CRYSTAL STRUCTURES AND REACTIVITY OF 3a,5a,8a,10a-TETRAAZAPERHYDROPYRENE DERIVATIVES. AN ALTERNATIVE APPROACH TO SELECTIVE NITROGEN ALKYLATION OF 1,4,8,11-TETRAAZACYCLOTETRADECANE (CYCLAM)

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Received December 10, 1999
Accepted January 20, 2000

1-Alkyl and 1,8-dialkyl-1,4,8,11-tetraazacyclotetradecanes (alkyl = benzyl or methyl) were synthesised through *cis*-aminal of cyclam which was obtained by reaction of glyoxal and cyclam. The corresponding *trans*-aminal was synthesised from the respective linear tetraamine and glyoxal followed by cyclisation using 1,2-dibromoethane. The *trans*-aminal derivatives cannot be used for preparation of cyclam or its derivatives due to exceptional stability of the aminal bridge. The different reactivity of both *cis*- and *trans*-aminals is discussed on the basis of the X-ray structures determined for a series of the cyclam derivatives and could be explained by steric hindrance in the *trans*-aminals.

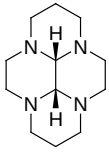
Key words: Azacrown compounds; N-Ligands; Amines; *cis*-Tetraazaperhydropyrene; *trans*-Tetraazaperhydropyrene; Selective protection; Cyclam; Crystal structure; NMR spectroscopy ^{13}C; X-Ray diffraction.

Chemistry of complexes of macrocyclic ligands, in particular polyazamacrocycles, is a vital part of inorganic chemistry[1]. For the polyazamacrocycles with pendant arms, the research has been focused mainly on ligands containing the same kind of substituents. Of them, the most common pendants are acetates[2], phosphonates[3], phosphinates[3,4], amides[5] and alkoxy derivatives[5b,6]. Some of the ligands complexes have found extensive use as magnetic resonance imaging (MRI) contrast agents[7] or antibody conjugates containing metal radionuclides[7c,8].

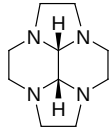
To change properties (*e.g.*, selectivity, thermodynamic or kinetic stability of complexes) of this type of ligands, methods for preparation of less or differently substituted polyazamacrocycles have been sought[1]. An effort has been focused on developing methods for selective protection of two most common tetraazamacrocycles, 1,4,7,10-tetraazacyclododecane (cyclen) and

1,4,8,11-tetraazacyclotetradecane (cyclam, **1**). Consequently, unsymmetrically or partially substituted macrocycles were synthesised. At an early stage, the simplest but ineffective and/or costly strategy was used. The partially substituted ligands were synthesised by the reaction of a large excess of macrocycle with a reactive precursor of a pendant arm[9] or using appropriately protected/substituted open-chain precursors[10]. The procedures suffer from a need of large amounts of expensive macrocyclic amines, tedious purification of reaction mixtures and/or a multistep reaction sequence. Lately, several groups have been suggested for direct protection of tetraazamacrocycles, mainly for cyclen. They include tosyl[11,12], phosphorus[12,13], boron[14] or silicon[15] amides, and metal carbonyls[16]. The methods have been widely used in spite of expensive reagents, problems with deprotection or use of inert atmosphere techniques. More recently, a more sophisticated methods have appeared for cyclen derivatives like methylsulfonic acid[17] (>N–CH_2SO_3H) or carbamate[18] protection based on large differences in basicity of nitrogen atoms in the amine. For cyclam, a similar approach was less successful, *e.g.* for carbamates[19]. Orthoformate aminal protection followed by alkylation with benzyl group was employed in the synthesis of the commercial cyclen-based MRI contrast agents[20].

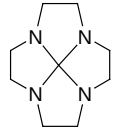
We focused on synthesis of macrocycles containing methylenephosphonic or methylenephosphinic pendant arms and on investigation of their complexing properties[21]. In addition to the fully substituted cyclam derivatives we wanted to prepare 1,8-disubstituted cyclams with the two phosphorus acid pendant groups. However, synthesis of the target ligands requires a suitable protection or substitution of two opposite nitrogen atoms of cyclam ring. Based on literature suggestions, we decided to develop protection through an aminal derived from glyoxal (structures **I** and **II**). We also tested the synthesis of cyclam itself through an aminal "carbon template" method similar to the procedure used for synthesis of cyclen[22,23]. However, in the course of our work, procedures for "carbon template" synthesis of tetraazacycles appeared[24] as well as similar approaches to synthesis of mono- and disubstituted derivatives through protection of cyclen using orthocarbonate aminal[25a] (structure **III**) or glyoxal aminal[25b] or of cyclam



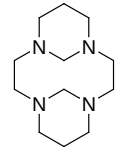
Structure **I**



Structure **II**



Structure **III**



Structure **IV**

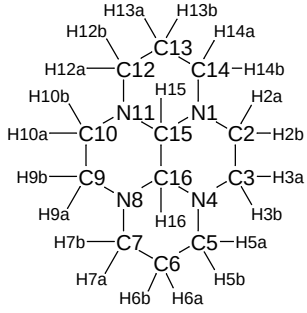
through formaldehyde aminal[26] (structure **IV**). Syntheses of 1,4- and 1,8-dimethylated cyclam[27] have been published as well as routes to "*cis*" (1,11- or 1,4-) protection/substitution of cyclam[28]. In the present paper, synthesis of partially substituted cyclam derivatives as well as crystal structures of a series of tetraazaperhydropyrene derivatives with *cis* and *trans* orientation of hydrogen atoms of the central bridge are described and their different reactivity is discussed.

EXPERIMENTAL

General

Cyclam **1** (ref.[29]) and *cis*-3a,5a,8a,10a-tetraazaperhydropyrene **2** (ref.[30]) were synthesised following literature procedures. Hydroxylamine (2 M solution in anhydrous EtOH) was prepared by reaction of $NH_2OH{\cdot}HCl$ with an equivalent amount of NaOEt in dry EtOH. Other chemicals available from commercial sources (Fluka, Aldrich, Avocado, and Lachema) were used as obtained. Solvents were purified and dried by the established procedures[31]. TLC was performed on "Silufol" silica gel sheets (Kavalier, Votice, Czech Republic) in the mixtures propan-2-ol–25% aqueous NH_3–water 7 : 3 : 3 (A) and EtOH–25% aqueous NH_3 20 : 1 (B); ninhydrin detection was used.

Elemental analyses were done in the Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic. Melting points were determinated using a Kofler hot-stage apparatus (Boetius) and are uncorrected. NMR spectra were recorded on a Varian Unity Plus at 400 MHz for ^1H and 100 MHz for ^{13}C (internal references for both nuclei: TMS for $CDCl_3$ solutions and *t*-BuOH for D_2O solutions). Assignments of NMR spectra was based on 2D-correlation experiments. For the numbering scheme of the 3a,5a,8a,10a-tetraazaperhydropyrene skeleton for NMR assignments and X-ray studies, see structure **V**. All samples in D_2O were measured just after dissolving. ^{13}C NMR spectra of **2** and **9** were also run in H_2O at pH 0.7 and 12.7; coaxial capillary with D_2O was used for lock and *t*-BuOH as internal reference.



Structure **V**

X-Ray Structure Determination

The diffraction-quality crystals of compounds **5b**, **10**·1.5H_2O, **3a**·2H_2O, **9**·2HBr·H_2O, and **4a**·4HCl·4H_2O were grown from aqueous solutions (by slow evaporation), with exception of **5b** which were obtained by cooling its hot ethanolic solution. The chosen crystals were mounted on glass fibres in random orientation using an epoxy glue. Diffraction data (λ = 0.71073 nm) were collected at 293(1) K using a CAD4 diffractometer (Enraf–Nonius). The lattice parameters of the studied compounds were always determined from 25 reflections (θ-intervals: for **5b** 13.0–14.0°; for **10**·1.5H_2O 14.5–15.0°; for **3a**·2H_2O 14.0–15.0°; for **9**·2HBr·H_2O 12.5–14.0°; **4a**·4HCl·4H_2O 13.5–14.5°). The intensities were collected by ω–2θ scan; three standard reflections were always measured after 1 h (mean variations 3% for **5b**, 7% for **10**·1.5H_2O, 3% for **3a**·2H_2O, 4% for **9**·2HBr·H_2O, and 3% for **4a**·4HCl·4H_2O). Lorenzian-polarisation corrections were applied for all compounds using program JANA 98 (ref.[32]); absorption corrections were applied to compounds **10**·1.5H_2O (T_{min} = 0.383, T_{max} = 0.633) and **9**·2HBr·H_2O (T_{min} = 0.0754, T_{max} = 0.1838) using program JANA 98.

