# Synthesis of [3⁵]Adamanzane, 1,5,9,13-Tetraazabicyclo[7.7.3]nonadecane, by Oxidative C–N Cleavage of [3⁶]Adamanzane, 1,5,9,13-Tetraazatricyclo[7.7.3.3⁵,¹³]docosane and Crystal Structure of the Tetraprotonated Bromide Salt of [3⁵]Adamanzane

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Reaction of the cage amine [3⁶]adamanzane, 1,5,9,13-tetraazatricyclo[7.7.3.3⁵,¹³]docosane, with sodium iodide in 93% sulfuric acid affords the bicyclic tetraamine [3⁵]adamanzane, 1,5,9,13-tetraazabicyclo[7.7.3]nonadecane which was isolated as its tetraprotonated bromide salt, $[H_4[3^5]adz]Br_4$ (yield 70%). The structure of the $[H_4[3^5]adz]Br_4$ has been determined by X-ray diffraction techniques at $T=120$ K; $M_r=529.09$, monoclinic, $P2_1/n$, $a=11.300(3)$, $b=12.563(3)$, $c=15.561(6)$ Å, $\beta=90.29(3)°$, $Z=4$, $D_x=1.78$ g cm$^{-3}$, Mo $K\alpha=0.710\,73$ Å, $\mu=72.9$ cm$^{-1}$, $F(000)=1176$, $R(F)=0.0734$ for 4028 reflections with $I>2\sigma(I)$ and $wR(F^2)=0.2116$ for all 6439 unique reflections. The conformation of the 16-membered ring is best described as a distorted 'rectangular' [3535] conformation. The distance between the bridging nitrogen atoms is 4.983(9) Å, and the distance between the non-bridging nitrogen atoms is 7.568(10) Å. The four acidic hydrogen atoms are all oriented away from the cavity. The concentration acid dissociation constants of $H_4[3^5]adz^{4+}$ were determined by potentiometric glass-electrode measurements and $^1H$ and $^{13}C$ NMR spectroscopy: $pK_{a1}=1–2$, $pK_{a2}=1–2$, $pK_{a3}=9.65(2)$ and $pK_{a4}=12.09(4)$ (1 M NaBr, 25 °C).

'Cross-bridging' of macrocyclic amines such as cyclen (1,4,7,10-tetraazacyclododecane) and cyclam (1,4,8,11-tetraazacyclotetradecane), i.e. bridging of nonadjacent nitrogens, leads to bicyclic tetraamines, so-called bowl adamanzanes and several synthetic methods for this class of amines have been reported.[1–10] Our own first successful preparation of a bowl adamanzane was achieved[1] by the reaction of *trans*-ditosylated cyclen with the ditosylate of 1,3-propanediol, which after detosylation gave the small bowl [2⁴.3¹]adamanzane (Fig. 1). Further strapping of [2⁴.3¹]adamanzane by the reaction with the ditosylate of 1,3-propanediol was later shown to give the cage adamanzane [2⁴.3²]adz as illustrated (Fig. 1).[11] We recently reported[12] the synthesis of another small tetrahedral cage

[3⁶]adamanzane, 1,5,9,13-tetraazatricyclo[7.7.3.3⁵,¹³]-docosane, obtained by the reaction of 1,5,9-triazacyclododecane with tris(3-chloropropyl)amine. Both cages are formed with an inside coordinated proton and are thus isolated as salts, $[H[2^4.3^2]adz]ClO_4$ and $[H[3^6]adz]Br$, respectively. The inside coordinated protons are unusually inert as to reaction with base and the rate constant for the dissociation of the inside coordinated proton of $H[3^6]adz^+$ in 0.1 M NaOD is less than $4 \times 10^{-8}$ s$^{-1}$ at 25 °C. In this work it is shown how the novel bowl amine [3⁵]adamanzane, 1,5,9,13-tetraazabicyclo[7.7.3]nonadecane, can be synthesized in high yield from the corresponding bowl adamanzane $H[3^6]adz^+$ by reaction with sulfuric acid in the presence of bromide or iodide. Abbreviations are given in the Experimental section.

