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Regioselective synthesis of 1,7-diprotected 1,4,7,10-tetraazacyclododecane and preparation of a dialcohol dicarboxylic macrocyclic ligand

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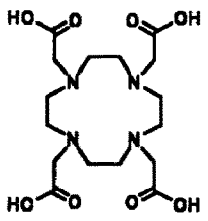
Abstract: The reaction of 1,4,7,10-tetraazacyclododecane with p-toluenesulfonyl chloride in pyridine or with diethyl phosphite and CCl_4 in a water/CH_2Cl_2 mixture yields selectively the 1,7-diprotected regioisomer. The 1,7-diprotected tetraaza cycles are interesting starting materials, for instance for the preparation of 4,10-bis(2'-hydroxyethyl)-1,7-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

Nuclear magnetic resonance imaging (MRI) stands to benefit enormously from the use of paramagnetic agents that are able to increase the contrast of images because they drastically modify the relaxation times T_1 and T_2 of water *in vivo*[1a]. Trivalent gadolinium is the paramagnetic species that is most often used but this ion is too toxic to be injected as such at the concentration levels required in MRI. Rapid excretion through the kidneys is achieved by complexing Gd(III) with chelating agents that are able to form kinetically and thermodynamically stable species for instance the macrocyclic ligand 1,4,7,10-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane, DOTA, **1**. Numerous analogues of DOTA have been prepared recently in view of achieving a better organ specificity or of binding the complexes to synthetic and biological polymers[1b]. Various methods[2a-g] have been devised to selectively protect three nitrogen atoms of 1,4,7,10-tetraazacyclododecane (hereafter called **DO**) thus allowing the synthesis of derivatives bearing different substituents. The synthesis of a 1,7-diprotected ring **2** is more difficult but can be achieved as indicated in the synthetic scheme shown below[3] because the tosyl groups (Ts) are readily removed in hot H_2SO_4 while keeping the mesyl moieties (Ms)[2g] (the starting diprotected triamine was obtained as previously reported[4]; yields: i: 80%, ii: 43%, iii: 78%). However, this procedure is time consuming and the mesyl groups have to be removed by a strong reducing agent that is prone to react with other functions such as amides after they have been added to the remaining unprotected nitrogen atoms. A more direct approach consists in starting from DO (commercially available) and directly reacting this macrocycle with p-toluenesulfonyl chloride in conditions that favor the formation of the 1,7 regioisomer. A mixture of mono-, di- and triprotected derivatives (hereafter called **DOTs**, **$DOTs_2$**, **2b**, and **$DOTs_3$** respectively) was obtained if a solution of TsCl in $CHCl_3$ was added dropwise at 40°C to a $CHCl_3$ solution of the macrocyclic amine in presence of a large excess of triethylamine. For a 1:1 DO/TsCl ratio, 63% of DOTs and 16% of $DOTs_2$ were obtained after isolation. For a 1:2 ratio, 15% (relative to tosyl chloride) of the mono-, 24% of the di- and 52% of the



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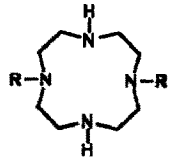
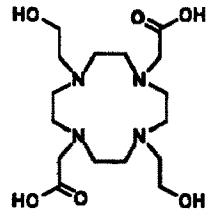


2a R: Ms
2b R: Ts
2c R: $P(=O)(OEt)_2$



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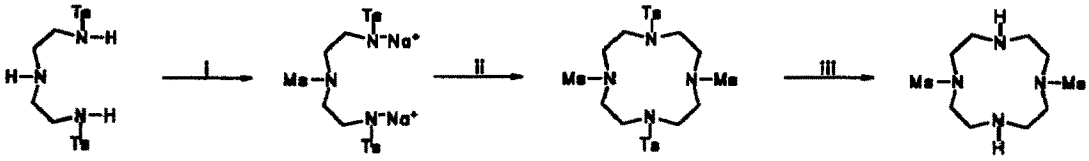