The structures were solved by the Patterson and Fourier method or by direct methods, and refined by full-matrix least-squares techniques (SHELXS86 and SHELXL97, refs[33,34]). the scattering factors used for neutral atoms were included in the program SHELXL97. The hydrogen atoms were found in all structures (with exception of one hydrogen atom of the hydrate water molecule in the structure of **9**·2HBr·H_2O) on difference maps and refined isotropically. Crystallographic parameters of the structures determined are given in Table I. Crystallographic data of the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-138284 (**5b**), CCDC-138280 (**10**·1.5H_2O), CCDC-138281 (**3a**·2H_2O), CCDC-138282 (**9**·2HBr·H_2O) and CCDC-138283 (**4a**·4HCl·4H_2O). Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

Syntheses

3a,8a-Dibenzyl-10b,10c-*cis*-3a,5a,8a,10a-tetraazaperhydropyren-3a,8a-diium Dibromide[35] (**3a**)

cis-Aminal **2** (2.00 g, 9 mmol) in 250 ml round-bottom flask equipped with a magnetic stirring bar was dissolved in 20 ml of dry acetonitrile. Benzyl bromide (9.25 g, 54 mmol) was quickly added and the mixture was stirred at room temperature. After 20 min, monobenzyl derivative almost quantitatively crystallised out as a white precipitate. After 1 h, the reaction mixture was diluted with another 250 ml of dry acetonitrile and the suspension was stirred at room temperature. After two days, the solid dissolved and the mixture was left standing for three weeks. Dibenzylated product slowly deposited. Slightly yellow product (3.15 g) was filtered off and washed with ether. A second crop was obtained on addition of ether to the filtrate (0.80 g). The overall yield of **3a**·2H_2O was 3.95 g (73%). Crystals suitable for X-ray analysis were obtained by crystallisation from water at room temperature. TLC (A): R_F 0.05–0.1; m.p. 175–177 °C, dec. ^{1}H NMR (D_2O): 1.80 m, 2 H (H6a=H13a); 2.20 m, 2 H (H6b=H13b); 2.87 m, 2 H (H5a=H12a); 3.22 m, 4 H (H3a=H10a + H5b=H12b); 3.45 m, 2 H (H7a=H14a); 3.50 m, 2 H (H2a=H9a); 3.58 m, 2 H (H2b=H9b); 3.77 m, 2 H (H7b=H14b); 4.75 d, 2 H, J = 12.4 (C(**H**)H-Ph); 5.20 s, 2 H (H15=H16); 5.30 d, 2 H, J = 12.4 (C(H)**H**-Ph); 7.60 m, 10 H (Ph). ^{13}C NMR (D_2O): 21.07 (C6=C13); 49.10 (C3=C10); 49.86 (C2=C9); 54.29

TABLE I
Experimental data for X-ray diffraction studies of cyclam derivatives **5b**, **10**·1.5H_2O, **3a**·2H_2O, **9**·2HBr·H_2O and **4a**·4HCl·4H_2O

Parameter	**5b**	**10**·1.5H_2O	**3a**·2H_2O	**9**·2HBr·H_2O	**4a**·4HCl·4H_2O
Formula	$C_{13}H_{25}IN_4$	$C_{20}H_{32}BrN_4O_{1.5}$	$C_{26}H_{40}Br_2N_4O$	$C_{12}H_{26}Br_2N_4O$	$C_{24}H_{48}Cl_4N_4O_4$
M	364.3	418.4	600.4	400.1	598.5
T, K	293(1)	293(1)	293(1)	293(1)	293(1)
Crystal dimension, mm	0,2 × 0.35 × 0.5	0.25 × 0.6 × 0.65	0.3 × 0.4 × 0.45	0.3 × 0.5 × 0.6	0.2 × 0.25 × 0.45
Colour and shape	colourless prism	colourless rod	colourless irregular	colourless rod	colourless prism
Space group	$P2_1/n$ (no. 14)	$C2/c$ (no. 15)	$P2_1/n$ (no. 14)	$C2/c$ (no. 15)	$P2_1/n$ (no. 14)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
a, Å	12.231(1)	16.668(3)	10.236(2)	17.901(1)	7.179(1)
b, Å	7.141(1)	8.449(1)	16.472(3)	11.762(1)	12.589(1)
c, Å	17.602(2)	28.482(3)	15.687(3)	7.427(1)	17.987(1)
β, °	98.244(5)	98.61(1)	97.61(1)	96.130(5)	100.072)8)
U, Å^3	1 521.5(3)	3 966(1)	2 621.8(8)	1 554.8(3)	1 600.5(3)
Z	4	4	4	4	4
Goodness-of-fit on F^2	1.134	1.045	1.043	1.110	1.080
Final *R*; *R*′ indices [$I \geq 2\sigma(I)$][a]	0.0404; 0.1065	0.0372; 0.1102	0.0275; 0.0755	0.0529; 0.1259	0.0310; 0.0827

[a] $R = \Sigma|F_o - F_c|/\Sigma|F_c|$; $R' = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ (SHELXL97, ref.[34]); $w = 1/\sigma^2(F_o^2) + (A\,P)^2 + B\,P]$ (SHELXL97, ref.[34]).

(C5=C12); 63.55 (C7=C14); 65.45 (N-CH_2-Ph); 79.88 (C15=C16); 127.77, 132.57, 134.50, and 136.32 (Ph).

1,8-Dibenzyl-1,4,8,11-tetraazacyclotetradecane (**4a**)

Crude bromide **3a**·2H_2O (3.90 g, 6.5 mmol) was dissolved in 75 ml of water, solid NaOH (6.0 g, 150 mmol) was added and the solution was left standing under stirring for 1 h and then extracted with chloroform (5 × 40 ml). Organic phases were collected and evaporated on a rotary evaporator to give a yellow oil. The oil was dissolved in 20 ml of ethanol and 5 ml of concentrated HCl was added dropwise with cooling and stirring. A white precipitate was filtered off and washed with acetone. The crude product was dissolved in 20 ml of boiling water and 25 ml of concentrated HCl was added. The suspension was left in a refrigerator overnight; the product was filtered off, washed with EtOH and acetone and dried in vacuum over P_2O_5. Slow evaporation of a water solution of **4a** at room temperature gave single crystals of **4a**·4HCl·4H_2O suitable for X-ray analysis. The yield of **4a** tetrahydrochloride tetrahydrate was 3.72 g (95%). TLC (A): R_F 0.9; TLC (B): R_F 0.3; m.p. 240–241 °C, dec. ^{1}H NMR (D_2O): 2.08 m, 4 H (H6=H13); 3.27 m, 8 H (H5=H12 + H7=H14); 3.53 m, 8 H (H2=H9 + H3=H10); 4.32 s, 4 H (N-CH_2-Ph); 7.43 m, 10 H (Ph). Elemental analysis of several batches gave different results due to the presence of nonstechiometric amounts of water and hydrogen chloride, but with the correct C : N (6 : 1) ratio in all cases.

Free amine **4a** was obtained from a strong alkaline water solution of the hydrochloride hydrate after extraction with chloroform, drying (anhydrous Na_2SO_4) and evaporation of the organic phase as a colourless slowly crystallising oil in almost quantitative yield; m.p. 67–68 °C.

3a,8a-Dimethyl-10b,10c-*cis*-3a,5a,8a,10a-tetraazaperhydropyren-3a,8a-diium Diiodide[36] (**3b**)

cis-Aminal **2** (1.00 g, 4.5 mmol) was dissolved in 50 ml of dry acetonitrile, methyl iodide (5 g, 35 mmol) was added to the solution and the mixture was stirred for 3 days. The white solid was filtered off and washed with ether. The yield of **3b** was 1.48 g (65%). TLC (A): R_F 0.05; m.p. 218–219 °C, dec. ^{1}H NMR (D_2O): 1.93 m, 2 H (H6a=H13a); 2.42 m, 2 H (H6b=H13b); 2.75 m, 2 H (H5a=H12a); 3.20 m, 6 H (H2a=H9a + H3a=H10a + H5b=H12b); 3.31 m, 2 H (H3b=H10b); 3.37 s, 3 H (N-CH_3); 3.65–3.85 m, 4 H (H7a=H14a + H7b=H14b); 4.50 m, 2 H (H2b=H9b); 4.71 s, 2 H (H15=H16). ^{13}C NMR (D_2O): 21.41 (C6=C13); 49.25 (C3=C10); 51.28 (N-CH_3); 52.77 (C2=C9); 54.17 (C5=C12); 68.19 (C7=C14); 79.81 (C15=C16).

