

The Purification of Crown Ether Samples by a Quaternary Solvent Flash Chromatography System



Chromatography Application Note
AN030

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Introduction

Crown ethers are heterocyclic chemical compounds that consist of a ring containing several ether groups. The most common crown ethers are oligomers of ethylene oxide, the repeating unit being ethyleneoxy (-CH₂CH₂O-). Important members of this series are the tetramer (n = 4, or four ethyleneoxy units), the pentamer (n = 5), and the hexamer (n = 6). The term "crown" refers to the resemblance between the structure of a crown ether bound to a cation, and a crown sitting on a head. The first number in the name of a crown ether refers to the number of atoms in the cycle, and the second number refers to the number of those atoms that are oxygen. Crown ethers are much broader than the oligomers of ethylene oxide; an important group is derived from catechol.

In 1967, Charles Pedersen, a chemist working at DuPont, discovered a simple method of synthesizing crown ether when he was trying to prepare a complexing agent for divalent cations [1]. Citing earlier work on the dissolution of potassium in 16-crown-4, he realized that the cyclic polyethers represented a new class of complexing agents that were capable of binding alkali metal cations. He proceeded to report systematic studies of the synthesis and binding properties of crown ethers in a seminal series of papers [2]. The fields of organic synthesis, phase transfer catalysts, and other emerging disciplines benefited from the discovery of crown ethers. Pedersen shared the 1987 Nobel Prize in Chemistry for the discovery of the synthetic routes to and binding properties of crown ethers.

The special properties of crown ethers are their strong coordination ability for alkali metal and alkaline earth metal cations. Depending on the

size of the ether ring hole, the type of heteroatom and the number of atoms, this coordination effect shows distinct selectivity for specific metal ions. As the important compound in many fields such as coordination chemistry, extraction chemistry, phase transfer catalysis, ion-selective carriers, etc. crown ether has attracted more and more attention [3-8]. The different properties of the substituent groups on the crown ether compound will affect its complexing strength with metal ions, selectivity and solubility. Compared with unsubstituted crown ethers, benzocrown ethers have attracted more attention in research due to their better lipophilicity [9, 10]. However, benzocrown ethers do not have good solubility in solvents with low polarity, making it difficult to be used directly. In order to improve the properties of benzocrown ethers, many researchers have focused their work on the research and development of benzocrown ether derivatives in recent years.

In this application note, the sample to be purified is a benzocrown ether derivative obtained by organic synthesis. The sample is composed of multiple components with diverse polarity, making it impossible to separate each component by conventional binary solvent gradient. Considering the sample property, the application engineers from Santai Technologies utilized a quaternary solvent system SepaBean machine T combined with SepaFlash normal phase silica cartridge for the purification of the sample. By online switching between solvents of different polarity, the target products meeting the purity requirements were successfully obtained, suggesting a feasible solution for the purification of complex sample composed of multiple components with diverse polarity.

Experimental Section

The sample used in this application was a benzocrown ether derivative which was kindly provided by a university chemistry lab. The chemical structure of the sample molecule is shown in Figure 1. The sample has poor solubility in weak polar organic solvents since the components of the sample have diverse polarity. Therefore dichloromethane (DCM) should be used as the solvent for complete dissolution of the raw sample.

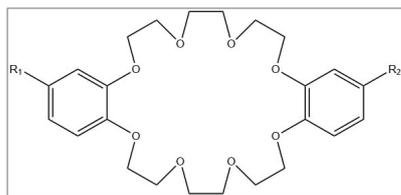


Figure 1. The chemical structure of benzocrown ether derivative sample

To prepare the sample solution, 4.9 g of the raw sample was dissolved in small amount of DCM and absorbed onto 3.5 g of silica gel of 200-400 meshes. DCM was removed by vacuum and the absorbed sample was then placed in a 4g SepaFlash iLOK empty cartridge (order number: SD-0000-004) for solid sample loading. Sample was eluted automatically by a Flash chromatography system SepaBean machine T according to the parameters as shown in Table 1.