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## Experimental

*Abbreviations and nomenclature.* The simplified nomenclature suggested for adamanzanes (bowl and cages) have been discussed recently[12,13] and is illustrated in Fig. 1 and below: $[2^4.3^1]$adz $= [2^4.3^1]$adamanzane $=$ 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane. $[2^4.3^2]$adz $=$ $[2^4.3^2]$adamanzane $=$ 1,4,8,11-tetraazatricyclo[6.6.2.2$^{4,11}$]-octadecane. $[3^5]$adz $= [3^5]$adamanzane $=$ 1,5,9,13-tetraazabicyclo[7.7.3]nonadecane. $[3^6]$adz $= [3^6]$adamanzane $=$ 1,5,9,13-tetraazatricyclo[7.7.3.3$^{5,13}$]docosane.

*Materials.* $[H[3^6]$adz]Br was synthesized by the previously published method.[12] All other chemicals were of analytical grade.

*Analyses.* C, H and N analyses were made at the Microanalytical Laboratory, the H.C. Ørsted Institute, Copenhagen. Bromide analyses were made by potentiometric titration with silver nitrate.

*Mass spectra.* Positive ion FABMS were obtained on a Jeol AX505W mass spectrometer using glycerol or NBA (3-nitrobenzylalcohol) as matrix.

*NMR spectra.* $^1$H and $^{13}$C NMR spectra were measured at 5.87 T on a Bruker AC 250 NMR spectrometer equipped with a 5 mm probe. $^1$H chemical shift values ($\delta$) are referenced to internal dioxane [$\delta$(dioxane) $=$ 3.75 ppm] for $D_2O$ solutions. $^{13}$C chemical shift values ($\delta$) are reported in ppm relative to internal TMS in $CDCl_3$ [$\delta$(TMS) $= 0$] and referenced to internal dioxane in $D_2O$ or $H_2O$ [$\delta$(dioxane) $= 67.4$ ppm]. $^{13}$C dept NMR spectra were used to distinguish $CH_3$ and $CH_2$ carbon atoms.

*X-Ray techniques.* Crystal and experimental data for the compound are listed in Table 1. The possible space group was established from rotation and Weissenberg photographs using Cu radiation. The crystals were cooled to 120 K using the Cryostream nitrogen gas cooler system.[14]
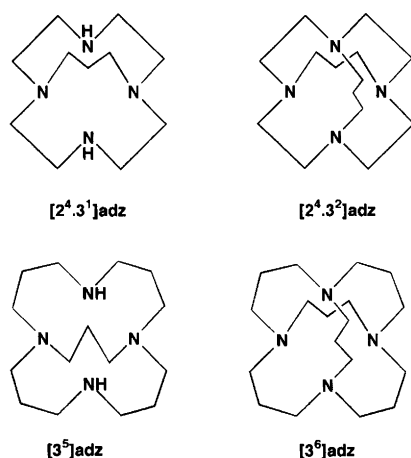


[2⁴.3¹]adz    [2⁴.3²]adz

[3⁵]adz    [3⁶]adz

*Fig. 1.* Bowl and cage adamanzanes.

*Table 1.* Crystal and experimental data.

| | |
|---|---|
| Formula | $[C_{15}H_{36}N_4]^{4+},4Br^-$ |
| Formula weight | 592.09 |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| Unit-cell dimension: | |
| $a$/Å | 11.300(3) |
| $b$/Å | 12.563(3) |
| $c$/Å | 15.561(6) |
| $\beta$/° | 90.29(3) |
| Unit-cell volume, $V$/Å$^3$ | 2209(1) |
| Formula units per unit cell, $Z$ | 4 |
| $F(000)$ | 1176 |
| Calculated density, $D_x$/g cm$^{-3}$ | 1.78 |
| Radiation | Mo $K\alpha$ |
| Wavelength, $\lambda$/Å | 0.71073 |
| Linear absorption coefficient/ cm$^{-1}$ | 72.9 |
| Temperature, $T$/K | 120 |
| Crystal description | Colourless |
| Crystal size/mm | 0.40 × 0.10 × 0.08 |
| Diffractometer | Enraf-Nonius CAD-4F |
| Unit-cell determination | |
| No. of reflections used | 25 |
| $\theta$-range/° | 9.9–15.4 |
| Intensity data collection | |
| $\theta_{max}$/° | 30 |
| Range of $h$ | −15–15 |
| Range of $k$ | 0–17 |
| Range of $l$ | 0–21 |
| Scan mode | $\omega$ |
| Scan range, $\Delta\omega$ | $1.30 + 0.35 \tan \theta$ |
| Total number of unique reflections | 6439 |
| No. of independent reflections, $[I > 2\sigma(I)]$ | 4028 |
| Corrections | Decay, Lorenz-polarization absorption |
| Transmission factors | 0.4669–0.5233 |
| Structure refinement: | |
| Minimization of | $\Sigma w(\|F_o\|^2 - \|F_c\|^2)^2$ |
| Anisotropic thermal parameters | All non-hydrogen atoms |
| Isotropic thermal parameters | Hydrogen atoms |
| No. of refined parameters | 208 |
| Weighting scheme | $[\sigma^2(F_o^2) + (0.1185P)^2 + 1.21P]^{-1}$, $P = (F_o^2 + 2F_c^2)/3$ |
| $R = \Sigma \|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$ | 0.0743 (4028 reflections) |
| $wR2 = [\Sigma w\|F_o^2 - F_c^2\|^2/\Sigma wF_o^4]^{1/2}$ | 0.2116 (6439 reflections) |
| $S = [\Sigma w(\|F_o\|^2 - \|F_c\|^2)^2/(N_{obs} - N_{var})]^{1/2}$ | 1.06 |
| Final $(\Delta/\sigma)_{max}$ | 0.33 |
| Final $\Delta\rho_{min}$ and $\Delta\rho_{max}$/e Å$^{-3}$ | −2.76 and 1.88 |

