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On the synthesis of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

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ABSTRACT

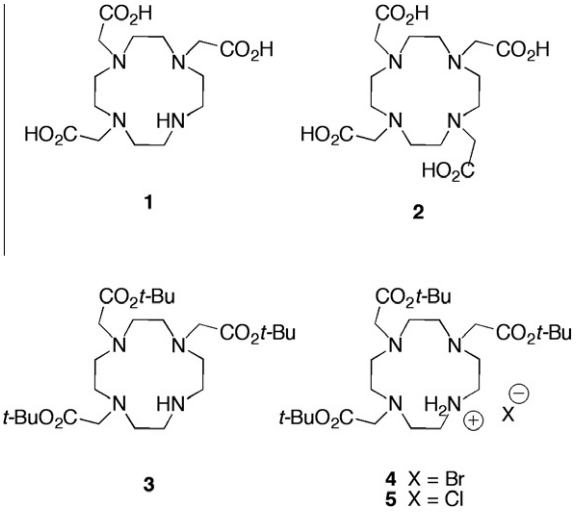
1,4,7-Tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane is widely used as an intermediate in the preparation of medically important DO3A and DOTA metal chelators. Despite its commercial availability and importance, the literature describing the preparation and properties of the free base is limited and sometimes unclear. We present herein an efficient synthesis of the hydrobromide salt of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane, characterize this compound spectroscopically and by X-ray crystallographic analysis, describe its simple conversion to the corresponding free base, characterize this compound spectroscopically and by X-ray crystallographic analysis, and make observations on the reactivity of this interesting and useful compound.

1. Introduction

Many Magnetic Resonance Imaging (MRI) examinations employ gadolinium(III)-based contrast agents (CAs).[1–3] Clinically-approved MRI CAs are primarily suited for highlighting anatomical features after intravenous administration and vascular distribution throughout the body. The efficacy of an MRI CA is dependent on its relaxivity. Much work in the last two decades has been devoted to understanding the parameters that influence the relaxation properties of MRI CAs.[4–6] Recent years have seen the development of targeted MRI CAs that are sensitive to physiochemical and biochemical changes, such as pH, pO_2, metal ion concentration, enzymatic activity, and redox state.[7] This work has been largely driven by structural modifications of the chelators 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (**1**, DO3A) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (**2**, DOTA). Derivatives of **1** and **2** are often synthesized from 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**3**) or the corresponding hydrobromide or hydrochloride salts **4** and **5**.[8] Despite its commercial availability and importance, the literature describing the preparation and properties of the free base **3** is limited and often lacks clarity. We present herein an efficient, scalable synthesis of the hydrobromide salt **4**, characterize this salt spectroscopically and by X-ray crystallographic analysis, describe the conversion of **4** to the corresponding free base **3**, characterize the free base spectroscopically and by X-ray crystallographic analysis, and make observations on the reactivity of this interesting and useful compound.

2. Background

The synthesis of the hydrobromide salt **4** in pure form and in high yield once presented a challenge owing to contamination of the desired product with di- and tetra-alkylated biproducts. A literature search revealed that there are two generally applied methods for the synthesis of **4**. The first method involves tris-alkylation



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of cyclen with *tert*-butyl bromoacetate in dimethylacetamide in the presence of sodium acetate. The procedure of Himmelsbach et al.[9] employed a reaction time of 19 days to produce a 56% yield of **4**. The related protocol of Berg et al.[10] required six days and a chromatographic purification to afford **4** in 60% yield. The procedure of Axelsson and Olsson[11] took five days and employed modified work up procedures to produce **4** in 73% yield. Recently, Moore[12] prepared **4** in 65–80% yield by a related procedure that required 60 h.

The second method for the synthesis of **4**, originated by Dadabhouy et al.,[13] involves reacting *tert*-butyl bromoacetate with cyclen in acetonitrile using sodium bicarbonate as the base. Although the procedure is simple, the reported yields range from 42% to 54% and the method has thus far been limited to relatively small scale syntheses.[13–15] Li and Wong[16] reported preparation of the hydrochloride salt **5** in 77% yield by tris-alkylation of cyclen with *tert*-butyl bromoacetate in chloroform using triethylamine as the base, followed by chromatographic purification.