1,8-Dimethyl-1,4,8,11-tetraazacyclotetradecane (**4b**)

Iodide **3b** (1.00 g, 2 mmol) was dissolved in 20 ml of water, NaOH pellets (2.0 g, 50 mmol) were added and the mixture was stirred for 2 h. The product was extracted with chloroform (5 × 10 ml), the extracts were combined and evaporated to dryness. The product was isolated as hydrochloride by precipitation from acidified (HCl) solution with acetone. The yield of **4b**·4HCl·4H_2O was 0.71 g (80%). TLC (A): R_F 0.3; m.p. 233–235 °C, dec. For $C_{12}H_{40}Cl_4N_4O_4$ (446.3) calculated: 32.30% C, 9.03% H, 31.78% Cl, 12.55% N; found: 32.76% C, 8.74% H, 31.47% Cl, 12.89% N. ^{1}H NMR (D_2O): 2.28 m, 4 H (H6=H13); 3.11 s, 6 H (N-CH_3); 3.52 m, 8 H (H5=H12 + H7=H14); 3.75 m, 8 H (H2=H9 + H3=H10).

3a-Benzyl-10b,10c-*cis*-3a,5a,8a,10a-tetraazaperhydropyren-3a-ium Bromide (**5a**)

cis-Aminal **2** (1.00 g, 4.5 mmol) in a 25 ml round-bottom flask equipped with a magnetic stirring bar was covered with 5.5 ml of dry acetonitrile and almost dissolved on stirring. Benzyl bromide (1.54 g, 9 mmol) was quickly added and the mixture was stirred at room temperature. After 15 min, a white crystalline product precipitated quantitatively. After 2 h, the precipitate was filtered off, washed with ether (2 × 10 ml) and dried in vacuum over KOH. The yield of **5a**·$2H_2O$ was 1.70 g (90%). TLC (A): R_F 0.1; m.p. 139–141 °C, dec. (ref.[37] 159–161 °C). ^{1}H NMR (D_2O): 1.48 m, 1 H (H13a); 1.80 m, 1 H (H6a); 2.21 m, 2 H (H6b + H13b); 2.25 m, 1 H (H5a); 2.28 m, 1 H (H12a); 2.47 m, 2 H (H3a + H7a); 2.63 m, 1 H (H14a); 3.03 m, 1 H (H9a); 3.05 m, 2 H (H3b + H5b); 3.12 m, 3 H (H10a + H12b + H14b); 3.26 m, 2 H (H2a + H9b); 3.51 m, 2 H (H2b + H7b); 3.68 s, 1 H (H15); 4.20 m, 1 H (H10b); 4.36 s, 1 H (H16); 4.78 d, 1 H, J = 13.2 (N-C(**H**)H-Ph); 5.07 d, 1 H, J = 13.2 (N-C(H)**H**-Ph); 7.60 m, 5 H (Ph). ^{13}C NMR (D_2O): 21.06 (C6); 21.44 (C13); 45.03 (C7); 49.67 (C9); 51.68 (C10); 54.40 (C12); 55.04 (C5); 56.36 (C3); 57.02 (C14); 62.86 (C2); 65.67 (N-CH_2-Ph); 72.63 (C16); 84.91 (C15); 128.75, 132.40, 134.14 and 136.33 (Ph).

1-Benzyl-1,4,8,11-tetraazacyclotetradecane (**6a**)

A solution of 2 M hydroxylamine in anhydrous EtOH (25 ml, 50 mmol) was added to crude **5a**·$2H_2O$ (2.00 g, 4.7 mmol), the mixture was refluxed in dry atmosphere for 3 h (TLC monitoring; mixture A). After cooling, aqueous NaOH (25 ml, 10%) was added and the product was extracted with chloroform (3 × 50 ml). The combined organic phases were evaporated on rotary evaporator. The resulting oil was dissolved in 15% aqueous HCl (15 ml) and heated to reflux temperature in a heating mantle, 70 ml of EtOH was added and mixture was left to cool slowly in the mantle. The cooled mixture was left in refrigerator overnight. The product was filtered off, washed with EtOH and ether and dried in vacuum over P_2O_5. The yield of **6a**·4HCl·$2H_2O$ was 2.40 g (90%). TLC (A): R_F 0.2; m.p. 214–216 °C dec. ^{1}H NMR (D_2O): 2.07 m, 4 H (H16 + H13); 3.29 br m, 8 H (H5, H7, H12 and H14); 3.51 m, 8 H (H2, H3, H9 and H10); 4.35 s, 2 H (N-C**H**$_2$-Ph); 7.43 m, 5 H (Ph). Elemental analysis of several batches gave different results due to the presence of nonstechiometric amount of water and hydrogen chloride, but with the correct C : N (17 : 4) ratio in all cases.

Extraction of a strongly alkaline solution of the hydrated hydrochloride with chloroform, drying of the organic phase (Na_2SO_4) and evaporation gave a free base as an oil which solidified on standing in vacuum desiccator over KOH giving an off-white solid of **6a** as monohydrate.

3a-Methyl-10b,10c-*cis*-3a,5a,8a,10a-tetraazaperhydropyren-3a-ium Iodide (**5b**)

The compound was synthesised according to literature procedure[37,38] with yield 85%. TLC (A): R_F 0.1; m.p. 232–233 °C, dec. (ref.[37] 233–235 °C). ^{13}C NMR (D_2O): 21.04 (C6); 21.79 (C13); 45.12 (C9); 49.42 (C3); 51.78 (N1-CH_3); 54.23 (C2 + C10); 55.08 (C12); 56.00 (C7); 56.87 (C5); 67.63 (C14); 72.43 (C16); 85.80 (C15). Crystals suitable for X-ray analysis were obtained by crystallisation from hot ethanol.

1-Methyl-1,4,8,11-tetraazacyclotetradecane (**6b**)

Quaternary salt **5b** (0.70 g, 1.9 mmol) was dissolved in solution of hydroxylamine in anhydrous EtOH (2 M, 10 ml, 20 mmol) and the mixture was refluxed in dry atmosphere for 4 h (TLC monitoring, mixture A). Aqueous NaOH (25%, 10 ml) was added and ethanol was evaporated in vacuum. The mixture was extracted with chloroform (8 × 15 ml). The combined organic phases were dried (Na_2SO_4) and evaporated on a rotary evaporator. The resulting oil was dissolved in 10 ml of EtOH and 5 ml of concentrated HCl were added. The product was precipitated with acetone added dropwise. After standing in a refrigerator overnight, small white leaves were filtered off, washed with acetone, and dried in air. The yield of **6b**·4HCl·3H_2O was 0.47 g (60%). TLC (A): $R_F \approx 0.05$; m.p. 224–226 °C, dec. For $C_{11}H_{36}Cl_4N_4O_3$ (414.3) calculated: 31.89% C, 8.76% H, 34.23% Cl, 13.53% N; found: 32.63% C, 8.52% H, 33.42% Cl, 13.66% N. ^{1}H NMR (D_2O): 2.04 m, 4 H (H6=H13); 2.84 s, 3 H (N-CH_3); 3.26 m, 8 H (H5=H12 + H7=H14); 3.45 m, 8 H (H2=H9 + H3=H10).