The unit cells were derived from a least-squares fit of refined diffractometer setting angles for 25 reflections. Four standards were measured for intensity and orientation control after every 4 h. A loss of intensity of about 30% was observed. Therefore, a linear decay correction was applied. Afterwards, the intensities were corrected for Lorentz, polarization and absorption (Gaussian integration) effects.[15] The structure was solved by Patterson method with partial structure expansion and refined by a full-matrix least-squares technique. The hydrogen atoms were all [except the H atom on N(4)] located from electron density difference maps. The non-

hydrogen atoms were refined anisotropically. The hydrogen atoms were at calculated positions using a riding model with C–H = 0.99 Å and N–H = 0.93 Å, and fixed thermal parameters, $U(H) = 1.2 \times U$ for attached atoms. The crystallographic computations were performed with SHELXS86[16] and SHELXL93.[17] The atomic scattering factors were taken from the literature.[18] The PLUTO program[19] was used for illustrations and PLATON[20] for molecular geometry calculations. The final positional parameters are listed in Table 2. Anisotropic thermal parameters, positional parameters for the hydrogen atoms and list of observed and calculated structure factors may be obtained from one of the authors (I.S.) on request.

*Potentiometric titrations.* The concentration of hydrogen ions were measured using Metrohm equipment and a Radiometer glass electrode combined with a calomel reference electrode (GK2401 B). In the pH region 2 –10 ($pH = - \log[H^+]$) the hydrogen ion concentrations were calculated from the electrode measurements using linear extrapolation based upon measurements in 0.01 M HBr, 0.99 M NaBr and 0.001 M HBr, 0.999 M NaBr. The concentration of H⁻ ions in the acidic region (pH < 2) were determined using a non-linear calibration curve based upon EMK measurements of solutions with known H⁺ concentrations varying from 0.01–0.1 M. In the basic region corrections for the sodium error of the glass-electrode have been made using a non-linear correction curve based upon EMK measurements of solutions with known OH⁻ concentrations varying from 0.0001–0.01 M

*Table 2.* Fractional atomic coordinates and equivalent isotropic thermal paramters (in Å²).