Kohl et al.[17] published the synthesis and characterization of 1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclo-dodecane in the free base form (**3**) by a multistep procedure unrelated to the syntheses described above. Moore,[18] Barge et al.,[8] and Liu et al.[19] describe methods for obtaining **3** from **4**, but in each case the identity and purity of **3** were not established. Other articles claim syntheses of **3**, but due to incomplete characterization it is unclear if the compounds isolated were the free base or hydrohalide salts.[20–24]

What is clear is that most of the existing synthetic routes to the free base **3** are overly long, time consuming, involve complex work-up procedures and/or a chromatographic purification step, and are thus unattractive for use in large scale syntheses. Most fail to establish the identity and purity of the product. Our interest in the development of redox sensitive MRI CAs[25] motivated the development of a simple, concise, scalable synthesis of **3**.

3. Synthesis of 1,4,7-Tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane Hydrobromide (4) and Generation of the Corresponding Free Base (3)

Our synthesis of the trialkylated hydrobromide salt **4** is an adaptation of the first method described above. This method offers the advantage of selectivity in that the trialkylated salt precipitates from the reaction mixture, thus making it attractive for large-scale preparations. We reasoned that if the addition of *tert*-butyl bromoacetate to cyclen were done at a lower temperature, tetraalkylation would be further prevented, thereby increasing the yield of **4**.

In a typical procedure, 3.3 equiv of *tert*-butyl bromoacetate in dimethylacetamide were added to a stirred suspension of 1 equiv of cyclen and 3.3 equiv of sodium acetate in dimethylacetamide at −20 °C. After stirring for 24 h at room temperature, the reaction mixture was poured into water to give a clear solution. Solid potassium bicarbonate was then added until **4** precipitated as a white solid. The precipitate was collected by filtration and dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$), filtered, and concentrated. Upon the addition of ether, **4** crystallized as a white fluffy solid in ~80% yield. Repetition of the procedure on scales from 1 to 5 g of cyclen gave similar results.

Recrystallization of the hydrobromide salt **4** was attempted from ethyl acetate and toluene without much success. Both solvents failed to yield a crystalline material, and instead shiny amorphous solids were obtained. However, crystallization from water produced crystals that were suitable for X-ray crystallographic analysis. The hydrobromide salt **4** crystallized in space group *P*2/*c* as a hemihydrate (Fig. 1) with half of a molecule of water per asymmetric unit.[26] In the crystal, compound **4** forms an intramolecular N–H···N hydrogen bond between N4 and N2 and exhibits an intermolecular N–H···Br interaction. Two O–H···Br interactions connect adjacent formula units.

The hydrobromide salt **4** was dissolved in water at 70 °C. The solution was allowed to cool to 40 °C, at which point 2 equiv of 10% aqueous potassium hydroxide were added. After stirring for 15 min, **3** had separated as a viscous oil. This oil was extracted into hexanes, the organic layer was dried ($MgSO_4$), filtered, and concentrated to give **2** as a colorless oil in 95% yield. When stored at −20 °C, the oil solidified to give a white solid, mp 44–47 °C, lit.[17] mp 47–50 °C, that was characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analysis. The free base **3** (1 g) was partitioned between water and ether (1:1, 100 mL). Slow evaporation of the ether produced crystals of **3** suitable for X-ray analysis. The free base **3** crystallized in space group *C*2/*c* as a hydrate (Fig. 2) with 1.3 disordered water