3a-Benzyl-8a-methyl-10b,10c-*cis*-3a,5a,8a,10a-tetraazaperhydropyren-3a,8a-diium Diiodide (**3c**)

Compound **5a** (1.00 g, 2.3 mmol) was suspended in 40 ml of dry acetonitrile and methyl iodide (2.50 g, 17.6 mmol) was added with stirring. The solid slowly dissolved and crystallisation of slightly yellow product was finished after three days standing at room temperature. The solid was filtered off, washed with ether and dried in air. Yield 1.22 g (82%). TLC (A): $R_F \approx 0.05$; m.p. 142–143 °C, dec. For $C_{20}H_{32}I_2N_4$ (582.3) calculated: 41.25% C, 5.54% H, 0% Br, 43.59% I, 9.62% N; found: 42.32% C, 5.77% H, 2.28% Br, 39.32% I, 10.70% N. ^{1}H NMR (D_2O): 1.82 (H13a); 1.98 (H6a); 2.23 (H13b); 2.46 (H6b); 2.71 (H12a); 2.92 (H5a); 3.14 (H12b); 3.19 (H9a); 3.21 (H2a); 3.23 (H5b); 3.32 (H9a); 3.40 (H14a); 3.42 (H3a); 3.45 s, 3 H (N8-CH_3); 3.48 (H9b); 3.51 (H2b); 3.68 (H14b); 3.78 (H7a); 3.82 (H7b); 4.38 (H3b); 4.52 (H9b); 4.72 d, 1 H, J = 13.1 (N1-C(**H**)H–Ph); 4.84 (H15); 5.03 (H16); 5.21 d, 1 H, J = 13.1 (N1-C(H)**H**–Ph); 7.52–7.70 (Ph). ^{13}C NMR (D_2O): 21.06 (C13); 21.46 (C6); 49.48 (N8-CH_3); 49.55 (C3 + C10); 51.29 (C2); 52.65 (C9); 54.16 (C12); 54.26 (C5); 63.42 (C14); 65.55 (N1-CH_2–Ph); 68.28 (C7); 79.64 (C15); 79.85 (C16); 127.76, 132.58, 134.51 and 136.33 (Ph).

1-Benzyl-8-methyl-1,4,8,11-tetraazacyclotetradecane (**4c**)

Quaternary salt **3c** (0.50 g, 0.86 mmol) was dissolved in 10 ml of water, aqueous NaOH (10%, 10 ml) was added and the mixture was stirred at room temperature for 6 h. Free amine was extracted with chloroform (5 × 10 ml). The combined organic phases were evaporated on a rotary evaporator. The resulting oil was dissolved in 5 ml EtOH, 5 ml concentrated HCl was added dropwise and the product was precipitated with acetone added dropwise. After standing in a refrigerator overnight, white solid was filtered off, washed with acetone and dried in air. The yield of **4c**·4HCl·H_2O was 0.38 g (95%). TLC (A): $R_F \approx 0.3$; m.p. 200–202 °C, dec. For $C_{18}H_{38}Cl_4N_4O$ (468.3) calculated: 46.16% C, 8.18% H, 30.28% Cl, 11.96% N; found: 45.68% C, 7.63% H, 31.81% Cl, 11.22% N. ^{1}H NMR (D_2O): 2.22 m, 4 H (H6 + H13); 3.02 s, 3 H (N-CH_3); 3.45 m, 8 H (H5 + H7 + H12 + H14); 3.69 m, 8 H (H2 + H3 + H9 + H10); 4.48 s, 2 H (N-C$\mathbf{H}_2$-Ph); 7.55 m, 5 H (Ph).

10b,10c-*trans*-4,5,8a,10a-Tetraazaperhydrophenanthrene (**8**)

Amine **7** (5.00 g, 29 mmol) was dissolved in 100 ml of EtOH. Glyoxal (5.90 g of 30% aqueous solution, 31 mmol) was added dropwise during 5 min and the mixture was heated to reflux overnight. The solvent was evaporated in vacuum and the resulting brown oil was refluxed with 1 g of anhydrous sodium sulfate in 100 ml of petroleum ether. The extract was filtered and the solvent was evaporated. White needles of product crystallised during evaporation. The yield of **8** was 5.08 g (90%). TLC (A): $R_F \approx 0.6$; m.p. 97 °C, sublim. (ref.[39] 103–105 °C). ^{1}H NMR (D_2O; tertiary amine = N1 and N4, secondary amine = N8 and N11, no C9 and C10): 1.63 m, 4 H (H6a=H13a + H6b=H13b); 2.27 m, 2 H (H5a=H14a); 2.38 m, 2 H (H2a=H3a); 2.57 m, 2 H (H7a=H12a); 2.68 m, 2 H (H2b=H3b); 2.92 m, 2 H (H5b=H14b); 3.06 m, 2 H (H7b=H12b). ^{13}C NMR (D_2O): 27.37 (C6=C13); 44.71 (C7=C12); 54.49 (C2=C3), 56.57 (C5=C14); 80.51 (C15=C16).

10b,10c-*trans*-3a,5a,8a,10a-Tetraazaperhydropyrene (**9**)

Aminal **8** (2.00 g, 10 mmol) was dissolved in 15 ml of dry DMF and dry K_2CO_3 (5.00 g, 36 mmol) together with 1,2-dibromomethane (2.30 g, 12.2 mmol) was added to the solution. The mixture was stirred at room temperature for 10 days. Volatiles were removed on a rotary evaporator, the residue was extracted 4 × 30 ml of petroleum ether (b.p. 40–60 °C) and the combined extracts were evaporated. The residual oil contained some starting compound **8** (TLC) which was decomposed by dissolving the oil in 15 ml of acetic acid and standing overnight. Acetic acid was evaporated, the residue was dissolved in 15 ml of 10% aqueous NaOH and extracted with chloroform (4 × 15 ml). The organic phases were evaporated and the resulting oil was refluxed in 50 ml of petroleum ether together with 1.0 g of anhydrous Na_2SO_4. After filtration, the filtrate was evaporated. The product crystallised from CH_2Cl_2 solution by slow evaporation of the solvent. The yield 1.47 g (65%). TLC (A): R_F 0.7; m.p. 120–121 °C (ref.[40] 129–132 °C). ^{13}C NMR (D_2O): 25.98 (C6=C13); 54.23 (C2=C3=C9=C10); 56.12 (C5=C7=C12=C14); 84.90 (C15=C16).

10b,10c-*trans*-3a,5a,8a,10a-Tetraazaperhydropyrene Bis(hydrobromide) Hydrate (**9**·2HBr·H_2O)

trans-Aminal **9** (0.20 g, 0.9 mmol) was dissolved in 5 ml of aqueous HBr (48% aqueous HBr–water 1 : 3) and the hydrobromide was precipitated on addition of acetone yielding 0.34 g (95%) of bromide. Slow evaporation of solution of **9** in dilute aqueous HBr at room temperature gave crystals of the dihydrobromide salt suitable for X-ray analysis; m.p. 246 °C, dec. For $C_{12}H_{26}Br_2N_4O$ (400.2) calculated: 35.84% C, 6.52% H, 39.74% Br, 13.93% N; found: 36.22% C, 6.39% H, 38.56% Br, 13.99% N. ^{1}H NMR (D_2O): 2.02 m, 2 H (H6a=H13a); 2.12 m, 2 H (H6b=H13b); 2.89 m, 4 H (H5a=H7a=H12a=H14a); 3.12 m, 4 H (H2a=H3a=H9a=H10a); 3.39 m, 4 H (H2b=H3b=H9b=H10b); 3.42 m, 4 H (H5b=H7b=H12b=H14b); 3.75 s, 2 H (H15=H16). ^{13}C NMR (D_2O): 24.41 (C6=C13); 52.88 (C2=C3=C9=C10); 55.25 (C5=C7=C12=C14); 81.03 (C15=C16).

3a-Benzyl-10b,10c-*trans*-3a,5a,8a,10a-tetraazaperhydropyren-3a-ium Bromide (**10**)

