An Inert Proton Coordinated Inside the Tetrahedral Cage [3⁶]Adamanzane. Synthesis of the Inside Monoprotonated Amine 1,5,9,13-Tetraazatricyclo[7.7.3.3⁵,¹³]docosane

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The reaction of 1,5,9-triazacyclododecane with tris(3-chloropropyl)amine affords the inside monoprotonated form of the tricyclic amine 1,5,9,13-tetraazatricyclo[7.7.3.3⁵,¹³]docosane ([3⁶]adamanzane), which was isolated as the bromide salt, [H[3⁶]adz]Br·0.5H$_2$O (27%) and the dithionate salt, [H[3⁶]adz]$_2$[S$_2$O$_6$] (28%). The tricyclic structure of H[3⁶]adz$^+$ was established by ^{1}H and ^{13}C NMR spectroscopy, which shows that the cation in solution has a time-averaged T$_d$ symmetry. H[3⁶]adz$^+$ is unusually inert as to reaction with base. From ^{1}H NMR measurements it is estimated that the rate constant for the dissociation the inside coordinated proton of H[3⁶]adz$^+$ in 0.1 M NaOD is less than 4×10^{-8} s^{-1} at 25°C. In chloroform and in aqueous solutions (pH > 2) the dominant form of the cage has all four lone pairs pointing inside the cavity.

The class of tricyclic tetraamines, whose smallest member is the classical compound urotropin or 'hexamethylenetetraamine', has until now only been studied scarcely. The crystal structure of hexamethylenetetraamine, reported by Dickinson and Raymond in 1923, was the first structure of an organic compound obtained by X-ray diffraction.[1] As shown in Fig. 1 the four lone pairs of the nitrogen bridgehead are oriented outside the cavity. Only few examples of larger tricyclic amines have been reported. Schmidtchen[2-7] has synthesized and studied the large tricyclic tetraamines L3 and L4 shown in Fig. 1. Related large tricyclic compounds with 1,3-xylenane bridges have been reported by Takemura et al.,[8] and Graf and Lehn have reported cages based upon 5-oxapentamethylene chains.[9,10-13] The studies of these compounds have been focused mainly on the ability of the quaternary derivatives (or the protonated forms) to form inclusion compounds with anions and biological important compounds such as AMP, ATP and NAD.[4] We recently presented[14] a facile method for the synthesis of the inside protonated form of a small tricyclic tetraamine H[2⁴.3²]adz$^+$ (L2 in Fig. 1). This is the first example of a macrotricyclic compound containing only small chains (n = 2 or 3) with four donor atoms in an approximately tetrahedral arrangement. From the X-ray crystal structure determination it was shown that the proton in the center is hydrogen-bonded to two nitrogen atoms with only weak interactions to the
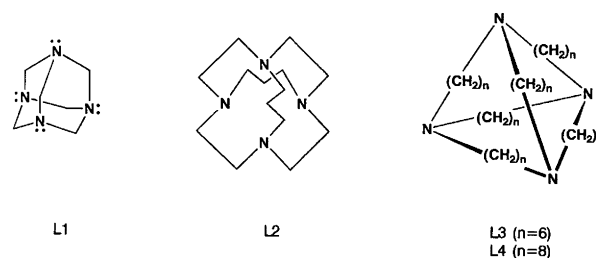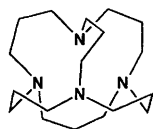
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Fig. 1. [1⁶]adamanzane (L1, urotropin or hexamethylenetetramine) and some higher members of the tricyclic tetraaza cages: [2⁴.3²]adamanzane (L2) reported by Springborg et al.[14] and [6⁶]adamanzane (L3) and [8⁶]adamanzane (L4) reported by Schmidtchen.[2]

other two nitrogen atoms. From ^{1}H and ^{13}C NMR studies it was shown that the cation in solution has a time-averaged D$_{2d}$ symmetry. The protonated amine is aprotic in the pH range 0–14 and it is extremely inert with respect to exchange of the inside bound proton. The rate constant for the dissociation of the proton in 1 M NaOD is less than 2×10^{-8} s^{-1} at 25°C.

Our ultimate goal with this project is to synthesize small tetraaza cages in order to study their coordination compounds with Lewis acid. This goal was only fulfilled partially with the cage H[2⁴.3²]adz$^+$. Apart from H$^+$, this cage is too small to accommodate space for encapsulation of most other Lewis acids. Encapsulation of metal ions clearly requires cages with larger cavities. A

L5

Fig. 2. [3⁶]adamanzane **(L5)**.