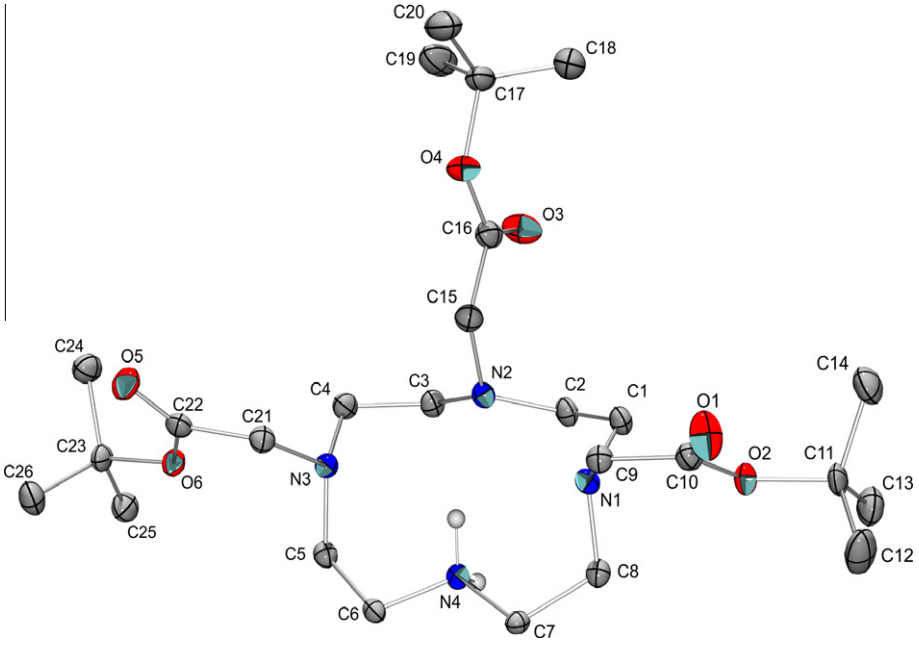

Figure 1. The structure of the cation in **4**. Displacement ellipsoids are at the 50% probability level and C-bound H atoms are omitted.

molecules per asymmetric unit.[27] The structure exhibited substantial positional disorder of the part of the ring which contains the secondary amine. This was modeled using a two-part disorder model with a refined major/minor occupancy ratio of 56:44%.

When dichloromethane was used instead of hexanes for extraction in the above procedure, a crystalline, high melting product (mp 204–205 °C) was isolated. Upon X-ray crystallographic analysis, this product was discovered to be the known hydrochloride salt **5** which crystallized as the hemihydrate[16] and was isomorphous with the hydrobromide salt **4** (Fig. 3).[28,29] Secondary amines are known to react rapidly with dichloromethane to give mixtures of amine hydrochlorides and aminals.[30] In the case of **3**, the secondary amine appears to have decomposed dichloromethane to generate the hydrochloride salt, which was obtained in quantitative yield. This result is consistent with the observation of Li and Wong, who obtained **5** from the reaction of cyclen with *tert*-butyl bromoacetate in chloroform.[16]

In summary, a simple and concise synthesis of the free base **3** was demonstrated via the hydrobromide salt **4**. The procedure was scalable to 5 g of cyclen and seems amenable to further scale-up. Water, a green solvent, was used for crystallization of **4**. The first X-ray crystal structures of the hydrobromide salt **4** and the free base **3** were obtained, along with an X-ray crystal structure of the hydrochloride salt **5**.