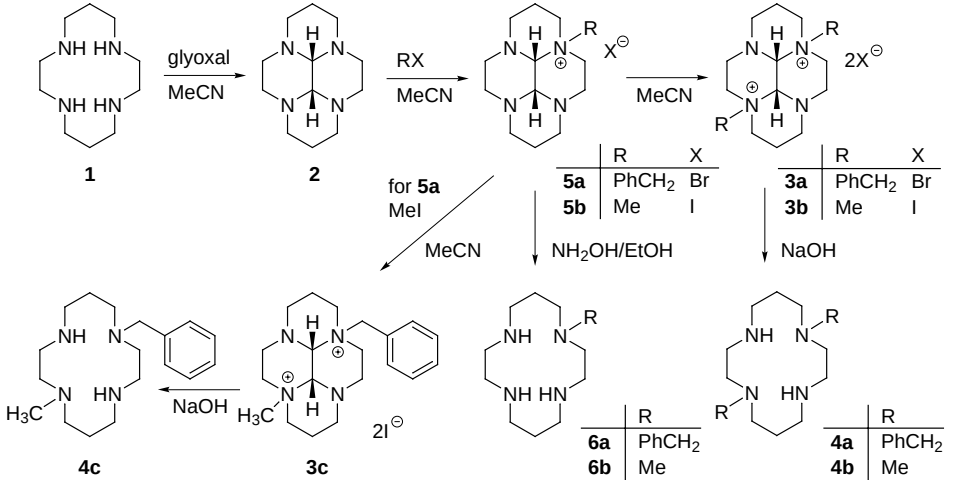
trans-Aminal **9** (0.50 g, 2.3 mmol) was dissolved in 5 ml of dry acetonitrile and benzyl bromide (0.77 g, 4.5 mmol) was quickly added under vigorous stirring. After 30 min stirring at

room temperature, the product crystallised. After 2 h at room temperature, the bulky precipitate was filtered, washed with ether (2 × 10 ml) and dried in vacuum over KOH. The yield 0.84 g (95%). TLC (A): R_F 0.1; m.p. 214–216 °C, dec. For $C_{19}H_{29}BrN_4$ (393.4) calculated: 58.01% C, 7.43% H, 20.31% Br, 14.24% N; found: 57.53% C, 7.49% H, 20.69% Br, 14.21% N. ^{1}H NMR (D_2O): 1.77–1.95 m, 4 H (H6 + H13); 2.31–2.69 m, 8 H (H5 + H7 + H12 + H14); 2.80 d, 1 H, J = 8.0 (H16); 2.99–3.60 m, 8 H (H2 + H3 + H9 + H10); 3.78 d, 1 H, J = 8.0 (H15); 4.94 d, 1 H, J = 14.0 (N-C(**H**)H-Ph); 5.16 d, 1 H, J = 14.0 (N1-C(H)**H**–Ph); 7.56–7.60 m, 5 H (Ph). ^{13}C NMR (D_2O): 21.97 (C13); 25.89 (C6); 48.96 (C3); 53.36 (C9); 54.39 (C10); 55.33 (C7); 56.04 (C5); 56.18 (C12); 59.02 (C2); 62.24 (C14); 62.34 (N1-C-Ph); 78.50 (C16); 90.78 (C15); 129.10, 132.58, 134.01 and 135.65 (Ph).

RESULTS AND DISCUSSION

Syntheses

3a,5a,8a,10a-Tetraazaperhydropyrene exists in two isomeric forms with *cis* or *trans* orientation of the hydrogen atoms of the glyoxal bridge. *cis*-Aminal **2** (Scheme 1) was synthesised following the literature procedure[30]. As the synthesis required relatively expensive cyclam, we tried to synthesise cyclam protected by the aminal bridge directly from linear 1,5,8,12-tetraazadodecane analogously to the preparation of cyclen[23] (Scheme 2). Recently, a similar approach using butan-2,3-dione aminal was also employed for synthesis of cyclen, homocyclen (1,4,7,10-tetraazacyclotridecane) and cyclam[24b]. However, the direct reaction of glyoxal and 1,5,8,12-tetraazadodecane (**7**) led to *trans*-aminal **8**; the yield of the reaction was similar to



SCHEME 1

the previous syntheses[39,40]. *trans*-Aminal **9** formed after reaction of **8** with 1,2-dibromoethane in DMF in the presence of anhydrous K_2CO_3. The use of DMF obviously suppressed side reactions leading to polymeric products. Literature procedures for *trans*-aminal **9** using **8**, glyoxal and $NaBH_4$ (ref.[40]) and benztriazole mediated cyclisation[41] proceeded in similar yields. Hervé *et al.*[24b] also tried the same reaction in acetonitrile, which was unsuccessful.

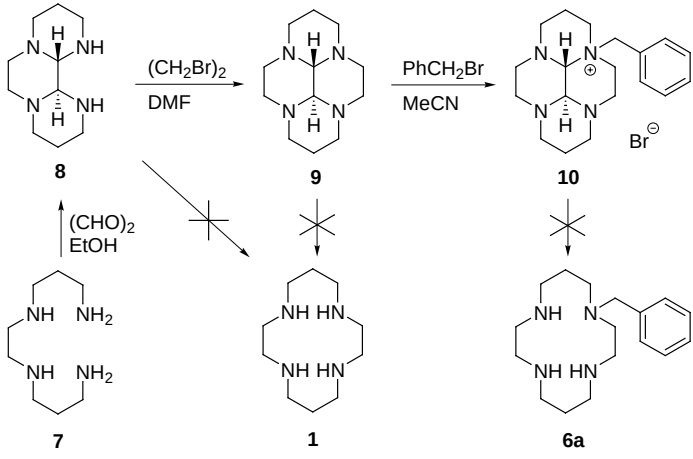
According to the Hubin's paper[38], formation of *cis*-aminal **2** from cyclam and glyoxal is thermodynamically favoured compared with formation of *trans*-aminal **9**. If the linear tetraamine **7** is used for the reaction, our results indicate formation of the *trans* orientation on the glyoxal bridge of **8**. Aminal **8** seems to be a rigid molecule and its conformation is not influenced by additional reaction with 1,2-dibromoethane.

Our route for derivatisation of cyclam employed a known double 1,8-quaternisation of *cis*-3a,5a,8a,10a-tetraazaperhydropyrene (**2**) with benzyl bromide[35] and methyl iodide[36,38] (Scheme 1) and mono-quaternisation[37,38] with the same reagents. We used modified protocol in less polar solvent giving slightly higher yields mainly due to a lower solubility of products in acetonitrile. According to previous results, we found that the process of double quaternisation is clearly separated into two stages. Reaction of *cis*-aminal **2** with the first equivalent of benzyl bromide giving **5a** was fast and quantitative in the solvent used. Formation of the double ion required excess of benzyl bromide and a long reaction time at room temperature. Optimisation of the conditions led to a high yield of the product, controlled by crystallisation of the insoluble bromide **3a** as a driving force of the reaction. Heating of the reaction mixture usually gave a lower yield of more impure product. Under the same conditions, reaction with methyl iodide giving **5b** and **3b** was similar but faster in both steps. The two distinct steps in the procedure were also illustrated by synthesis of **3c** (partial replacing bromide anion by iodide anion from excess of MeI was observed).

In contrast to the reaction of *cis*-aminal **2**, *trans*-aminal **9** reacts with benzyl bromide (Scheme 2) producing only monobenzyl derivative **10** and the reaction is slower. Because of unreactivity of *trans*-aminal bridge (see below) other derivatives were not synthesised. Monomethyl derivative has already been prepared[37] using a similar procedure, however, dimethyl derivative was obtained[41] only under harsh conditions (large excess of MeI, sealed ampoule). Dibenzyl derivative was not possible to obtain even under the harsh conditions.

Removal of the glyoxal aminal group was more problematic than we expected. Similar problems were noted[24b] in preparation of cyclen using the

glyoxal "carbon template" (structure **II**) and being solved using hydroxylamine[22,24a], aqueous hydrazine[24c] or oxidation of the bridge followed by deprotection with strong alkali hydroxide[36]. In addition, we tested common procedures for the deprotection such as concentrated H_2SO_4, concentrated aqueous HBr–AcOH, 10% aqueous NaOH. Usually, the procedures led to mixtures of compounds. Finally, different procedures for mono- and 1,8-disubstituted cyclams were used. Reflux of **5a**, **5b** in a hydroxylamine solution in anhydrous EtOH led to **6a**, **6b** and reactions of **3a**–**3c** with 10% aqueous NaOH gave **4a**–**4c**.

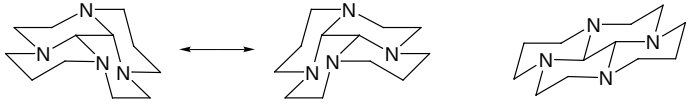


SCHEME 2

No successful procedure was found for removal of the glyoxal bridge from the *trans* derivatives. Treatment of *trans*-aminals **9** or **10** with an alkali solution under reflux (20% aqueous NaOH) or in autoclave[42] (180 °C, 20% aqueous NaOH), or with concentrated sulfuric acid[43] at 100 °C or concentrated aqueous HBr–acetic acid under reflux led only to complex mixtures (**10**) or to isolation of unchanged starting material (*trans*-aminal **9**). In the reaction of HBr with unsubstituted *trans*-aminal **9**, the starting material was recovered as dihydrobromide (see below for X-ray analysis). We also attempted to synthesise cyclam from **8** by reduction similarly to Weisman's procedure[23] used for cyclen. However, reduction (hydrogenation on 10% Pd/C, hydride reduction using $LiAlH_4$–THF or $(iBu)_2AlH$–toluene under reflux) led only to the unchanged starting material. Kolinski[37] notised a similar unreactivity in $NaBH_4$ reduction of monomethyl derivative of **9**.