Table 1. Selected ^{13}C and ^1H NMR chemical shift data at 25°C for [H[3⁶]adz]Br.

Solvent	δ(ppm)		
	N–*C*	C–*C*–C	N···*H*
1 M NaOD	54.02	21.65	9.83
0.01 M NaOD	54.03	21.64	9.83
0.01 M DCl	54.02	21.64	9.83
CDCl₃	53.50	21.22	9.69

promising candidate seems to be the tetraamine cage with six trimethylene bridges, [3⁶]adamanzane **(L5** shown in Fig. 2). Models show that this cage may exist in a relatively strain-free conformation with all four lone pairs of the nitrogen donor atoms pointing inside the cavity and with a distance from the center to each nitrogen atom of approximately 2.0 Å, which is the ideal distance for forming coordination compounds with many transition-metal ions. In this paper we present the synthesis of the inside monoprotonated form of this new cage. Abbreviations and a simplified nomenclature for this series of tricyclic tetraamines are given in the Appendix.

Experimental

Materials. 1,5,9-Triazacyclododecane was prepared by modifications[15–17] of the method of Koyama and Tamotsu[18] or by the method of Alder *et al.*,[19] and tris(3-chloropropyl)amine was prepared by published methods.[20,21] All other chemicals were of analytical grade.

Analyses. C, H, N, Br and S analyses were made by the Microanalytical Laboratory at the H.C. Ørsted Institute, Copenhagen.

Mass spectra. Positive ion FABMS were obtained on a Jeol AX505W mass spectrometer using NBA as a matrix.

NMR spectra. ^1H and ^{13}C NMR spectra were measured at 5.87 T on a Bruker AC 250 NMR spectrometer equipped with a 5 mm probe. ^1H chemical shift values (δ) are reported in ppm and are referenced to internal dioxane [δ(dioxane) = 3.75 ppm] for D₂O solutions. ^{13}C chemical shift values (δ) are referenced to internal dioxane [δ(dioxane) = 67.40 ppm] for D₂O solutions. For CDCl₃ solutions chemical shift values (δ) are referenced to internal TMS [δ(TMS) = 0 ppm]. ^{13}C DEPT NMR spectra were used to assign CH₂ carbon atoms.

Synthesis
[H[3⁶]adz]Br·0.5H₂O A mixture of 1,5,9-triazacyclododecane (1.63 g, 9.5 mmol), tris(3-chloropropyl)amine (2.34 g, 9.5 mmol) and Na₂CO₃ (3.02 g, 28.5 mmol) in acetonitrile (190 ml) was refluxed for eight days. Evaporation of the filtered reaction mixture to dryness gave a white solid, which was washed thoroughly with diethyl ether and dried in the air (1.97 g). The product was dissolved in 0.1 M NaOH (25 ml) and heated to 80°C and

then kept at this temperature for 10 min. A yellow 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 1.0 ml of a saturated solution of sodium bromide was added, and colourless crystals separated. After 1 h the precipitate was filtered off, washed three times with 1.0 ml ice-cold water and dried in the air. This gave 1.01 g of pure [H[3⁶]adz]Br·0.5H₂O (yield 27%). FABMS (*m/z*): 309 (H[3⁶]adz⁺). Analytical data: Calculated for C₁₈H₃₇N₄Br·0.5H₂O: C, 54.3; H, 9.61; N, 14.06; Br, 20.1. Found: C, 55.1; H, 9.82; N, 14.15; Br, 20.0. NMR data are given in Table 1 and Fig. 3 (see also Results).

[H[3⁶]adz]₂[S₂O₆]. This salt was isolated as described above with the exception that the final precipitation was made by addition of 3.0 ml of a saturated solution of sodium dithionate. The product was washed three times with 2.0 ml of ice cold water and air-dried. This gave 1.05 g of pure [H[3⁶]adz]₂[S₂O₆] (yield 28%). FABMS (*m/z*): 309 (H[3⁶]adz⁺). Analytical data: Calculated for C₁₈H₃₇N₄SO₃: C, 55.5; H, 9.57; N, 14.38; S, 8.23. Found: C, 55.9; H, 9.83; N, 14.00; S, 8.32. The ^1H and ^{13}C NMR spectra of this salt are identical to the respective spectra of the bromide salt described above.