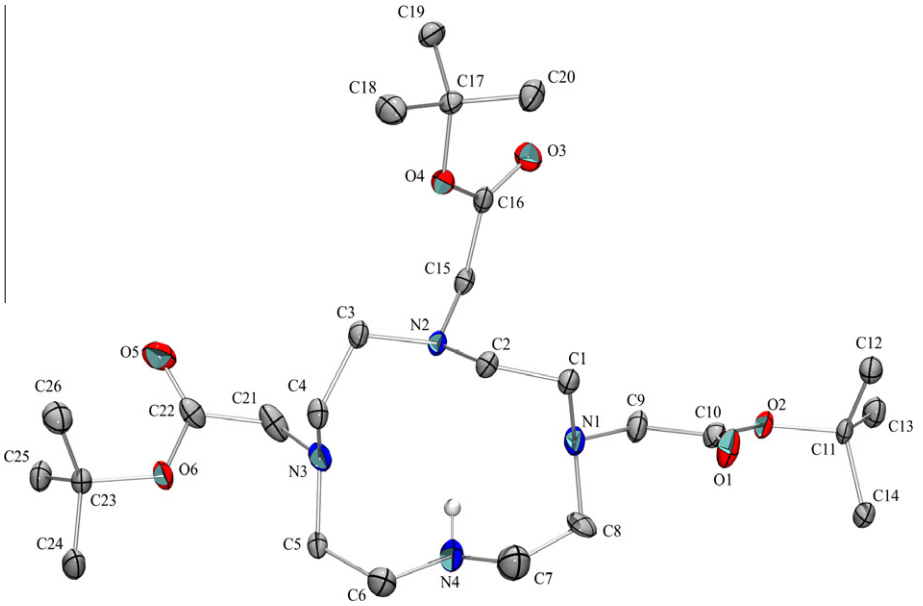

Figure 2. The structure of the free base **3**. Displacement ellipsoids are at the 30% probability level. The minor disorder component, C-bound H atoms, and water molecules are omitted.

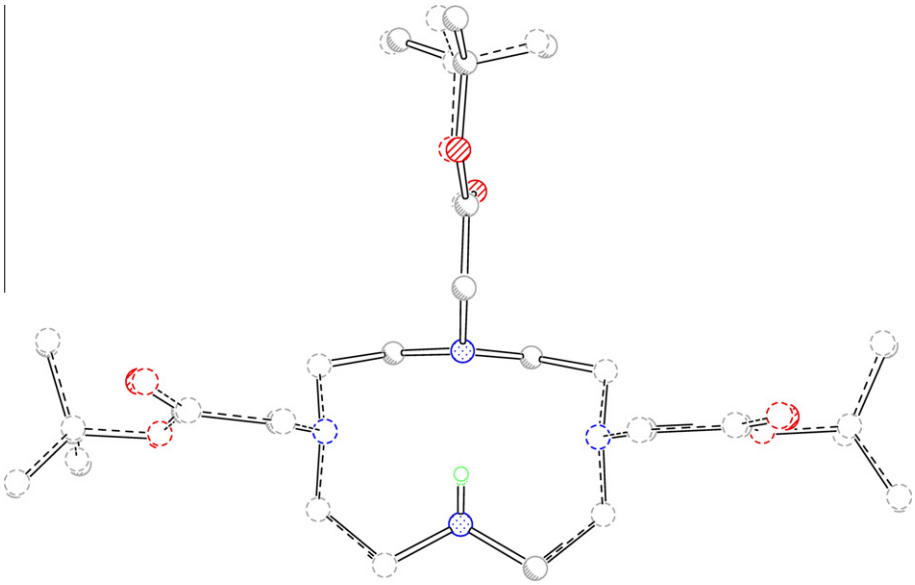

Figure 3. An overlay of the cationic parts of **4** (solid lines) with **5** (dashed lines) formed by a least squares fit of all non-H atoms of the tetraazacyclododecane rings (rms deviation = 0.016 Å).

4. Experimental section

4.1. 1,4,7-Tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane hydrobromide (4)

To a suspension of cyclen (5.00 g, 29 mmol) and sodium acetate (7.86 g, 96 mmol) in *N*,*N*-dimethylacetamide (DMA, 60 mL) at −20 °C was added a solution of *t*-butyl bromoacetate (18.7 g, 14.1 mL, 96 mmol) in DMA (20 mL) dropwise over a period of 0.5 h. The temperature was maintained at −20 °C during the addition, after which the reaction mixture was allowed to come to room temperature. After 24 h of vigorous stirring, the reaction mixture was poured into water (300 mL) to give a clear solution. Solid $KHCO_3$ (15 g, 150 mmol) was added portion wise, and **4** precipitated as a white solid. The precipitate was collected by filtration and dissolved in $CHCl_3$ (250 mL). The solution was washed with water (100 mL), dried ($MgSO_4$), filtered, and concentrated to about 20–30 mL. Ether (250 mL) was added, after which **4** crystallized as a white fluffy solid, mp 190–191 °C (lit.[12] mp 179–181 °C, lit.[13] mp 178–180 °C), R_f 0.28 (10:1 DCM/MeOH on silica gel 60 F_{254}). Yield: 13.6 g (23 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.46 (s, 18H), 2.87 (m, 4H), 2.93 (m, 8H), 3.10 (m, 4H), 3.29 (s, 2H), 3.38 (s, 4H), 10.03 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 47.4, 48.7, 49.1, 51.2, 51.3, 58.1, 81.6, 81.8, 169.5, 170.4.