Molecular and Crystal Structures

The X-ray structures were determined for **5b**, **10**·1.5H_2O, **3a**·2H_2O, **9**·2HBr·H_2O, and **4a**·4HCl·4H_2O. Selected bond distances and angles are listed in Table II and their molecular structures are shown in Figs 1–5. For comparison, the selected distances for the compounds **2**, **9**, diprotonated **2** (((H_2-**2**)$_2$[Fe_2OCl_6]Cl_2·CH_3CN), monoprotonated amine of **5b** (Me-**2**·$HClO_4$), and **3b** from literature X-ray structure data are also listed in Table II. Better than in the figures, orientation of the nitrogen atoms and conformation of the rings is shown in structure **VI**. From this scheme, it is clear that the *trans* derivatives have the nitrogen atoms and four cyclohexane-like rings in a plane arrangement. Orientation of the nitrogen atoms and rings in *cis* derivatives is different and the *cis* isomers can form two enantiomers[45].



cis isomer *trans* isomer

Structure **VI**

The bond distances in the glyoxal bridge for *cis*-aminal **2** and *trans*-aminal **9** are virtually the same, some differences are observed for the connection of N11 and N4 with carbons of the azamacrocycle and, clearly, in orientation of bonds and angles. Quaternisation led to the extension of both N–C(glyoxal) and N–C(azamacrocycle) bonds and the changes are virtually the same for both *trans* and *cis* isomers. The biggest changes were observed after protonation. Comparing N–C(glyoxal) bond lengths in for *cis*-aminals **2**, **3a** and double-protonated **2**, (H_2-**2**)$^{2+}$ cation, we can follow extension from 1.47 to 1.53 Å after quaternisation and to 1.54 Å after protonation of a nitrogen. Simultaneously, the N–C(glyoxal) bonds become shorter for non-quaternised or non-protonated nitrogen and this shortening points to their partial double character[46]. However, the bond lengths are not affected in the *trans*-aminals **9**, **10** and **9**·2HBr series. The NH^+–C(glyoxal) bond lengths in **9**·2HBr (1.50 Å) is even shorter than N(quaternised)–C(glyoxal) (1.53 Å) in **10**. This corresponds with the hydrogen bond formation between N1–H1···N11 in **9**·2HBr. The H1···N11 distance is 2.31(7) Å and the H1–N1–N11 angle is only 74(5)°. These differences clearly point to "structural anomeric effect" observed[46] for protonated cyclam formaldehyde aminal (structure **IV**) and also for the

TABLE II
Selected bond lengths (Å) and angles (°) in 3a,5a,8a,10a-perhydrotetraazapyrene derivatives

Parameter	**2** (ref.[44])	**9** (ref.[44])	**5b**	**10**·1.5H_2O	**3a**·2H_2O	**9**·2HBr·H_2O	H_2-**2**$^{2+}$ (ref.[38])	MeH-**2**$^{2+}$ (ref.[38])[a]	Me_2-**2**$^{2+}$ (ref.[38])[a]
					Bond lengths				
N1–C15	1.461(6)	1.463(5)	1.527(4)	1.535(4)	1.535(3)	1.503(4)	1.441(7)	1.531(5)	1.522(3)
N4–C16	1.471(5)	1.470(5)	1.472(4)	1.458(4)	1.459(3)	1.448(4)	1.548(7)	1.534(5)	1.458(3)
N8–C16	1.461(6)	1.463(5)	1.453(4)	1.461(4)	1.527(3)	1.503(4)	1.438(8)	1.431(5)	1.522(3)
N11–C15	1.471(5)	1.470(5)	1.454(4)	1.440(4)	1.454(3)	1.448(4)	1.540(7)	1.447(5)	1.455(2)
C15–C16	1.520(6)	1.534(6)	1.543(4)	1.528(4)	1.548(3)	1.519(7)	1.496(8)	1.542(5)	1.548(3)
N1–C14	1.443(7)	1.464(6)	1.524(5)	1.510(4)	1.522(3)	1.486(5)	1.474(9)	1.534(5)	1.524(3)
N1–C2	1.469(7)	1.463(6)	1.506(4)	1.511(4)	1.510(3)	1.499(4)	1.459(9)	1.509(5)	1.517(3)
N11–C12	1.501(7)	1.461(6)	1.467(5)	1.478(6)	1.479(3)	1.488(5)	1.491(8)	1.437(5)	1.480(3)
N11–C10	1.437(6)	1.469(5)	1.469(4)	1.469(5)	1.466(3)	1.462(5)	1.496(7)	1.485(5)	1.472(3)
N4–C5	1.501(7)	1.461(6)	1.483(5)	1.475(5)	1.474(3)	1.488(5)	1.486(9)	1.518(5)	1.477(3)
N4–C3	1.437(6)	1.469(5)	1.451(5)	1.451(5)	1.470(3)	1.462(5)	1.497(9)	1.491(5)	1.470(3)
N8–C7	1.443(7)	1.464(6)	1.4475(5)	1.478(5)	1.523(3)	1.486(5)	1.466(8)	1.475(5)	1.523(3)
N8–C9	1.469(7)	1.463(6)	1.463(5)	1.464(5)	1.511(3)	1.499(4)	1.466(8)	1.466(5)	1.505(3)

TABLE II
(*Continued*)

Parameter	**2** (ref.[44])	**9** (ref.[44])	**5b**	**10**·1.5H_2O	**3a**·2H_2O	**9**·2HBr·H_2O	H_2-**2**$^{2+}$ (ref.[38])	MeH-**2**$^{2+}$ (ref.[38])[a]	Me_2-**2**$^{2+}$ (ref.[38])[a]
				Angles					
N1–C15–N11	111.7(3)	109.3(3)	109.4(3)	107.8(2)	109.8(2)	108.5(3)	112.5(5)	110.9(3)	109.8(2)
N4–C16–N8	111.7(3)	109.3(3)	112.6(3)	110.392)	110.0(2)	108.5(3)	112.3(5)	112.4(3)	109.8(2)
N1–C15–C16	108.8(4)	109.7(3)	109.2(2)	110.8(2)	108.4(2)	108.1(3)	112.9(5)	110.2(3)	108.6(2)
N11–C15–C16	112.2(3)	108.7(3)	112.3(3)	114.0(3)	112.0(2)	110.8(3)	112.2(5)	109.3(3)	112.0(2)
N4–C16–C15	112.2(3)	108.7(3)	112.1(2)	107.9(2)	111.7(2)	110.8(3)	111.3(5)	110.0(3)	111.4(2)
N8–C16–C15	108.8(4)	109.7(3)	107.7(3)	106.7(2)	108.7(2)	108.1(3)	112.6(5)	110.3(3)	108.4(2)
				Torsion angles					
N1–C15–C16–N8	–169.4	–180	–179.1(2)	–179.8(2)	–179.7(2)	–180	–178.1(6)	–179.8(4)	–179.9(3)
N1–C15–C16–N4	–52.3	–60.5	–54.7(4)	–61.3(3)	–58.8(2)	–61.2(4)	–51.1(7)	–55.6(5)	–59.3(3)
N11–C15–C16–N4	65.1	180	66.2(3)	176.9(2)	62.5(5)	180	77.4(7)	66.5(4)	62.2(3)
N11–C15–C16–N8	–52.4	60.5	–58.3(3)	58.4(3)	–59.0(3)	61.2(4)	–49.7(6)	–58.1(4)	–58.7(3)

[a] At 180 K.

other glyoxal aminals derived from tet-b (5,5,7,12,14-hexamethyl-*rac*-1,4,8,11-tetraazacyclotetradecane) discussed in Hubin's paper[38].

Other interesting features were observed comparing structure of **5b** with Hubin's results[38] or double-protonated **2**, $(H_2\text{-}\mathbf{2})^{2+}$ cation. Surprisingly, protonation of the *cis*-aminals took place on the internal concave nitrogen atoms; however, methyl iodide quaternised the convex nitrogen atoms (see structure of **3a** and **5b**, Figs. 1 and 3). This was explained by a higher basicity of the concave nitrogens and a small size of proton.