Instrument	SepaBean machine T				
Cartridges	12 g SepaFlash silica cartridge (irregular silica, 40 - 63 μ m, 60 Å, Order number: S-5101-0012)		25 g SepaFlash silica cartridge (irregular silica, 40 - 63 μ m, 60 Å, Order number: S-5101-0025)		
	Wavelength				
254 nm, 280 nm					
Mobile phase	Solvent A: DCM Solvent B: Methanol		Solvent A: N-hexane; Solvent B: Ethyl acetate; Solvent C: DCM; Solvent D: Methanol		
	Flow rate		30 mL/min		
25 mL/min					
Sample loading	500 mg (including 250 mg of the sample)		3.0 g (including 1.5 g of the sample)		
	Gradient				
	Time (CV)	Solvent B (%)	Time (CV)	Solvent B (%)	Solvent D (%)
	0	0	0	0	/
	4.0	0	3.0	0	/
	13.5	10	6.0	16	/
	19.0	10	10.0	16	/
	23.5	16	20.0	50	/
	23.8	100	30.0	50	/
28	100		44.0	80	/
			44.5	100	/
			63.0	100	/
			63.1	/	0
			85.0	/	4.0
			110	/	4.0

Table 1. The experimental setup for Flash purification.

Results and Discussion

Considering the sample property, conventional binary solvent system DCM/methanol was employed as the mobile phase for the elution of the sample. The Flash chromatogram of the sample in this condition was shown in Figure 2.

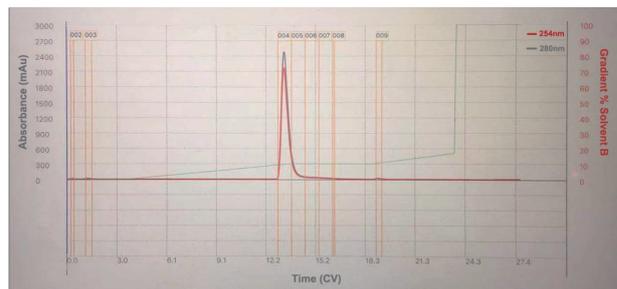


Figure 2. The Flash chromatogram of the sample by binary solvent gradient.

As shown in Figure 2, the sample had a good retention on the silica cartridge when eluted by DCM/methanol binary solvent system. However, there was no resolution for the components in the sample mixture. Go back to the synthetic route of the sample and refer to the classic synthetic route of dibenzo-18-crown-6 (as shown in Figure 3), besides the non-polar (lipophilic) target product in the sample mixture, there are excessive or unreacted starting material of strong polarity (such as catechol) or other by-products, resulting in multiple components in diverse polarity. When simple binary solvent gradient was utilized, the DCM/methanol system is suitable for polar components. The selectivity for less polar components of DCM/methanol system is not as good as that of those solvent systems such as n-hexane/EA. Therefore, as an improvement for simple binary solvent gradient, switching between binary solvent systems of different selectivity and continuously eluting the column could offer better resolution for the components in complex sample mixture, especially for those composed of non-polar and strong polar components.

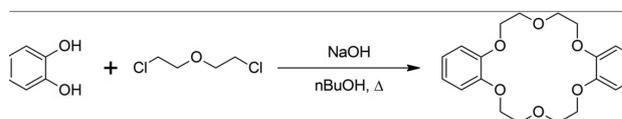


Figure 3. The classic synthetic route of dibenzo-18-crown-6.

Referring to the Snyder's Solvent Selectivity Triangle (as shown in Figure 4), commonly used solvents can be roughly divided into eight groups according to its different acidic, basic or dipole properties. Each group of solvents occupies a certain position in this triangle. According to the rule of "like dissolves like", different groups of solvents have different selectivity for the same sample. Therefore, better selectivity and improved resolution for the components in the sample mixture could be obtained by optimizing the solvent combination.

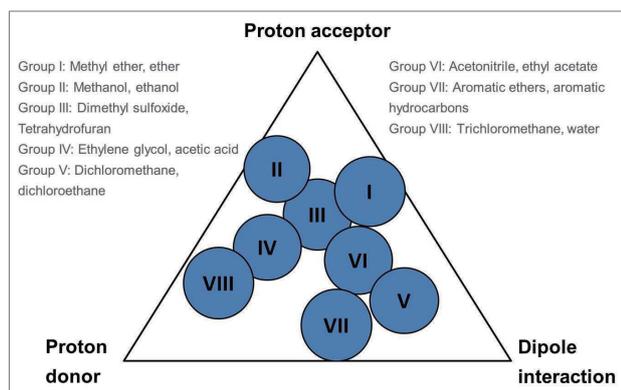


Figure 4. The schematic diagram of Snyder's Solvent Selectivity Triangle.