Results

Synthesis and characterization. The macrotricyclic cage H[3⁶]adz⁺ has been made by the reaction of 1,5,9-tri-

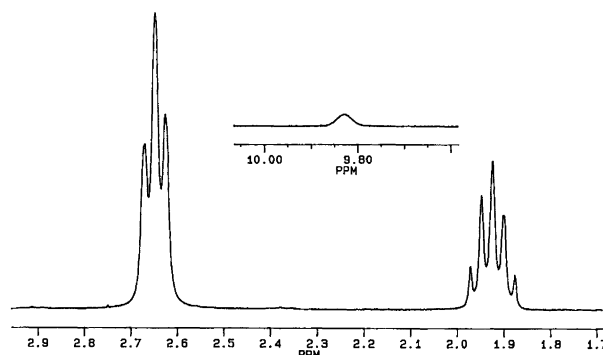*Fig. 3.* ^1H NMR spectrum of [H[3⁶]adz]Br in 0.01 M NaOD at 25°C.

azacyclododecane with tris(3-chloropropyl)amine as shown in Scheme 1. The monoprotonated amine H[3^6]adz$^+$ was isolated as a bromide salt (yield 27%) and as a dithionate salt (yield 28%). The tricyclic structure of this new cage was established unambiguously by its elemental analysis, FABMS (see Experimental) and ^{1}H and ^{13}C NMR spectra. The elemental analysis together with the FABMS strongly indicate that the cation in the isolated salts has the composition as shown for H[3^6]adz$^+$ in Scheme 1. The ^{13}C NMR spectrum in D_2O exhibits two sharp signals (both CH_2) with the relative intensities 2:1. The chemical shift values are in the expected[14] regions (Table 1). The ^{1}H NMR spectrum shown in Fig. 3 has a quintet centered around 1.92 ppm (12 protons, C–CH_2–C), a triplet centered around 2.65 ppm (24 protons, CH_2–N) and a singlet at 9.83 ppm (one inside coordinated proton, see also below). It is seen that the observed NMR spectra are in complete agreement with the proposed structure, and it is also noted that all other possible products would have much more complex spectra than observed. The NMR spectra show that the cation in solution has a time-averaged T_d symmetry. The high symmetry is explained by fast equilibria between different conformations of the trimethylene chains and different sites for the inside coordinated proton. From the present data it is not possible to determine whether the proton is bound to one or several of the four inside oriented lone pairs. If the proton is not bound symmetrically to all four nitrogen donors the present NMR results show that it must shuttle fast, on the NMR timescale, between the different sites. The observed T_d symmetry suggests that each lone pair on the four nitrogen donors are pointing inside the cavity. The fact that an X-ray crystal structure has shown that the related cage H[2^4.3^2]adz$^+$ has this conformation[14] in the crystal indirectly supports this proposal. Furthermore, the ^{1}H NMR spectra of aqueous solutions of H[3^6]adz$^+$ are unchanged for pH 2–14. This shows that protonation of the cage does not occur in this pH region and that inversion reactions leading to forms with one or several lone pair(s) pointing outside do not occur to any significant extent. The ^{1}H and ^{13}C NMR spectra of H[3^6]adz$^+$ in D_2O are nearly identical to those obtained for a solution in $CDCl_3$ (Table 1), thus indicating that the same structure is present in the two solvents. It is concluded that the new cage has the tricyclic structure as shown in Fig. 2 with one proton coordinated to one or several of the four nitrogen donors, which all have the lone pair oriented inside the cavity.
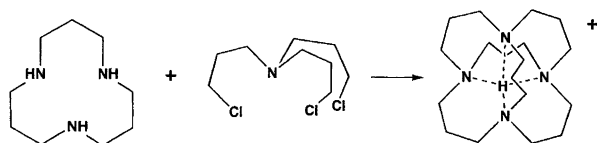
Scheme 1. Reflux (CH_3CN, Na_2CO_3) for 8 days affords the tricyclic cage, which was isolated as [H[3^6]adz]Br·0.5H_2O in 27% yield.

The fact that the product is H[3^6]adz$^+$ and not the free amine prompts the interesting question of whether the proton is encapsulated during or after the formation of cage. For the corresponding amine H[2^4.3^2]adz$^+$ it has been proposed[14] that the reaction directly yields the inside protonated form. In the case of H[2^4.3^2]adz$^+$ the reactant is protonated with one proton bound to the two bridgehead nitrogen atoms and thereby prevents these groups from reacting with the tosylate causing quaternary side-products and also forces the intermediate in a conformation which favours the last step (Scheme 2).[14,22] In this case the reaction may be described as proton assisted, i.e. the proton acts as an internal template similar to the more common metal-assisted and template organic reactions.[9,23] A similar mechanism may explain that H[3^6]adz$^+$ is formed directly as its inside monoprotonated form (Scheme 2).