| Atom | x | y | z | $U_{eq}{}^a$ |
|------|------|------|------|------|
| N(1) | 0.2804(6) | 0.5864(5) | 0.2585(4) | 0.0200(19) |
| N(2) | 0.5460(6) | 0.7550(5) | 0.0734(4) | 0.0173(17) |
| N(3) | 0.9253(6) | 0.6125(5) | 0.1314(4) | 0.0193(17) |
| N(4) | 0.6691(6) | 0.6393(5) | 0.3668(4) | 0.0147(17) |
| C(1) | 0.3135(7) | 0.6778(6) | 0.2025(5) | 0.019(2) |
| C(2) | 0.3642(7) | 0.6424(6) | 0.1156(5) | 0.018(2) |
| C(3) | 0.4148(8) | 0.7335(7) | 0.0628(5) | 0.022(2) |
| C(4) | 0.6227(7) | 0.6677(7) | 0.0345(5) | 0.020(2) |
| C(5) | 0.7552(8) | 0.6877(6) | 0.0435(5) | 0.022(2) |
| C(6) | 0.8222(8) | 0.5872(6) | 0.0739(5) | 0.022(2) |
| C(7) | 0.8974(8) | 0.6519(6) | 0.2220(5) | 0.022(2) |
| C(8) | 0.8449(7) | 0.5655(6) | 0.2779(5) | 0.016(2) |
| C(9) | 0.7975(7) | 0.6058(6) | 0.3633(5) | 0.018(2) |
| C(10) | 0.5841(7) | 0.5466(6) | 0.3599(5) | 0.018(2) |
| C(11) | 0.4535(7) | 0.5783(7) | 0.3631(5) | 0.021(2) |
| C(12) | 0.3802(7) | 0.5194(6) | 0.2958(5) | 0.019(2) |
| C(13) | 0.5803(7) | 0.7900(6) | 0.1604(5) | 0.018(2) |
| C(14) | 0.6064(7) | 0.6972(6) | 0.2198(5) | 0.016(2) |
| C(15) | 0.6399(7) | 0.7325(6) | 0.3091(5) | 0.0170(19) |
| Br(1) | 0.37967(8) | 0.07168(7) | 0.07007(5) | 0.0286(3) |
| Br(2) | 0.11051(7) | 0.41727(6) | 0.15920(5) | 0.0189(2) |
| Br(3) | 0.41077(8) | 0.29817(7) | 0.44382(5) | 0.0228(2) |
| Br(4) | 0.59767(7) | 0.39900(6) | 0.14979(5) | 0.0204(2) |

$^a U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

and values of $K_w$ determined in this study. The ionic strength was kept constant with NaBr ($I = 1.00$ M). The ionic product of water in 1 M NaBr was determined from pH measurements in 0.000 100 M NaOH, 1.00 M NaBr, which gave ($pK_w = -\log[H^+][OH^-]$): $pK_w(15.0\,°C) = 14.15(1)$, $pK_w(25.0\,°C) = 13.80(1)$ and $pK_w(40.0\,°C) = 13.32(2)$. From these values $\Delta H (K_w) = 57.7(5)\,kJ\,mol^{-1}$ and $\Delta S (K_w) = -70.8(18)\,J\,mol^{-1} K^{-1}$ were calculated. The concentration acid dissociation constants were determined by dissolution of $[H_4[3^5]adz]Br_4$ in an excess of acid and titration with NaOH. The constants were calculated from the titration data by non-linear least-squares calculation using the program PROC NLIN (DUD method) from the SAS Institute INC, Cary, USA.

*Synthesis.*

*[H₄[3⁵]adz]Br₄.* A mixture of [H[3⁶]adz]Br (1.00 g, 2.6 mmol), NaI (0.36 g, 2.4 mmol) and 93% sulfuric acid (2.4 ml) in a small test tube was heated with stirring to 100 °C for 24 h. During the first 2 h a vigourous evolution of bromine and iodine gas occured. After 4 h the test tube was covered, but not closed, and the heating was continued further 20 h. The resulting black solution was cooled to room temperature. Water (20 ml) was slowly added and the mixture was centrifuged. The precipitate was extracted with two 20 ml portions of water, and the combined aquoeus solutions were filtered through a sintered glass filter (porosity G3). An aqueous solution of 40% NaOH (30 ml) was then added and the strong basic mixture was extracted four times with 40 ml portions of chloroform. The combined chloroform extracts was dried 24 h with solid anhydrous $Na_2SO_4$, filtered and evaporated to dryness using a rotatory evaporator (water bath temperature initially 40 °C and then 80 °C). The residue was extracted with water (one 10 ml portion followed by four 5 ml portions), and hydrobromic acid (47%, 9 ml) was added to the combined, filtered, extracts. Evaporation to dryness using a rotatory evaporator (water bath temperature 60 °C) followed by washing with two 3 ml portions of methanol and drying in the air gave a pale yellow crude product (1.35 g). Dissolution in water (1.35 ml) at room temperature, filtration, addition of hydrobromic acid (47%, 2.6 ml) and cooling in ice gave a white crystalline precipitate. The product was isolated by filtration, washed with 96% ethanol (three 2 ml portions) and dried in the air. This gave 1.06 g of pure $[H_4[3^5]adz]Br_4$ (yield 70%). FABMS ($m/z$): 269 ($M + H^+ = H[3^5]adz^+$). Analytical data: Calculated for $C_{15}H_{36}N_4Br_4$: C, 30.4; H, 6.13; N, 9.46; Br, 54.0. Found: C, 29.6; H, 5.85; N, 9.07; Br, 54.0. NMR data are given later in Table 4.