Anal. Calcd for $C_{26}H_{51}BrN_4O_6$: C, 52.43; H, 8.63; N, 9.41. Found: C, 52.36; H, 8.69; N, 9.45.

4.2. 1,4,7-Tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (3)

Hydrobromide **4** (5.00 g, 8.40 mmol) was dissolved in water (250 mL) at 70 °C. The solution was allowed to cool to 40 °C, after which 10% aqueous KOH solution (9.4 mL, 16.8 mmol) was added. The reaction mixture was stirred for 15 min and then extracted with hexanes (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give **3** as a colorless, viscous oil which solidified upon storage at −20 °C; mp 44–47 °C (lit.[17] mp 47–50 °C). Yield: 4.10 g (8.00 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.46 (s, 18H), 2.56 (m, 4H), 2.72–2.78 (m, 8H), 2.81 (m, 4H), 3.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 (2), 47.7, 50.7, 52.3, 52.4, 53.2, 57.1, 80.7 (2), 171.2, 171.4; HRMS-ESI calcd for $C_{26}H_{51}N_4O_6$ $(M+H)^+$ 515.3803, obsd 515.3806.

Anal. Calcd for $C_{26}H_{50}N_4O_6$: C, 60.67; H, 9.79; N, 10.89. Found: C, 60.26; H, 9.28; N, 10.80.

Acknowledgments

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26. Crystal data for **4**: $2C_{26}H_{51}N_4O_6 \cdot 2Br^- \cdot H_2O$, M_r = 1209.25 g mol^{-1}; colorless rod 0.35 × 0.08 × 0.07 mm^3; T = 100 K, MoKα radiation (λ = 0.71073 Å); space group $P2/c$, unit cell parameters a = 21.631(2) Å, b = 6.8054(7) Å, c = 23.564 (3) Å, V = 3213.0(6) Å^3; 22,521 measured reflections, 6804 unique reflections, 5002 reflections with $F^2 > 2\sigma$; final $R1$ = 0.0344 ($F^2 > 2\sigma$), $wR2$ = 0.0768 (all data).
27. Crystal data for **3**: $C_{26}H_{49}N_4O_6 \cdot 1.3H_2O$, M_r = 538.12 g mol^{-1}; colorless rod 0.37 × 0.07 × 0.06 mm^3; T = 100 K, MoKα radiation (λ = 0.71073 Å); space group $C2/c$, unit cell parameters a = 25.515(5) Å, b = 5.9055(10) Å, c = 41.474 (8) Å, V = 6196.7(19) Å^3; 25,268 measured reflections, 3222 unique reflections, 2546 reflections with $F^2 > 2\sigma$; final $R1$ = 0.0531 ($F^2 > 2\sigma$), $wR2$ = 0.1559 (all data).
28. Crystal data for **5**: $2C_{26}H_{51}N_4O_6 \cdot 2Cl^- \cdot H_2O$, M_r = 1120.33 g mol^{-1}; colorless rod 0.55 × 0.08 × 0.07 mm^3; T = 100 K, MoKα radiation (λ = 0.71073 Å); space group $P2/c$, unit cell parameters a = 21.8420(12) Å, b = 6.6031(3) Å, c = 23.3715(13) Å, V = 3126.9(3) Å^3; 42,356 measured reflections, 8394 unique reflections, 6035 reflections with $F^2 > 2\sigma$; final $R1$ = 0.0383 ($F^2 > 2\sigma$), $wR2$ = 0.0971 (all data).
29. 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-795054, CCDC-793547, and CCDC-793548 for compounds **3**, **4**, and **5**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC by e-mail: deposit@ccdc.cam.ac.uk.
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