Structure of $\mathbf{4a}\cdot 4HCl\cdot 4H_2O$ is the first structure determined for 1,8-disubstituted cyclam (Figure 5 and Table III). The conformation of the macrocyclic cation corresponds to the most common conformation[2] of fully protonated cyclam ($(H_4\text{cyclam})^{4+}$) which is denoted as (*3,4,3,4-A*). The conformation, showing all the four protonated nitrogen atoms in the corners of a virtual rectangle, was proved to be most stable by molecular mechanics calculations[2]. The bond distances within the macrocyclic chain are similar to those in other compounds with the $(H_4\text{cyclam})^{4+}$ cation. The benzyl substituents are situated to the opposite directions towards the plane defined by nitrogen atoms of the macrocycle. The substitution does not influence

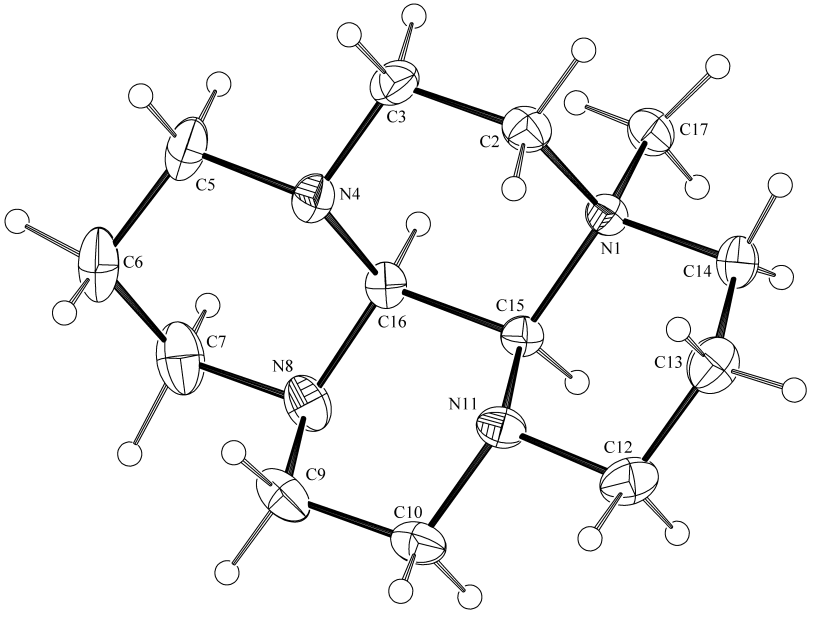


FIG. 1
ORTEP representation of molecular structure of $(\text{Me-}\mathbf{2})^{+}$ in crystal structure of **5b**

the conformation of the macrocycle. The structure is stabilised by a network of hydrogen bonds between protonated nitrogen atoms and water molecules. Chloride anions also show contacts with protonated nitrogen atoms. The macrocycle molecules are arranged in hydrophobic stacks forming hydrophilic tubules filled with water molecules and chloride anions

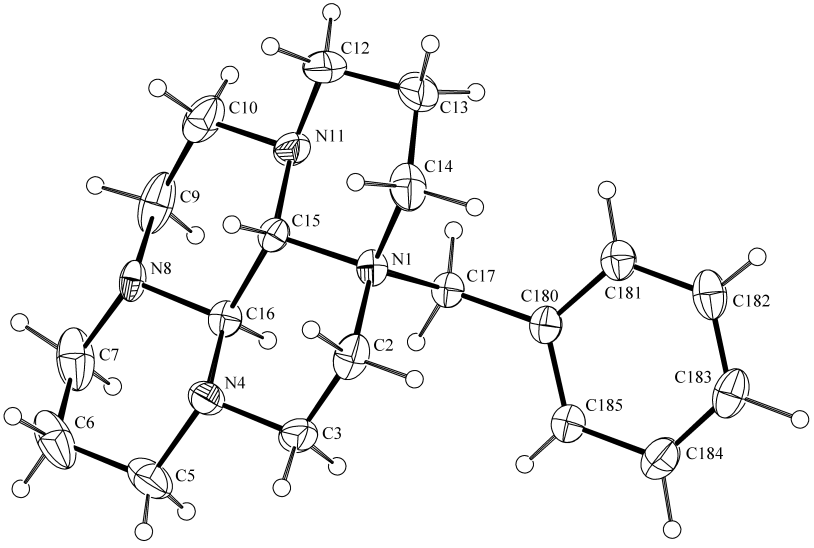


FIG. 2
ORTEP representation of molecular structure of $(Bn\text{-}\mathbf{9})^{+}$ in crystal structure of $\mathbf{10}\cdot 1.5H_2O$

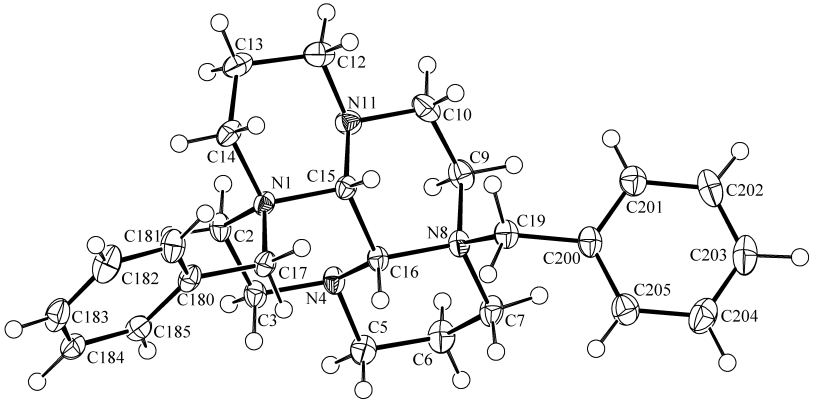


FIG. 3
ORTEP representation of molecular structure of $(Bn_2\text{-}\mathbf{2})^{2+}$ in crystal structure of $\mathbf{3a}\cdot H_2O$

(Fig. 6). One of the hydrate water is partly disordered. Hence, we tried to place the water molecule in two positions. In the best model, the occupancy factor refined were about 60 and 40%.

^{13}C NMR Spectra

Table IV contains ^{13}C NMR signals assigned to the carbon atoms of 3a,5a,8a,10a-tetraazaperhydropyrene skeleton based on 2D correlation spectra. The numbering scheme is shown in structure **V**. The spectra of **9** at

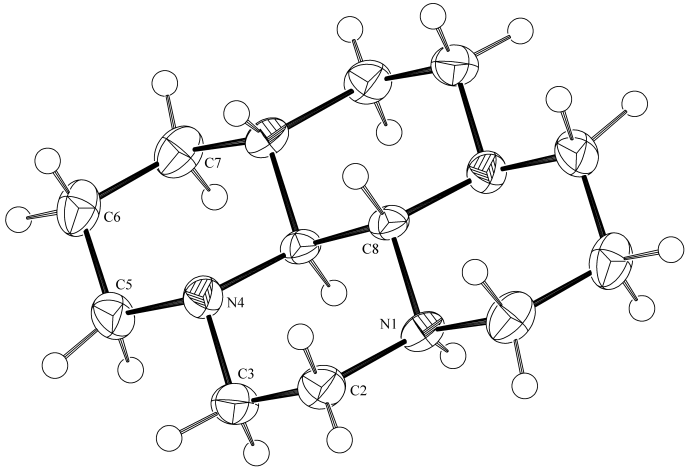


FIG. 4
ORTEP representation of molecular structure of $(H_2\text{-}\mathbf{9})^{2+}$ in crystal structure of $\mathbf{9}\cdot 2HBr\cdot H_2O$

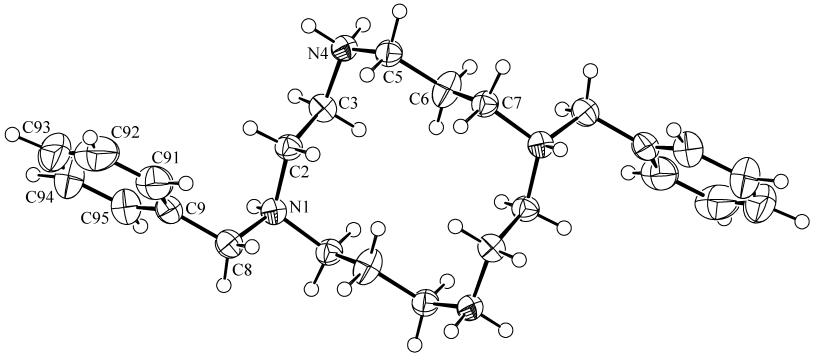


FIG. 5
ORTEP representation of molecular structure of $(H_4\text{-}\mathbf{4a})^{4+}$ in crystal structure of $\mathbf{4a}\cdot 4HCl\cdot 4H_2O$

