC.
2) Flash chromatography gives similar results to the PrepLC.
3) Flash chromatography is much cheaper than using the PrepLC.

Each of these perceptions is not factual.

1) EASE OF USE

FLASH CHROMATOGRAPHY:

The article mentions a time frame of 10-15 min. to run a flash column. From my personal experience and observation of others, to separate > 1 gram it takes about one hour to pack the column, load the sample, and elute the components. (Loading the sample is the most difficult part. The preferred method of many chromatographers involves adsorbing it onto silica by dissolving the sample in a low boiling solvent. Five times its weight in silica is added and the solvent is removed by rotary evaporation under vacuum. The adsorbed sample is then layered on the column.) Separation work up depends upon the number of fractions cut. In a two compound mixture where the ΔR_f (by TLC) is large (>0.2), less than five fractions may need to be cut. In a 3-4 component mixture where the ΔR_f is smaller (≈0.1), as many as 10-20 fractions may be cut. Some chromatographers collect in 15 ml test tubes and may have 40 fractions to check. If these fractions are very dilute, sample work up can take an entire afternoon even before the appropriate fractions are combined and the solvent distilled off under vacuum.

PrepLC:

To the uninitiated, the Prep appears complicated. It has a lot of knobs, gauges, lights and valves on the front panel. In point of fact, two switches will activate the pressure system and two switches control the solvent flow. Although the flow rate is fast, the dual collection outlets allow for easy and convenient collection of fractions. Run time is less, and far fewer fractions need be collected and analyzed because they can be cut by monitoring the RI detector chart. For the chromatographer familiar with it, using the PrepLC is the most efficient way to achieve separations.

2) QUALITY OF RESULTS

The perception that flash chromatography gives similar results to the PrepLC is a fallacy. Even Still et al. promote their technique as a method for obtaining moderate resolution. In their paper they report only 16 plates for efficiency. Yes, simple separations can easily be achieved on a flash column. For instance, a synthetic chemist reduces a ketone to an alcohol. The reaction mixture contains 95% alcohol and 5% unreacted starting material. These two components have very different adsorption characteristics and are easily separated. However, many separations have similar components with the same functional groups. Often two components may differ only in the stereochemistry at one carbon (e.g., epimers) or a reaction mixture may contain three or four by-products as well as starting material and product. In these cases, the optimum packing density of radial compression as well as recycle capability clearly makes PrepLC performance far superior to flash columns. Indeed, certain separations at the > 1 gram level are not feasible or even attainable without the PrepLC.

3) COSTS

There is no question that the PrepLC requires an initial substantial capital outlay (20,000 vs ≈ $200 to buy several columns or have them made). However, even after the purchase has been made, there is the feeling that day-to-day operation of the PrepLC is too costly as compared to other methods. A rough breakdown of costs shows this to be untrue.

SILICA GEL

Merck (EM) Silica Gel 60 (40-63 μm) Catalog #9385 is sold for $90 per 100 grams. For a moderately difficult separation (ΔR_f=0.1), 50 g of silica per gram of sample would be used. Assuming two grams of material is to be separated, the cost per column would be $9.00. If an $85 Prep PAK Cartridge is reused 6 times, the cost of the separation is $14. This is not a substantial difference and in situations where increased load is desirable, the cost differential approaches zero.

SOLVENT

According to Still et al., a moderately difficult separation (ΔR_f=0.1) will use 1 liter of solvent to separate 1 gram. Thus a 2.5 gram sample would need 2.5 liters of solvent. On the PrepLC an average separation will be eluted in 4 column volumes. Assuming that the column is washed with one column volume of solvent and that the first column volume of the run is recirculated, 2.5 liters of solvent would be used. For the same sample with a ΔR_f=0.1, 5-10 g of sample could be isolated with the 2.5 liters of solvent on the PrepLC versus only 2.5 grams with flash chromatography. Recycling can also help to minimize solvent usage. Therefore,in terms of solvent costs, the PrepLC is not more expensive to use than flash column chromatography.

The PrepLC is truly the preferred means of purifying > 1 gram quantities when productivity is the key motivation.

Joan Newburger 3/3/82