Crystals for the crystallographic work were obtained as follows. To a solution of $[H_4[3^5]adz]Br_4$ (105 mg) in water (0.14 ml) at room temperature was added 47% hydrobromic acid (0.28 ml) and the mixture was kept at room temperature for 4 h. The crystals were isolated by

filtration, washed with ice cold methanol and dried in the air.

*[H[3⁶]adz]OH·4H₂O.* The crude product from the synthesis of the cage was treated with base as described in Ref. 12. The sample (0.5 g) was dissolved in 0.1 M NaOH (6.4 ml), heated to 80 °C and then kept at this temperature for 10 min. A white oil of polymeric by-products separated, the mixture was cooled to room temperature and the solution was filtered through a fine porosity filter. To the filtrate was added a 40% solution of NaOH (3 ml), and pale yellow crystals separated. The precipitate was isolated by filtration, washed with diethyl ether and dried in the air. The product was dissolved in water (4.0 ml) at 80 °C and a yellow impurity was removed by filtration of the solution while hot. Then a 40% solution of NaOH was added and colourless crystals separated. After 1 h, the precipitate was filtered off, washed with diethyl ether and dried in the air. This gave 113 mg of [H[3⁶]adz]OH·4H₂O (yield 12% based upon 1,5,9-triazacyclododecane). Analytical data: Calculated for $C_{18}H_{38}N_4O \cdot 4H_2O$: C, 54.24; H, 11.63; N, 14.06. Found: C, 54.82; H, 9,42; N, 13.49.

## Results and discussion

*Crystal structure of [H₄[3⁵]adz]Br₄.* Bond lengths and bond angles are listed in Table 3. The compound consists of $[C_{15}H_{36}N_4]^{4+}$ and $Br^-$ ions. The labelling of the atoms in the cation is shown in Fig. 2. In the 16-membered ring the average C–N bond length of 1.513(5) Å and the average C–C bond length of 1.527(4) Å are somewhat longer than the average C–N bond of 1.457(2) Å and the average C–C bond length of 1.511(1) Å, found in 1,5,9,13-tetraazacyclohexadecane ([16]aneN₄).[21] The values of the present structure are
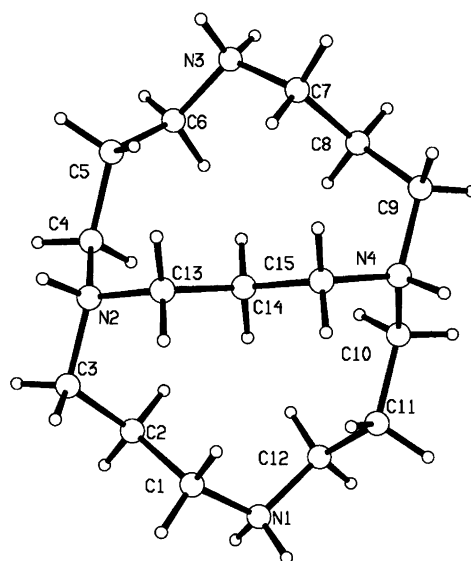


*Fig. 2.* View of the $H_4[3^5]adz^{4+}$ cation with atomic labelling.