Scheme. Reagents: i: 1) MsCl, pyridine, 2) $NaOCH_3$, CH_3OH; ii: 1,4,7-trimesyl-diethanolamine, DMF, 100°C; iii: H_2SO_4 conc., 100°C.

triprotected derivatives were collected. Each derivative was easily isolated because of its solubility properties. Water was added to the reaction mixture and the unreacted amine DO was found in the aqueous phase together with DOTs. The organic phase was brought to dryness and the solid residue was treated with hot methanol (50 mL for 3.3 g of DO). The insoluble material was the tritosylated compound $DOTs_3$ and $DOTs_2$ crystallized out after cooling the solution[5]. $DOTs_2$ always was the 1,7 isomer **2b** and we could not find even traces of the 1,4 derivative in contrast to what has been reported for larger tetraaza macrocycles[6]. Performing the tosylation reaction in pyridine by adding the tetraaza ring DO to twice the amount of TsCl led[7] exclusively to the 1,7 isomer of $DOTs_2$ (yield 90%). Unreacted DO (55%) and $DOTs_2$(45%) were isolated after carrying out the reaction with a 1:1 DO/TsCl ratio. The preparation of the 1,7-$DOTs_2$ isomer is thus surprisingly easy. When the above reaction was carried out with a 1:2 DO/TsCl ratio in $CHCl_3$ rather

than in pyridine, 36% of DOTs and 64% of $DOTs_2$ were isolated. If the reaction was performed by the addition of an equimolecular quantity of TsCl in pyridine to a solution of DO in the same solvent, 48% of DOTs and 52% of $DOTs_2$ were isolated..

The surprising selectivity of the 1,7 protection of DO was also found when the macrocycle was reacted with CCl_4 and $HP(=O)(O\text{-}CH_2\text{-}CH_3)_2$ in a 1:2 DO/phosphite ratio in a two phase system with a transfer agent[8,9]. The N-P bonds in **2c** were easily cleaved by a 6 M HCl aqueous solution.

In all the syntheses described above, the diprotected derivative was found to be the 1,7-regioisomer whether the protection was carried out with tosyl chloride or with diethyl phosphite and whether the macrocyclic amine was added to the protecting reagent or vice versa. It can thus be assumed that the outcome of the reactions is essentially governed by steric effects. Steric effects have been invoked to explain the selective formation of 1,7-derivatives in the alkylation of DO by hindered α-halo esters[10]. In the reactions investigated in the present work, steric effects could be specially important because the nitrogen atoms in sulfonamides[11] and phosphoramidates[12] adopt a planar or nearly planar conformation that should impart some rigidity to the tetraaza ring of DO. In contrast to the observations made if $CHCl_3$ was the solvent, no formation of DOTs and $DOTs_3$ was observed when the reaction was carried out by adding DO to a solution of TsCl in pyridine. The remarkable selectivity observed in pyridine probably stems not only from steric effects but also from electric charge effects. It has been shown[13] that the protons in the diprotonated tetraazacyclododecane ring are located on the 1,7 nitrogen atoms in order to reduce electrostatic repulsions between the NH^+ groups. These repulsions are strong enough to prevent further protonation of the ring except at very low pH. The 1,7-bis(methylsulfonate) isomer is predominantly formed at pH 7 presumably because of the same charge repulsion effects[14]. The 1-(p-toluenesulfonyl)pyridinium chloride that is produced in pyridine is much more reactive than tosyl chloride in chloroform and probably forms immediately a dication with DO by an amine exchange mechanism. The reaction would then be unable to proceed further because of charge repulsion.

