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1,4-Bis-(4-toluenesulphonyl)-1,4,7,10-tetraazacyclododecane from the direct tosylation of 1,4,7,10-tetraazacyclododecane

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Abstract—The reaction between 1,4,7,10-tetraazacyclododecane and 4-toluenesulphonyl chloride in triethylamine/chloroform yields both the disubstituted isomers of bis-(4-toluenesulphonyl)-1,4,7,10-tetraazacyclododecane. This has been confirmed by ^{1}H NMR and X-ray crystallographic analyses.

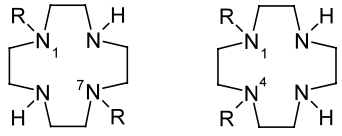
Derivatives of 1,4,7,10-tetraazacyclododecane (cyclen) have attracted interest because of the stability of their lanthanide complexes and the potential use of these as MRI contrast agents.[1] 1-(4-Toluenesulphonyl)cyclen provides a convenient starting point in the synthesis of unsymmetrically substituted compounds bearing one non-identical group that can then be subject to further functionalization. Additionally, cyclen is unique in that the 1,7-ditosylamide is available in high yield from the direct tosylation of the macrocycle in pyridine.[2] Apparently, the 1,4-ditosylamide has not been observed as a byproduct from this reaction or from the alternative route using chloroform/triethylamine as the reaction medium.[2,3] Previously, 1,4-bis-(4-toluenesulphonyl)-cyclen has only been accessible via the macrocyclization of open chain ditosylates.[4]

In this note, we would like to report that the 1,4-bis-(4-tosylamide) is, in fact, accessible via the direct reaction of 1,4,7,10-tetraazacyclododecane (Strem Chemical Co. Ltd.) with 4-toluenesulphonyl chloride in chloroform/triethylamine. In the synthesis of the 1-(4-toluenesulphonyl)cyclen there are inevitably some disubstituted and trisubstituted byproducts. These were isolated from the mono-substituted and unreacted macrocycle as previously reported,[2] the more highly substituted reaction products being insoluble in water. The more highly substituted reaction products were then recrystallized from methanol yielding a mixture of very small needle-like crystals along with larger pale yellow cubes. The structures of the two possible ditosylamides of cyclen are shown in Scheme 1.

A sample (100 mg) of the cube-like crystals was separated from the mixture and subjected to ^{1}H NMR and X-ray crystallographic analysis. The ^{1}H NMR spectrum could be unequivocally assigned to the 1,4-regioisomer.[5] The crystal structure provided final proof of identity and this is shown in Figs. 1 and 2.[6] The small needle crystals were identified as the 1,7-regioisomer from their ^{1}H NMR spectrum.

A sample of the crystalline mixture was also subject to ^{1}H NMR in order to obtain the composition and hence the yield of the 1,4-regioisomer although this was expected to be low since the initial experiment was aimed at the synthesis of the 1-monosubstituted macrocycle. The mixture contained approximately 30% of the 1,4-ditosylamide with the remainder being mostly the 1,7-derivative and a small amount (<1%) of what is probably the 1,4,7-tritosylamide. This composition equates to overall yields of 4% and 8% of the 1,4- and 1,7-ditosylamides, respectively. The monotosylamide was obtained in 68% yield leaving 19% macrocycle unreacted.

That no-one has detected the 1,4-ditosylamide from the reaction between cyclen and 4-toluenesulphonylchloride is rather unusual given that its presence is obvious from the ^{1}H NMR spectra of the mixture of ditosylamides.



Scheme 1. Ditosylamides derived from 1,4,7,10-tetraazacyclododecane; R = (4-toluenesulphonyl).