more in agreement with the values found in the 12-membered ring of 1,4,7,10-tetraazabicyclo[5.5.3]penta-decane dibromide perchlorate $(H_3[2^4.3^1]adz^{3+})^1$ the average C–N and the average C–C bond lengths being 1.495(6) and 1.514(4) Å, respectively. The conformation of the 16-membered ring is best described as a distorted 'rectangular' [3535] conformation[22] with N(1), C(3), N(3) and C(9) situated at the corner positions (Fig. 2). The N(1)–N(3) distance between the non-bridging nitrogen atoms is 7.568(10) Å and the N(2)–N(4) distance between the bridging nitrogen atoms is 4.983(9) Å. The conformation is not so elongated as found in $H_3[2^4.3^1]adz^{3+}$ [5.194(7) and 2.567(4) Å].[1] The N(1) and N(3) atoms have a deviation of −0.645(6) Å and the N(2) and N(4) atoms a deviation of 0.645(6) Å from the least-squares plane through them. In [16]aneN₄[21] the average deviation of the nitrogen atoms is 0.019 Å from their least-squares plane. All six N–H bonds are oriented away from the cavity (Fig. 3), and the H atoms are involved in hydrogen bonds with the bromide ions. The N(1)–H(1)···Br(2) bond and the N(1)–H(2)···Br(1) [1/2−x, 1/2+y, 1/2−z] bond being 3.249(7) and 3.236(7) Å, respectively. The N(2)–H(3)···Br(1) [1−x, 1−y, −z] bond is 3.233(6) Å and the N(3)–H(4)···Br(3) [3/2−x, 1/2+y, 1/2−z] and the N(3)–H(5)···Br(2) [1+x, y, z] are 3.204(7) and 3.252(7) Å, respectively. The N(4)–H(6)···Br(3) is 3.185(6) Å.
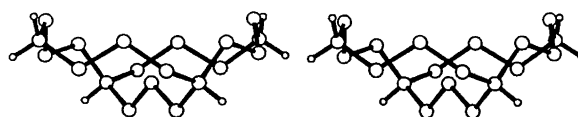
*Table 3.* Bond lengths (in Å) and bond angles (in °).

| | | | |
|---|---|---|---|
| N(1)–C(1) | 1.490(10) | N(1)–C(12) | 1.520(10) |
| N(2)–C(3) | 1.515(11) | N(2)–C(4) | 1.525(11) |
| N(2)–C(13) | 1.473(10) | N(3)–C(6) | 1.499(11) |
| N(3)–C(7) | 1.529(10) | N(4)–C(9) | 1.512(10) |
| N(4)–C(10) | 1.513(10) | N(4)–C(15) | 1.511(10) |
| C(1)–C(2) | 1.537(11) | C(2)–C(3) | 1.522(12) |
| C(4)–C(5) | 1.524(12) | C(5)–C(6) | 1.545(11) |
| C(7)–C(8) | 1.514(11) | C(8)–C(9) | 1.522(11) |
| C(10)–C(11) | 1.530(11) | C(11)–C(12) | 1.524(11) |
| C(13)–C(14) | 1.516(11) | C(14)–C(15) | 1.505(11) |
| | | | |
| C(1)–N(1)–C(12) | 117.5(6) | C(3)–N(2)–C(4) | 112.7(6) |
| C(3)–N(2)–C(13) | 113.9(6) | C(4)–N(2)–C(13) | 115.6(6) |
| C(6)–N(3)–C(7) | 117.1(6) | C(9)–N(4)–C(10) | 113.1(6) |
| C(9)–N(4)–C(15) | 113.6(6) | C(10)–N(4)–C(15) | 114.7(6) |
| N(1)–C(1)–C(2) | 112.8(6) | C(1)–C(2)–C(3) | 113.6(6) |
| N(2)–C(3)–C(2) | 116.4(7) | N(2)–C(4)–C(5) | 113.9(7) |
| C(4)–C(5)–C(6) | 111.9(7) | N(3)–C(6)–C(5) | 112.8(6) |
| N(3)–C(7)–C(8) | 112.4(6) | C(7)–C(8)–C(9) | 113.8(6) |
| N(4)–C(9)–C(8) | 117.8(6) | N(4)–C(10)–C(11) | 114.2(6) |
| C(10)–C(11)–C(12) | 111.9(7) | N(1)–C(12)–C(11) | 113.2(6) |
| N(2)–C(13)–C(14) | 112.3(6) | C(13)–C(14)–C(15) | 112.6(6) |
| N(4)–C(15)–C(14) | 111.9(6) | | |



*Fig. 3.* Stereo view of the $H_4[3^5]adz^{4+}$ cation showing that all N–H bonds are oriented away from the cavity.

*Synthesis and characterization.* Heating solutions of H[3⁶]adz⁺ in the presence of halide ions gives cleavage of one of the trimethylene bridges affording the bowl adamanzane, $H_4[3^5]adz^{4+}$, as the dominant product as shown in Scheme 1 for $X^- = Br^-$ or $I^-$. The cleavage reaction was studied using various temperatures and different concentrations of sulfuric acid and iodide. It was found that heating a solution of [H[3⁶]adz]Br in 93% $H_2SO_4$ for 24 h at 100 °C with NaI (0.9 mol per mol of amine) gave the highest yield. The reaction gives a large amount of black by product, which easily is removed by filtration. The pure tetrahydrobromide, $[H_4[3^5]adz]Br_4$ was obtained by one single recrystallization in a yield of 70% based upon cage amine. The presence of halide ions seems to be essential as heating of the hydroxide salt, [H[3⁶]adz]OH, in 93% sulfuric acid did not give formation of the bowl amine. Without addition of iodide, such that only bromide is present, the yield was only 24%.

