

SG1-nitroxide purification : A comparative study between CPC and semi-preparative HPLC



Cathie Marchal¹, Céline Le Quemener², Marion Rollet¹, Emmanuel Beaudouin¹, Denis Bertin¹, Grégoire Audo², Didier Giges¹.



¹: Laboratoire Chimie Provence, UMR 6264 Avenue Escadrille Normandie Niémen, Case 542, 13397 Marseille, Cedex 20, France
(tel (+33) 491 288 083, didier.giges@univ-provence.fr, cathie.marchal@cpe.fr)

²: ARMEN Instrument, ZI Kermelin, 16 rue Ampère, 56890 Saint-Avé, France (tel (+33) 297 618 400, gregoire.audo@armen-instrument.com)



Introduction

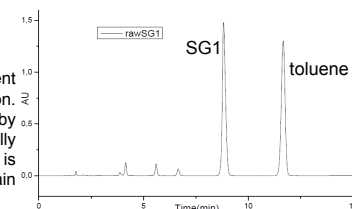
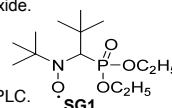
The N-tert-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (SG1) has been purified comparing two chromatographic techniques : Centrifugal Partition Chromatography (CPC) and semi-preparative High Performances Liquid Chromatography (HPLC).

The expected purity is >98%.

SG1

SG1-nitroxide is recognized as one of the most potent controller agent for the Nitroxide Mediated Polymerization. This nitroxide is currently produced at industrial scale by Arkema company and is an intermediate of the commercially available alkoxyamine BlocBuilder. The crude SG1 purity is about 80%. For some applications, it is mandatory to obtain very high purity samples of SG1 nitroxide.

In order to obtain much purity, we decided to investigate two different separation techniques namely CPC and semi preparative HPLC.



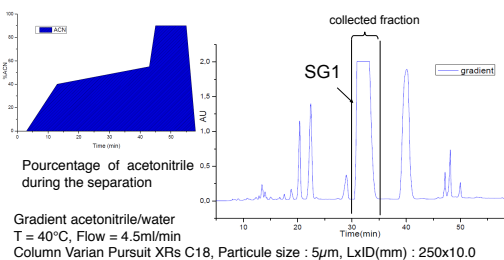
Analytical HPLC chromatogram of an industrial batch of SG1. Elution: ACN/water 60/40 with toluene as internal reference

Column Varian Pursuit XR8 C18, Particule size : 5µm, LxID(mm) : 250x4.6, Flow : 1ml/min

Semi-prep HPLC

Semi-Preparative High Performances Liquid Chromatography

A gradient mode from 100% water to 90% acetonitrile (detailed below) enables the separation of SG1 from its impurities.



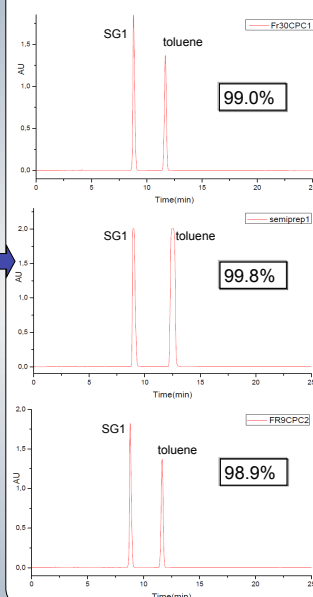
Only one fraction is collected and involves the whole SG1's peak.

Impurities are well separated from SG1. We have tried to inject more than 16mg and above 22.4mg SG1's peak might merge with its close preceding impurity.

The same system applied on a preparative HPLC column would be more appropriate. We were not equipped with this system.

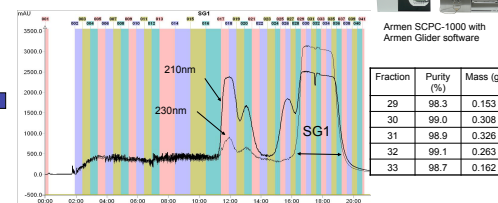
Analytical chromatograms of collected fractions

Eluent system : ACN/water 60/40, Flow : 1ml/min

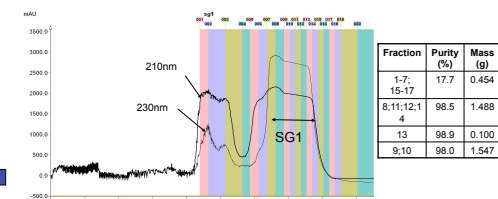


CPC

Centrifugal Partition Chromatography



2g SG1 in 10ml hexane (upper phase) were injected in CPC 1L in the descending mode. Biphasic system : acetonitrile/hexane. Flow : 30ml/min. Rpm: 1400



5g of SG1 in 20ml hexane (upper phase) were injected in CPC 1L in the descending mode. Biphasic system : acetonitrile/hexane. Flow : 30ml/min. Rpm: 1400.

HPLC mass balance

Injected Mass	Purified product mass	Yield (%)	Purity (%)
16.0mg	6.5mg	40.6	99.8
19.2mg	8.1mg	42.2	-
22.4mg	11.1mg	49.6	99.7

Solvents containing a sizeable amount of water are more difficult to separate from the product. Only lyophilisation is appropriate to remove the solvents.

Semi-prep HPLC

19	58	99.8	49.6
water : 126ml ; ACN : 135ml	Time (min)	Max. chrom. purity (%)	Best yield (%)
19	58	99.8	49.6
19	58	99.8	49.6
water : 6630ml ACN : 7100ml	Solvent volume (L) for 1g		

CPC

CPC mass balance

Injected Mass	collected product mass (total)	purified product mass	Yield (%) (>98)	Purity (%) (best)
2g	1.494	1.212	60.6	99.1
5g	3.589	3.135	62.7	98.9

Purified product masses (total) have been determined without proceeding the extrusion.

Conclusions

Semi-preparative HPLC and CPC enable the purification of SG1. Both techniques are convenient and lead to a pure SG1 over 98%. The HPLC technique allows purities to be very close to 100% (99.8%). However, the obtained masses are low. This is a limiting factor for the projected application. CPC technique enables the purification of more product at one time and uses proportionately less solvent. Purities at 98% are acceptable. To be more accurate, this study must be carried out on a preparative HPLC column. An extrapolation has been computed and leads to the same conclusions.