

Microwave Irradiation Accelerated Detosylations of Poly(*p*-tosyl) Macrocyclic Polyamines

by J.F. Wei*, X.Y. Shi, D.P. He and B.H. Ma

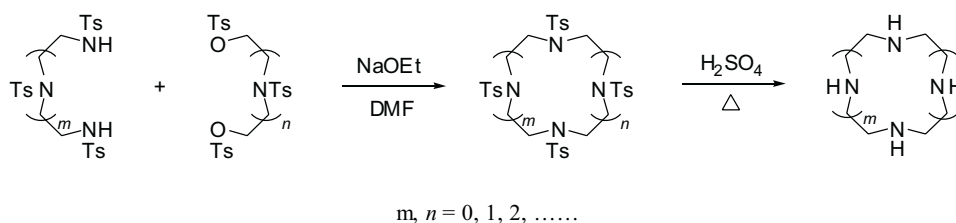
Laboratory of Organic Synthesis and Biomimetic Chemistry, Department of Chemistry, Shaanxi Normal University, 710062 Xi'an, P. R. China

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Macrocyclic polyamines and their derivatives have been a fascinating area in chemistry of crown ethers due to their wide applications in molecular recognition, molecular magnets, analytical reagents of metal ions and modeling biosites of metalloproteins, such as methane monooxygenase (MMO), hemerythrin (Hr), hemocyanin (Hc), tyrosinase (Tyr), dopamine β -hydroxylase (DBH), superoxide dismutase (SOD) [1–5] as well as the contrast agents for magnetic resonance imaging (MRI) and X-ray computed tomography (CT) [6,7].

Since the first report by Stetter and Mayer [8] of the synthesis of [12]aneN₄ in 1961 many synthetic methods have been proposed for various macrocyclic polyamines [7,9–19]. Atkins' synthetic route (Scheme 1) has been widely used and is generally considered as a classical method, due to its advantages of cheap starting materials, simplicity, and high yield [12–23]:

Scheme 1



The poly(*p*-tosyl) macrocyclic polyamines are the key intermediate products for preparing macrocyclic polyamines and can be synthesized conveniently by cyclocondensation in *N,N*-dimethylformamide in high yields. The detosylation reaction of these intermediate products, however, needs commonly to be carried out in 96–98% sulfuric acid at 140°C for 48–72 hrs (2–3 days) [12–21]. Due to significant effects of

*To whom correspondence should be addressed. E-mail: weijf@snnu.edu.cn

microwave irradiation on accelerating many synthetic reactions [22,23], we wish to report a rapid, efficient, and convenient method for the hydrolysis of poly(*p*-tosyl) macrocyclic polyamines at normal pressure under microwave irradiation.

The microwave irradiation accelerated (MIA) hydrolysis was performed in a Gelanz WP-750B model microwave oven, equipped with an electromagnetic stirrer and a condenser. In a typical experiment a mixture of 21.2 g of 1,4,7,10-tetra(*p*-tosyl)-1,4,7,10-tetraazacyclododecane and 40 mL of 98% H₂SO₄ in a 100 mL flask was placed in the refitted microwave oven and stirred electromagnetically. After the solid was dissolved or well suspended, the oven was started working under the pre-adjusted values of “power” and “time”. If necessary, this microwave irradiation procedure should be repeated until the reaction mixture can be dissolved completely in water. The reaction mixture was worked up in a similar way as in [16]. The results of the hydrolysis of several poly(*p*-tosyl) macrocyclic polyamines are listed in Table 1.

Table 1. The MIA hydrolysis of several poly(*p*-tosyl) macrocyclic polyamines [24].

| N _n Ts _n ^{a)} | H ₂ SO ₄ | | Irradiation power* | Irradiation time/s | N _n H _n · nH ₂ SO ₄ Yield/% |
|---|--------------------------------|-----------|--------------------|--------------------|---|
| | Conc./% | Amount/mL | | | |
| N ₄ Ts ₄ | 98 | 40 | 375 | 55 | 100.1 |
| | 98 | 20 | 75 | 150 | 148.0 |
| | 98 | 20 | 375 | 30 | 117.3 |
| | 98 | 40 | 75 | 330 | 110.3 |
| | 95 | 40 | 375 | 50 | 99.2 |
| | 80 | 40 | 375 | 80 | 76.9 |
| N ₄ 'Ts ₄ ^{b)} | 98 | 40 | 375 | 50 | 99.5 |
| N ₃ Ts ₃ | 98 | 40 | 375 | 30 | 92.2 |
| N ₅ Ts ₅ | 98 | 40 | 375 | 50 | 81.7 |

*Based on the “power” shown on the control panel of the microwave oven.

^{a)}20 g of N_nTs_n [25] were used in all experiments.

^{b)}N₄' denotes 1,4,7,10-tetraazacyclotridecane.

It can be seen that the hydrolysis and detosylation of poly(*p*-tosyl) macrocyclic polyamines in concentrated sulfuric acid were accelerated significantly by microwave irradiation. Under an irradiation power of 375 W the MIA hydrolysis was completed within 55 to 30 sec for 1,4,7,10-tetra(*p*-tosyl)-1,4,7,10-tetraazacyclododecane, which are 4700–8600 times shorter than those under normal heating condition. Even though the lowest power of microwave irradiation, *i.e.* 75 W, was used, the MIA hydrolysis can be completed within 330 sec, about 780 times faster than that under normal conditions. A ratio of H₂SO₄/poly(*p*-tosyl) macrocyclic polyamine = 1.8–2 mL/1g is the most favorable. If the amount of sulfuric acid in the reaction mixture is reduced to 1 mL/1g, the poly(*p*-tosyl) macrocyclic polyamines also can be hydrolyzed under microwave irradiation, but the polyammonium sulfate was given with 148% yield, because the impurities in the polyammonium sulfate were difficult to be removed.

The favorable concentration of sulfuric acid is in a range of 95–98%. When a diluted sulfuric acid is used, the yield of the sulfates is decreased significantly.

In conclusion, the MIA hydrolysis of poly(*p*-tosyl) macrocyclic polyamines under normal pressure provides a rapid, efficient, and convenient method, useful to remove *p*-tosyl groups from macrocyclopolyamine skeletons. One can expect that this MIA hydrolysis can be employed to the detosylation of *p*-toluenesulfonamide derivatives in sulfuric acid.

Acknowledgment

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24. All the products were confirmed by m.p., elemental analyses, IR, and ¹H NMR.
25. The poly(*p*-tosyl) macrocyclic polyamines (N_nTS_n) were synthesized according to [7].