The compound was identified by elemental analysis, FABMS, ¹H and ¹³C NMR spectroscopy and finally by X-ray analysis as described above. The ¹³C NMR spectra of $[H_4[3^5]adz]Br_4$ in acidic, neutral or basic solution exhibit five sharp signals (all $CH_2$). The assignments of the signals were made unambiguously on basis of the relative intensities (4:4:2:4:1), and the chemical shift values (the resonance of aliphatic carbon atoms bound to N in tertiary amines are generally shifted significantly downfield relative to aliphatic carbon atoms bound to N in secondary amines). In Table 4 ¹³C NMR chemical shift values for the four species $H_4[3^5]adz^{4+}$, $H_2[3^5]adz^{2+}$, $H[3^5]adz^+$ and $[3^5]adz$ are given. It is noted that no data for the $H_3[3^5]adz^{3+}$ species are given, since aqueous solutions of this cation allways contain significant amounts of either the di- or tetraprotonated
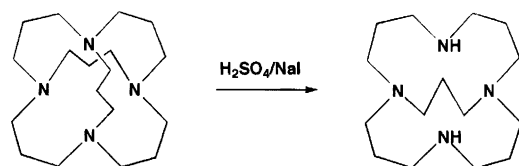
species (see also the $pK_a$ values discussed below). The ¹H NMR spectra of the four species consist of two multiplets centered around 2.25 ppm and 3.2 ppm ($H_4[3^5]adz^{4+}$) or three multiplets centered around 1.8–2.1 ppm, 2.4–2.7 ppm and 2.6–3.3 ppm ($H_2[3^5]adz^{2+}$, $H[3^5]adz^+$ and $[3^5]adz$).

The reaction mechanism for the cleavage reaction is not known. It seems likely that the first step is reaction of iodine (formed by the oxidation of iodide by sulfuric acid) with an amine group to give a N–I bond. The further sequence of the cleavage reaction is not known. In this context it should be mentioned that the oxidative cleavage of a series of primary, secondary and tertiary aliphatic amines by reaction with HOCl has been studied.[23] Chloroamine or enamines was suggested as possible intermediates but the mechanism was not solved. In the present case it is surprising that further cleavage of the bicyclic amine does not occur to any significant extent. In contrast, oxidation of H[3⁶]adz⁺ using conditions similar to those described in Ref. 23, aqueous bromine at pH 7, gave a complex mixture of unidentified products indicating that oxidation takes place at all four tertiary amine groups.

*Concentration acid dissociation constants of $H_4[3^5]adz^{4+}$.* The concentration acid dissociation constants ($K_{ai}$) of $H_4[3^5]adz^{4+}$ were studied by potentiometric titrations at three temperatures which gave values for $pK_{a3}$ and $pK_{a4}$ given in Table 5, which also contains the

*Table 5.* Thermodynamic data for the dissociation constants of $H_4[3^5]adz^{4+}$ (1 M NaBr).

| $T/°C$ | $pK_{a3}$(obs) | $pK_{a3}$(calc)[a] | $pK_{a4}$(obs) | $pK_{a4}$(calc)[b] |
|---|---|---|---|---|
| 15.0 | 9.938 | 9.90(1) | 12.323 | 12.35(2) |
| — | 9.851 | — | 12.370 | — |
| 25.0 | 9.668 | 9.65(2) | 12.107 | 12.09(4) |
| — | 9.665 | — | 12.137 | — |
| 40.0 | 9.312 | 9.31(4) | 11.727 | 11.75(6) |
| — | 9.296 | — | 11.764 | — |

[a] Calculated from $\Delta H°(K_{a3}) = 40(2)$ kJ mol⁻¹ and $\Delta S°(K_{a3}) = -49(6)$ J mol⁻¹ K⁻¹. [b] Calculated from $\Delta H°(K_{a4}) = 41(3)$ kJ mol⁻¹ and $\Delta S°(K_{a4}) = -93(9)$ J mol⁻¹ K⁻¹.



