

Direct electrochemical detosylation of tetratosylcyclen to cyclen with carbon cathodes

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Abstract

The electrochemical detosylation of tetratosylcyclen to cyclen (1,4,7,10-tetraazacyclododecane) in aprotic solvents at a carbon cathode was investigated both in a bench-scale batch electrochemical reactor and in a continuous batch recirculation reaction system equipped with a parallel-plate electrochemical cell. Yields and faradaic efficiency in cyclen, respectively, of 80 and 55% were obtained in the bench-scale reactor working in acetonitrile. It was found that the faradaic efficiency in cyclen depends on the competition between the reduction of the tetratosylcyclen and parasitic processes as the reduction of the tetraalkylammonium cations present in the supporting electrolyte. We have observed that the nature of the anolyte and catholyte and the concentrations of the substrate, the supporting electrolyte and the proton donor species dramatically influence the performances of the process.

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1. Introduction

The synthesis of polyazamacrocycles is, up to now, prevalently achieved with an expensive procedure despite the strong and increasing interest towards these products in metal complexation and as precursors of related pendant-armed and bridged polydentate ligands for biomedical applications [1]. The synthesis of polyazamacrocycles was developed first in 1974 by Richman and Atkins [2] by reacting tosylated polyamines with the respective dihalogeno or ditosyl fragments in the presence of a base, such as NaH, in dimethylformamide (DMF) at elevated temperatures. In particular, for the synthesis of cyclen (1,4,7,10-tetraazacyclododecane) the procedure worked out by Richman involves medium-dilution macrocyclization of the disodium salt of tritosyldiethylenetriamine with *N*-tosyl-diethanolamine ditosylate to give

tetratosylcyclen, which is then detosylated with concentrated sulphuric acid. The methodology remains, probably, the prevalent synthetic method for carbon-functionalized tetraazamacrocycles. In spite of this, the detosylation step presents very low selectivity and consequently requires an expensive procedure of separation and purification which leads to high prices for cyclen and its derivatives [3]. It is important to emphasize that the detosylation represents a key step in order to reach convenient yields and purity levels as required by pharmaceutical uses. On the other hand, detosylation carried out in concentrated sulphuric acid generates sulphates in large quantities that constitute a difficult waste treatment problem on an industrial scale.

Variation of the synthesis based on a Kellogg-type procedure with Cs₂CO₃ and K₂CO₃ [4] is not suitable for an industrial application. Hence, the importance of a new synthetic approach to the synthesis of cyclen derivatives is obvious. In particular, the Richmann procedure would be more attractive in the presence of a more selective step of detosylation.

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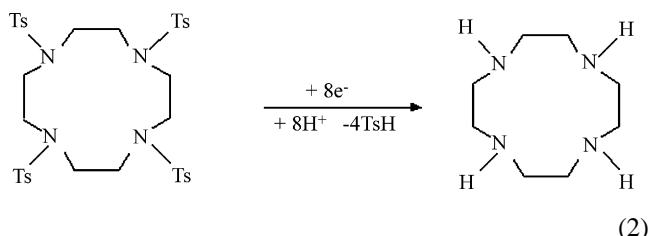
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In this paper, in particular, we focused our attention on the possibility of performing the detosylation step by an electroreduction process for the synthesis of cyclen from tetratosylcyclen.

The cathodic cleavage of protecting group has been widely investigated in the last decades [5]. In particular, it is well known that selected sulfonamides can be reductively cleaved to amines and sulfinic acids according to the equation:



Kossai and Simonet reported in 1979 the possibility of synthesizing polyaza and poly-oxa-aza-cycloalkanes by cathodic cleavage of N–S bonds in the poly-*p*-toluenesulfonamides [6].