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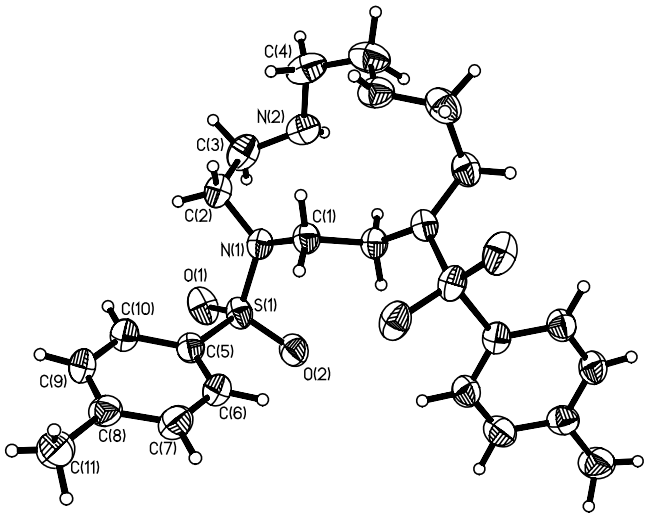

Figure 1. Molecular structure of 1,4-bis-(4-toluenesulphonyl)-1,4,7,10-tetraazacyclododecane. Probability ellipsoids at 30% level.

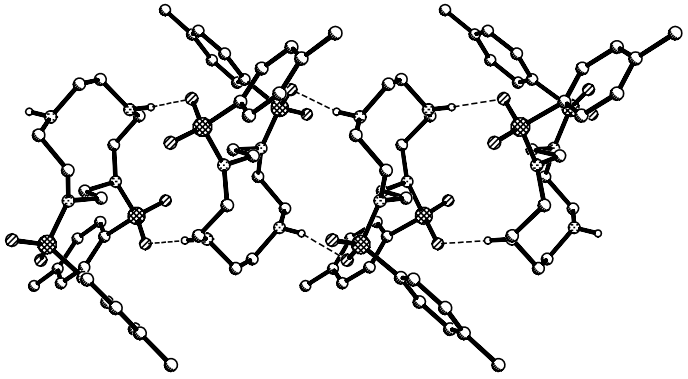

Figure 2. View of 1,4-bis-(4-toluenesulphonyl)-1,4,7,10-tetraazacyclododecane down the *a*-axis. Hydrogen bonding between adjacent molecules leading to chains.

However, the 1,7-derivative is predominant despite being the statistically less favoured isomer and the reason for this probably lies in a combination of steric and electrostatic effects.[7,8]

In the crystal, the molecule lies on a twofold rotational axis. The dimethylene unit between the substituted nitrogens has an *anti* configuration (torsion angle about C(1)–C(1′) 169.4°); the remaining three are *gauche* (torsion angles about C(2)–C(3) and C(4)–C(4′) are −57.7° and −74.9°, respectively). The molecules are linked by pairs of hydrogen bonds between N–H groups and sulphonyl oxygens into chains parallel to the crystal *c*-axis.

Currently, we are trying to ascertain whether the synthesis of the 1,4-ditosylamide can be optimized in a similar manner to that of the 1,7-ditosylamide. It appears that the isomers can be separated by virtue of their differing crystal habits rather than by chromatography so that exclusive synthesis of the 1,4-ditosylamide is not necessarily required.

Acknowledgements

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5. ^{1}H NMR ($CDCl_3$) of 1,4-bis-[(4-methylphenyl)sulphonyl)]-1,4,7,10-tetraazacyclo dodecane: 7.73 (4H, d), 7.35 (4H, d), 3.53 (4H, s), 3.14 (4H, t), 1.99 (4H, t), 2.73 (4H, s), 2.45 (6H, s). ^{1}H NMR ($CDCl_3$) of 1,7-bis-[(4-methylphenyl)-sulphonyl)]-1,4,7,10-tetraazacyclododecane: 7.75 (4H, d), 7.37 (4H, d), 3.19 (8H, t), 2.87 (8H, t), 2.44 (6H, s).
6. Crystal data: $C_{22}H_{32}N_4O_4S_2$, FW = 480.64; $T = 200$ K; orthorhombic, *Pbcn*, $Z = 4$, $a = 23.0510(13)$, $b = 10.2219(8)$, $c = 10.2806(5)$ Å, $V = 2422.4(3)$ Å^3; 8278 data, 2076 unique, $R_{int} = 0.0339$, 209 parameters (all non-H anisotropic, all H fully refined), $wR_2 = 0.0829$ (all data), $R_1 = 0.0341$ (1374 with $I > 2\sigma(I)$), largest diff. peak/hole +0.22/−0.20 e Å^{-3}. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 191103. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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