The ditosylamide and the diphosphoramidate of DO are particularly interesting starting materials for the preparation of symmetrically substituted macrocycles for instance ligand **3**. The reaction of $DOTs_2$ with an excess of ethylene oxide in the presence of $LiClO_4$ easily led to the formation of a dialcohol derivative (yield: 75%). The tosyl groups were then removed with a sodium amalgam (yield: 100%) and the acetate groups were added by reacting the bis-(2'-hydroxyethane) tetraaza macrocycle with bromoacetic acid (Yield: 85% after elution on a Dowex 50X2-200 ion-exchange column with 0.5 M NH_3 and on a Dowex 1X2-200 with 10^{-2} M formic acid)[15].

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3. **2a**.2HCl: ^{1}H-NMR (D_2O) 3.17 (6H, s), 3.69 (8H, broad), 3.47 (8H, broad)
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5. TLC: SiO_2, 100% methanol: $DOTs_3$: R_f= 0.72, $DOTs_2$: R_f= 0.1, DOTs: does not migrate.
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7. *A typical procedure as follows*: a solution of 4.98 g (26.2 mmol) of TsCl in 50 mL pyridine was chilled to 0°C. A solution of DO (2.25 g, 13.1 mmol) in 25 mL of pyridine was added dropwise at 0°C. The reaction mixture was stirred during 4 h. at room temperature after completing the addition. Pyridine was evaporated in a rotavapor, the residue was taken up by 20 mL of water and the mixture was stirred during 3 h. The insoluble material was $DOTs_2$. It was thoroughly washed with water, with a saturated aqueous solution of Na_2CO_3 and finally with water. $DOTs_2$ was obtained as a yellow solid. The color could not be removed but must be due to a very small amount of an impurity as the NMR spectra of $DOTs_2$ were identical whether this compound was obtained by the above procedure or in a $CHCl_3$/triethylamine mixture. In the latter case, a white solid was obtained. If necessary, unprotonated DO is easily obtained from its protonated form by stirring the solid material overnight in $CHCl_3$ saturated with NH_3. Yield: 90%. **2b**: melt. pt.: 232-234°C; ^{1}H-NMR ($CDCl_3$) 7.69 (4H, d), 7.33 (4H, d), 3.19 (8H, t), 2.88 (8H, t), 2.40 (6 H, s); ^{13}C-NMR ($CDCl_3$) 144.6, 135.8, 128.4, 50.8, 50.0, 22.4; FAB-MS (in NOBA): m/z = 481.9 ($M+H^+$).
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9. *A typical procedure as follows*: the protonated macrocycle (5g, about 12.8 mmol) was neutralized with 2.15g of LiOH in 10 mL of water and was added to a two phase system consisting of 10 mL of CH_2Cl_2, 10 mL of CCl_4, 10 mL of a 20% LiOH aqueous solution and 250 mg of benzyltriethylammonium chloride. A solution of diethyl phosphite (3.3 mL, 25.6 mmol) in 5 mL of CH_2Cl_2 was added dropwise to the reaction mixture cooled in an ice-water bath. Stirring was continued during 1 h at 0°C after completing the addition and then at room temperature during 1 h. The reaction mixture was extracted three times with 25 mL of CH_2Cl_2. All organic phases were combined and washed with water. A colorless oil remained after evaporation of the solvent. Yield: 90%. Traces of the trisubstituted derivative were found by FAB-MS but not by NMR. **2c**: ^{1}H-NMR ($CDCl_3$) 3.96 (8H, m), 3.09 (8H, m), 2.70 (8H, t), 1.24 (12H, t); ^{13}C-NMR ($CDCL_3$) 61.9, 49.2, 48.8, 16.0; FAB-MS (in NOBA): m/z = 445 ($M+H^+$).
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15. **3**: ^{1}H-NMR (D_2O, neutral pH) 4.4 (4H, t), 3.66 (4H, s), 3.45-3.35 (20H, broad, m); ^{13}C-NMR (D_2O, neutral pH) 59.5, 57.1, 53.2, 52.6; FAB-MS (in glycerol): m/z = 377 ($M+H^+$).

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