Inertness of the inside coordinated proton of H[3^6]adz$^+$. The inside coordinated proton was found to be very inert with respect to dissociation. For solutions of H[3^6]adz$^+$ in 0.1 M NaOD the ^{1}H NMR signal for the inside coordinated proton does not loose intensity within 1 month. Therefore, it can be concluded that the rate constant for dissociation of the proton from H[3^6]adz$^+$ must be less than 4×10^{-8} s^{-1} (0.1 M NaOD, 25°C). The inertness
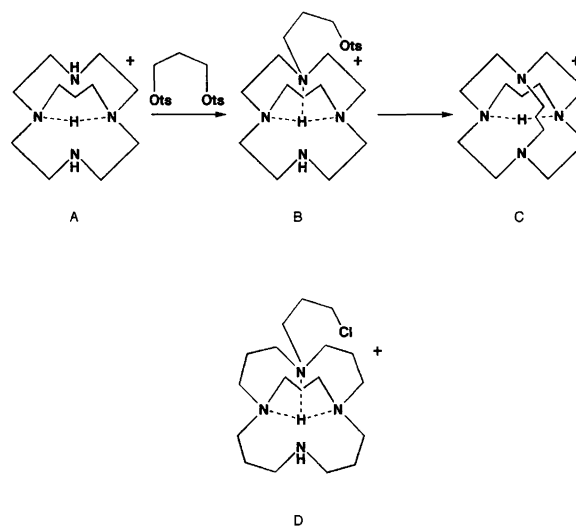
Scheme 2. The tetraaza cage H[2^4.3^2]adz$^+$ has previously[14] been synthesized by reacting the amine A with the ditosylate of 1,3-propanediol. A is a proton sponge[22] (the monoprotonated form has pK_a > 15). An X-ray crystal structure analysis has shown[22] that the proton is coordinated to the two bridgehead nitrogen atoms. It is assumed that the intermediate, B, also is a proton sponge. The proton keeps A as well as the intermediate B in conformations which favour the formation of the cage C (H[2^4.3^2]adz$^+$) and also protects the bridgehead nitrogens from reaction with the tosylate.[14] It is seen that the last intermediate, D, in the present synthesis of H[3^6]adz$^+$ closely resembles the intermediate B. It is proposed that the formation of H[3^6]adz$^+$ as well may be proton assisted and that it is formed directly in its protonated form.

of $H[3^6]adz^+$ with respect to proton exchange is easily understood considering that the proton is totally encapsulated in a very rigid, yet relatively strainless, cage. Any movement in the direction of dissociation of the proton will at some point go through a very strained transition state. This extreme inertness places the $H[3^6]adz^+$ cation together with the smaller cage $H[2^4.3^2]adz^+$ as some of the most inert protonated amines reported in the literature.[9,14,24,25] The free amine is probably, like $[2^4.3^2]$adamanzane, a strong base, but because of the inertness with respect to proton exchange it has not been possible to obtain an estimate for the base strength. In this context it is relevant that on the basis of strain energy changes it has been estimated[24] that the inside monoprotonated [4.4.4]diamine (1,6-diazabicyclo[4.4.4]tetradecane) has $pK_a = 25$.

Conclusions

The present study illustrates a new and easy strategy for the synthesis of adamanzanes. The inertness of $H[3^6]adz^+$ with respect to dissociation of the proton is parallel to that found for the smaller cage $H[2^4.3^2]adz^+$ and related to the properties of some bicyclic amines reported by Alder et al.[24,25] and Lehn et al.[9] These tetrahedral cages have interesting properties in their own right as indicated by the present results and by the chemistry of related bicyclo diazaalkanes (unusual redox chemistry and increased bridgehead reactivity).[24,25] As mentioned, $[3^6]$adamanzane has a center-to-nitrogen distance which is optimal for inside coordination of many metalions, and we are now trying to find methods for inserting metal ions. A few preliminary experiments indicate that this is not easy, as expected.