Let us go back to the conventional binary solvent system used in the previous experiment: DCM/methanol system. After querying the solvent polarity table (as shown in Table 2), we can find out the polarity of DCM and methanol is 3.1 and 5.1, respectively. As a comparison, the polarity of n-hexane and EA is 0.1 and 4.4, respectively. Comparing these two normal phase solvent systems, it can be speculated that for complex sample mixture composed of multiple components of diverse polarity, best resolution for these components could be obtained if one solvent system could be replaced by another one for continuous elution.

Solvent	P'	Solvent	P'	Solvent	P'
N-pentane	0.0	N-propanol	4.0	Acetone	5.1
N-hexane	0.1	THF	4.0	Methanol	5.1
Benzene	2.7	Chloroform	4.1	Acetonitrile	5.8
Diethyl ether	2.8	Ethanol	4.3	Acetic acid	6.0
DCM	3.1	EA	4.4	Water	10.2

Table 2. The polarity parameter P' of commonly used solvents.

In conventional configuration of binary solvent Flash chromatography system, the gradient of mobile phase is generated by a system pump in combination with a binary proportional valve. When the instrument with this configuration is used for continuous gradient elution that requires two solvents to be replaced at the same time, the column must be removed from the instrument and

then the tubing should be flushed with the solvent to be used in subsequent procedure. Afterwards the column should be re-installed on the instrument for next step elution. These operations will undoubtedly lower the work efficiency. In the configuration of SepaBean machine T, a quaternary proportional

valve is employed to generate binary gradient with the combination from any two of the four solvent lines, making it possible to continuously online switch between different solvent systems during the elution procedure. Considering solvent miscibility, n-hexane/EA system was employed as the beginning eluting solvent and then transit to DCM/methanol system for the continuous elution of the sample. The experimental setup was listed in Table 1. The Flash chromatogram of the sample in this condition was shown in Figure 5.

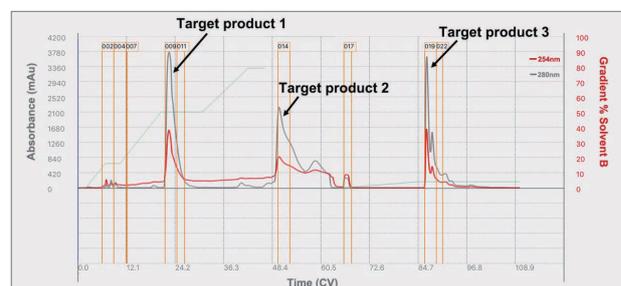


Figure 5. The Flash chromatogram of the sample by quaternary solvent gradient.

As shown in Figure 5, when n-hexane/EA system was employed as the eluting solvent in the first part of separation, less polar components in the sample were eluted out from the column. In the second part of separation, DCM/methanol system was utilized as the eluting solvent for the elution of more polar components. Therefore, multiple components of diverse polarity in the sample were separated and collected respectively. The collected fractions were further identified by TLC. A 0.5% potassium permanganate solution was used as the color developer for TLC analysis. After baked by a heat gun for 5 min, the TLC identification results was shown in Figure 6. It can be concluded that the components in the sample were effectively separated and can be used in next step research and development.

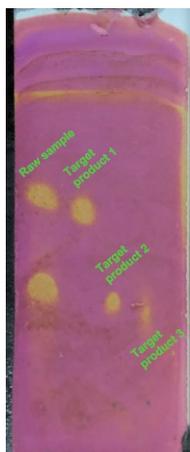


Figure 6. The TLC identification results of raw sample and collected fractions.

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Conclusion

For complex sample mixture such as benzocrown derivatives, due to the wide distribution range of component polarity, it is impossible for conventional binary solvent system to obtain good resolution for each component in the sample. Utilizing quaternary solvent Flash chromatography system SepaBean machine T for continuous online switching between solvent systems of different polarity, better purification result was obtained, suggesting a feasible and efficient solution for the preparative separation of this complex sample mixture.

For further information on detailed specifications of SepaBean machine, or the ordering information on SepaFlash series flash cartridges, please visit our website:

www.santaitech.com/index/.

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