*Scheme. 1.*

*Table 4.* ¹³C NMR chemical shift data at 25 °C.

| Species | Solvent | δ(ppm) $C$–N(tert) (bridge) | $C$–N(tert) | $C$–N(sec) | $C$–$C$–$C$ (bridge) | $C$–$C$–$C$ |
|---|---|---|---|---|---|---|
| $H_4[3^5]adz^{4+}$ | 1 M DCl[a] | 59.2 | 52.4 | 43.0 | 22.6 | 20.4 |
| $H_2[3^5]adz^{2+}$ | 1 M NaCl[b] | 53.4 | 53.2 | 47.1 | 21.5 | 21.4 |
| $H[3^5]adz^+$ | 1 M NaCl[c] | 53.8 | 53.1 | 47.4 | 22.7 | 22.0 |
| $[3^5]adz$ | 0.4 M NaOD[d] | 54.3 | 53.6 | 47.7 | 24.4 | 23.0 |

[a] The same spectrum was observed in 3 M DCl. A similar spectrum was obtained in 0.1 M DCl, 0.9 M NaCl. [b] The solution was made by mixing $[H_4[3^5]adz]Br_4$ with 2 equiv. of NaOD. [c] The same spectra were obtained for solutions made by mixing $[H_4[3^5]adz]Br_4$ with 3, 3.1 or 3.2 equiv. of NaOD. [d] $I = 1.0$ M (NaCl). Nearly the same values were obtained by dissolving the free amine in 0.1 M NaOD, 0.9 M NaCl.

*Table 6.* Acid dissociation constants of bowl adamanzanes (25 °C and $I = 1.00$ M).

| L | $pK_{a1}$ | $pK_{a2}$ | $pK_{a3}$ | $pK_{a4}$ |
|---|---|---|---|---|
| $H_4[2^4.3^1]adz^{4+,a}$ | $< -1$ | 3.202(7) | 7.242(8) | $> 15$ |
| $H_4[3^5]adz^{4+,b}$ | 1–2 | 1–2 | 9.65(2) | 12.09(4) |

$^a$ From Ref. 1, 1 M NaBr. $^b$ This work, 1 M NaBr.

respective values for $\Delta H°(K_{ai})$ and $\Delta S°(K_{ai})$. From the titration data it was not possible to estimate $K_{a1}$ and $K_{a2}$, which both are smaller than 0.001 M. The observation that the $^1$H and $^{13}$C NMR spectra of $[H_4[3^5]adz]Br_4$ in 1 M DCl and 3 M DCl are very similar to, but different from, those measured in less acidic solutions indicates that the amine is fully protonated in these solvents. It is therefore estimated that $pK_{a1}$ and $pK_{a2}$ are both in the region 1–2.

The acid–base properties of $H_4[3^5]adz^{4+}$ and $H_4[2^4.3^1]adz^{4+}$ are very different (Table 6). The small bowl adamanzane acts as a proton sponge, i.e. the free amine is monoprotonated even in 1 M NaOH, whereas the larger bowl is significantly less basic. The difference is explained by the size and geometry of the two species: In the small bowl, the inherent strain forces the two tertiary bridgehead nitrogen groups into a close position which facilitates the coordination of one proton to both nitrogen groups as shown in the crystal structure of $[H_3[2^4.3^2]adz]Br_2ClO_4$. From the present crystal structure it is seen that the $H_3[3^5]adz^{3+}$ ion may adopt a relatively flat conformation and a similar hydrogen bridging is not favoured. This amine therefore acts as a 'normal' base as also found for a series of analogous bowl adamanzanes. The first acid dissociation constant of $H_4[3^5]adz^{4+}$ lies in the region 0.01–0.1 M, while $H_4[2^4.3^1]adz^{4+}$ is a very strong acid $(K_{a1} > 10)$, and this difference may likewise be explained by the stabilty of the bridging proton in the case of the smaller triprotonated bowl.

*Reaction with metal ions.* The small bowl amine $[2^4.3^1]adz$ forms very inert metal ion complexes as shown recently in studies of mononuclear and trinuclear copper(II) complexes.[13,24] As mentioned, $[2^4.3^1]adz$ is a proton sponge and the formation of copper(II) complexes has been shown to be slow probably due to the inertness of the bridging proton in $H[2^4.3^1]adz^+$. The present amine is much less basic and a similar strong competition between the hydrogen ions and metal ions is therefore expected to be less dominant. In agreement with this, we have observed that the large bowl amine readily form complexes with copper(II) and zinc(II). These complexes and coordination compounds with other transition metal ions are now being studied.

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