The procedure worked out by Kossai involved the utilisation of a mercury cathode, a homogeneous charge-transfer catalyst and DMF as a solvent. In spite of the good yields achieved, the use of a mercury cathode makes this method unsuitable for a pharmaceutical application. Otherwise the electrochemical process, if performed with non-toxic cathodes, seems in principle a good candidate for the substitution of the traditional detosylation procedure. Hence, in this paper we have investigated the possibility of performing, by direct reduction with a graphite cathode, the detosylation of tetratosylcyclen to cyclen in order to analyse the preparative aspects of the methodology in two different systems: a divided cell

in a bench-scale system of 100 mL volume and a divided filter press cell in a continuous batch recirculation system with 500 mL hold-up electrolyte solution.

2. Experimental

2.1. Electrosyntheses and electroanalytical measures

Electrosyntheses were performed in two different systems: system **I** was constituted by a bench-scale two-compartment glass cell equipped with a cation-exchange membrane Nafion 324. The cathode zone was equipped with gas inlet and outlet, reference electrode (SCE) and working electrode (a rod of compact graphite; diameter 1.5 cm, surface area 15 cm²) with a distance between the cathode and anode of 7.5 cm. The volume of the cathode solution was 50 mL. System **II** was constituted by a continuous batch recirculation reaction system equipped with a filter press two-compartment microflow cell ElectroCell AB. The cell was equipped with an oxygen DSA as anode, one graphite cathode (surface area 12 cm², inter electrode gap 1.4 cm) and a cation-exchange membrane Nafion 324. An Ag/AgI/I⁻ 0.1 M in DMF reference electrode was inserted in the loop near the cell. The overall arrangement of the batch pilot reactor is shown in Fig. 1.

The electrolytic circulating solutions (250 mL volume each) were both saturated with a continuous stream of helium fed by two diffusers in the two jacketed solution reservoirs of 250 mL. The circulation of the solutions was provided by two centrifugal pumps. An Amel 2055 potentiostat and 3300 current integrator were used in all experiments. The graphite electrodes were mechanically polished.

Work up of cathode solution: after electrolysis, the solvent was evaporated under reduced pressure, the residue was solubilised in water and non-soluble components were

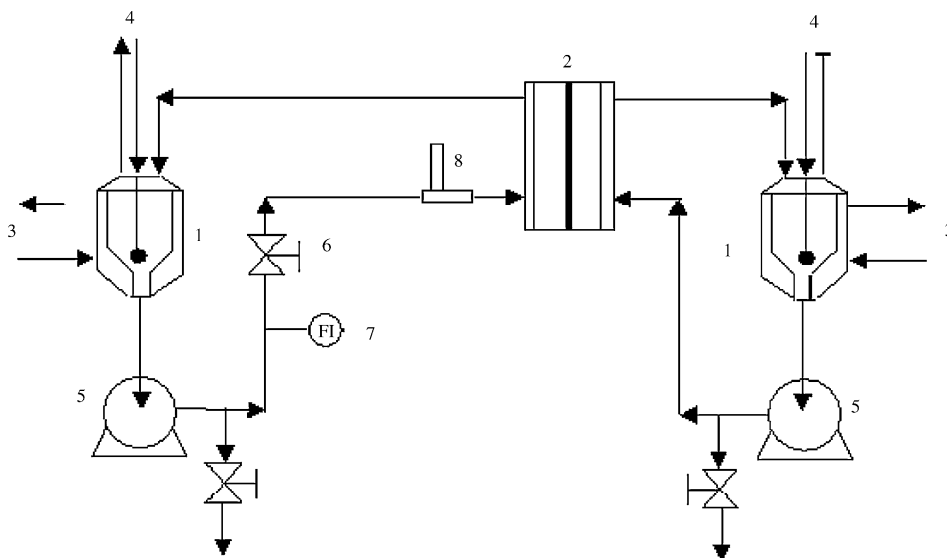


Fig. 1. Simplified flow-sheet of reaction system **II**: (1) saturation-jacketed tanks; (2) electrochemical cell; (3) thermal exchange fluid; (4) helium gas inlet and outlet; (5) centrifugal pumps; (6) flow regulation valve; (7) flow indicator; (8) reference electrode.

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