TABLE III
Selected bond lengths (Å), bond angles (°), torsion angles (°) and geometry of hydrogen bonds in crystal structure of **4a**·4HCl·4H_2O

Parameter	Bond lengths	Parameter	Angles	Parameter	Torsion angle
N1–C2	1.497(2)	C2–N1–$C7^i$	115.0(1)	$C7^i$–N1–C2–C3	64.9(1)
N1–$C7^i$	1.509(2)	C2–N1–C8	110.4(1)	N1–C2–C3–N4	–172.2(1)
N1–C8	1.517(2)	$C7^i$–N1–C8	110.6(1)	C2–C3–N4–C5	61.1(2)
N4–C5	1.501(2)	C5–N4–C3	116.9(1)	C3–N4–C5–C6	56.5(2)
N4–C3	1.496(2)			N4–C5–C6–C7	–169.7(1)
				C5–C6–C7–$N1^i$	175.2(1)
				C6–C7–$N1^i$–$C2^i$	–63.6(2)

Hydrogen bond	Distances	Angles
N1–H11···$C12^i$	3.040(2)	160(1)
N4–H41···$C11^{ii}$	3.099(2)	164(1)
N4–H42···$O1W^{iii}$	2.665(3)	170(2)
O1W–H1W···$O2WB^{iv}$	2.699(3)	168(2)

Symmetry codes: ^{i} $-x-1$; $-y$; $-z+1$; ^{ii} x –1/2; $-y+1/2$; $z+1/2$; ^{iii} $-x-1/2$; $-y-1/2$; $z+3/2$; ^{iv} $-x$; $-y+1$; $-z+1$.

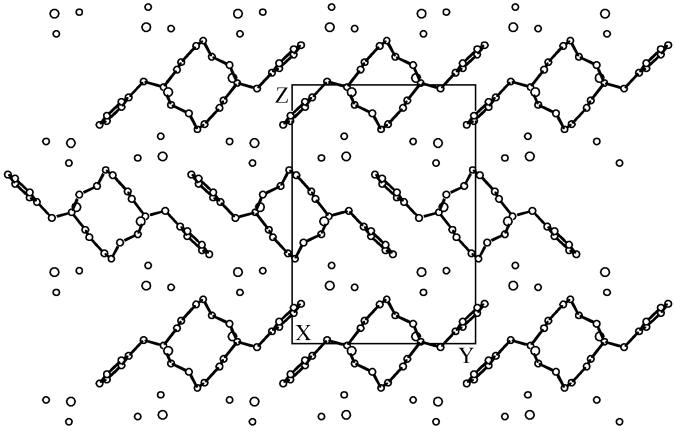


FIG. 6
Crystal packing in structure of **4a**·4HCl·4H_2O

TABLE IV
^{13}C chemical shifts (in D_2O, ppm) in 3a,5a,8a,10a-tetraazaperhyrdopyrenes

Carbon	**2**	**2**[a]	**2**[b]	**5a**	**5b**	**3a**	**3b**	**3c**	**9**	**9**·2HBr	**9**[b]	**10**
C2	55.70	53.87	56.01	62.86	54.23	49.86	52.77	52.65	54.23	52.88	54.20	59.02
C3	46.44	45.34	46.76	56.36	49.42	49.10	49.25	49.55	54.23	52.88	54.20	48.96
C5	57.77	56.61	58.08	55.04	56.87	54.29	54.17	54.16	56.12	55.25	56.09	56.04
C6	21.53	20.30	21.83	21.06	21.04	21.07	21.41	21.06	25.98	24.41	25.95	25.89
C7	53.99	53.34	54.28	45.03	56.00	63.55	68.19	63.42	56.12	55.25	56.09	55.33
C9	55.70	53.87	56.01	49.67	45.12	49.86	52.77	51.29	54.23	52.88	54.20	53.36
C10	46.44	45.34	46.76	51.68	54.23	49.10	49.25	49.55	54.23	52.88	54.20	54.39
C12	57.77	56.61	58.08	54.40	55.08	54.29	54.17	54.26	56.12	55.25	56.09	56.18
C13	21.53	20.30	21.83	21.44	21.79	21.07	21.41	21.46	25.98	24.41	25.95	21.97
C14	53.99	53.34	54.28	57.02	67.63	63.55	68.19	68.28	56.12	55.25	56.09	62.24
C15	64.63	77.05	78.70	84.91	85.80	79.88	79.81	79.85	84.90	81.03	84.88	90.78
C16	64.63	77.05	78.70	72.63	72.43	79.88	79.81	79.64	84.90	81.03	84.88	78.50

[a] pH 0.7 (in H_2O); [b] pH 12.7 (in H_2O).

pH 12.7 and at about 7 (after dissolving in D_2O) are virtually the same and it indicates full deprotonation at pH (pD) corresponding to solution of free amine (Table IV). From the values observed for **9** and double-protonated **9**, $(H_2\text{-}\mathbf{9})^{2+}$ cation, it is clear that both the molecules are symmetric, the diprotonation having no influence on the symmetry. Thus, two protons are shared by all four nitrogen atoms. After quaternisation of a nitrogen atom (*e.g.*, in **10**), the symmetry is lower than for *trans*-aminal **9** and each signal corresponds to one carbon atom.

To compare effect of protonation of *cis*-aminal **2** with *trans*-aminal **9**, compound **2** was also measured at pH about 0.7 and 12.7. The molecule shows lower symmetry than *trans*-aminal **9**. Except values for the glyoxal bridge C15 and C16, the other carbons show different signals. The shifts are caused by pH changes but also by change in conformation. Comparing signals for *cis*-aminal **2** with those for **5a** and **5b** on one hand and *trans*-aminal **9** with **10** on the other, we can see that quaternisation influences the adjacent glyoxal carbon C15 signal in *cis* isomers much more than in *trans* isomers. However, the differences observed for C2 and C14 are similar for both the isomers. Hence, quaternisation particularly influences the carbons of the glyoxal bridge in *cis* isomers.

CONCLUSIONS

An alternative route for synthesis of cyclam mono- and disubstituted on nitrogen atoms was found. For some of them, crystal structures were determined (**5b**, **10**·1.5H_2O, **3a**·2H_2O, **9**·2HBr·H_2O, and **4a**·4HCl·4H_2O).

Synthesis of **2** and **9** showed that formation of *cis* or *trans* isomers depends on the synthetic route used. The route starting from cyclam leads to the thermodynamically favoured *cis*-aminal **2**, while the route from linear tetraamine **7** leads to the *trans*-aminal **9**. This is caused by formation of **8**, whose *trans* orientation is probably more thermodynamically favoured. The conformation does not change even during the reaction with 1,2-dibromoethane. The different reactivity of *cis* and *trans* isomers is caused by the anomeric effect discussed previously for similar compounds. In addition, a comparison of structures of the aminals **2** and **9** shows that *trans*-aminal **9** is not fluxional and its rings are in plane (see structure **VI**). Its nitrogen lone electron pairs are sunk in hydrogen atoms of C–H bonds, and hence, the pairs are protected against reagent attack. In fluxional[45] *cis* isomers, the aminal bridge (and two nitrogen atoms) is exposed to outside of the cage ring atoms and hence is accessible to electrophilic/nucleophilic attack. The ^{13}C NMR spectra also show different behaviour of the glyoxal bridge with pH

change in *cis* isomers. Thus, different reactivity of the isomers can be explained by combination of both, anomeric and structure effects.

Presented route for synthesis of 1,8-disubstituted cyclam derivatives is slightly less convenient than the recently published synthesis of Guillard *et al.*[26] but it can be considered an alternative way. However, monosubstituted cyclam derivatives are obtained more easily than using known procedures. Syntheses of cyclam derivatives with one or two phosphorus acid moieties in pendant arms, based on the amines presented here, are under study and will be published in due course.

This work was supported by the Ministry of Education of the Czech Republic (grant No. VS96140), programme EU COST COST D18, and by the Grant Agency of the Charles University (grant No. 243/1999/BCH).

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