Appendix

The official IUPAC names for compounds such as the present tricyclic tetraaza cages are not very practical:

1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane = **L1** (Fig. 1)
1,4,8,11-tetraazatricyclo[6.6.2.2^{4,11}]octadecane = **L2** (Fig. 1)
1,8,15,22-tetraazatricyclo[13.13.6.6^{8,22}]tetracontane = **L3** (Fig. 1)
1,10,19,28-tetraazatricyclo[17.17.8.8^{10,28}]dopentacontane = **L4** (Fig. 1)
1,5,9,13-tetraazatricyclo[7.7.3.3^{5,13}]docosane = **L5** (Fig. 2)

We suggest a simplified nomenclature for the present compounds corresponding to that used for the series of bicyclic systems in which the numbers of carbon (and hetero) atoms in the three chains are given as a prefix in a square bracket.[9] The diamine 1,6-diazabicyclo[4.4.4]-tetradecane is thus given the name [4.4.4]amine. The
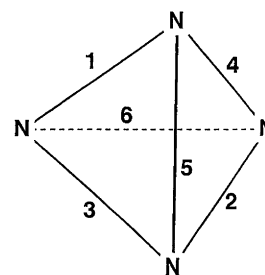

Fig. 4. Order of listing the six carbon chains in adamanzanes.

present cages may be considered as nitrogen analogues to the tetrahedral carbon cages whose smallest member is adamantane, tricyclo[3.3.1.1^{3,7}]decane. We name the series of tetraaza cages **adamanzanes** (adamantane + tetraza + amine) and follow the rules above with the additional rule that the carbon chains are listed in the order as shown in Fig. 4. The cages are thus named (an additional short notation for cases with several carbon chains of equal length in sequence is also given):

[1.1.1.1.1.1]adamanzane = [1^6]adamanzane = **L1**
[2.2.2.2.3.3]adamanzane = [2^4.3^2]adamanzane = **L2**
[3.3.3.3.3.3]adamanzane = [3^6]adamanzane = **L5**
[6.6.6.6.6.6]adamanzane = [6^6]adamanzane = **L3**
[8.8.8.8.8.8]adamanzane = [8^6]adamanzane = **L4**

Formulae for the protonated species may be written as, for instance, $H[3^6]adz^+$.

References

1. Dickinson, R. G. and Raymond, A. L. *J. Am. Chem. Soc. 45* (1923) 22.
2. Schmidtchen, F. P. *Angew. Chem. Int. Ed. Engl. 16* (1977) 720.
3. Schmidtchen, F. P. *Chem. Ber. 113* (1980) 864.
4. Schmidtchen, F. P. *Chem. Ber. 114* (1981) 597.
5. Schmidtchen, F. P. *Chem. Ber. 117* (1984) 725.
6. Schmidtchen, F. P. *Top. Curr. Chem. 132* (1986) 101.
7. Schmidtchen, F. P. *Pure Appl. Chem. 61* (1989) 1535.
8. Takemura, H., Hirakawa, T., Shinmyozu, T. and Inazu, T. *Tetrahedron Lett. 25* (1984) 5053.
9. Dietrich, B., Viout, P. and Lehn, J.-M. *Macrocyclic Chemistry*, VCH, Weinheim, Germany 1993.
10. Cheney, J. and Lehn, J. M. *J. Chem. Soc., Chem. Commun.* (1972) 487.
11. Graf, E. and Lehn, J. M. *J. Am. Chem. Soc. 97* (1975) 5022.
12. Graf, E. and Lehn, J. M. *Helv. Chem. Acta 64* (1981) 1040.
13. Graf, E., Kintzinger, J. P., Lehn, J. M. and LeMoigne, J. *J. Am. Chem. Soc. 104* (1982) 1672.
14. Springborg, J., Olsen, C. E. and Søtofte, I. *Acta Chem. Scand. 49* (1995) 555.
15. Richmann, J. E. and Atkins, T. J. *J. Am. Chem. Soc. Chem. 96* (1974) 228.
16. Searle, G. H. and Geue, R. *J. Austr. J. Chem. 37* (1984) 959.

17. Schaber, P. M., Fettingere, J. C., Churchill, M. R., Nale-wajek, D. and Fries, K. *Inorg. Chem. 27* (1988) 1641.
18. Koyama, H. and Tamotsu, T. *Bull. Chem. Soc. Jpn. 45* (1972) 481.
19. Alder, R. W., Mowlam, R. W., Vackon, D. J. and Weisman, G. R. *J. Chem. Soc., Chem. Commun.* (1992) 507.
20. Cooper, T. H., Mayer, M. J., Leung, K.-H., Ochrymowycz, L. A. and Rorabacher, D. B. *Inorg. Chem. 31* (1992) 3796.

21. Hahn, F. E. and Rupprecht, *Chem. Ber. 124* (1991) 481.
22. Springborg, J., Kofod, P., Olsen, C. E., Toftlund, H. and Søtofte, I. *Acta Chem. Scand. 49* (1995) 547.
23. Sargeson, A. M. *Pure Appl. Chem. 56* (1984) 1603.
24. Alder, R. W. *Chem. Rev. 89* (1989) 1215.
25. Alder, R. W. *Tetrahedron 46* (1990) 683.