Journal of Molecular Structure 1098 (2015) 277–288

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Structural features of neutral and cationic cyclams

Luis G. Alves, M. Teresa Duarte, Ana M. Martins*

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

ARTICLE INFO

Article history:
Received 18 March 2015
Received in revised form
27 May 2015
Accepted 29 May 2015
Available online 2 June 2015

Keywords:
Cyclam
Hydrogen bonds
Tetraaza rings
Macrocycles
Supramolecular structures

ABSTRACT

Dicationic compounds of general formula [1,8-R_2-1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane]X_2, where R = H, Me or Bn' and X is a halogen counterion were obtained by reactions of 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane with different electrophiles. The solid-state molecular structures of the compounds reveal that the hydrogen, methyl or benzyl groups are located on the nitrogen atoms that are not only the less sterically hindered but also have the electron lone pair pointing out of the macrocycle backbone. In all compounds it is observed a bond shortening between the N-C_{aminal} and the two other C—N bonds that may be attributed to an inductive effect. These compounds afford the corresponding *trans-N,N'*-disubstituted cyclams upon hydrolysis in basic medium.

1. Introduction

The growing interest in the design and synthesis of polyazamacrocycles during the past years is mainly associated to their ability to form stable complexes with a plethora of metal ions [1] and also with a variety of anions [2], if used in their protonated forms. Several synthetic approaches to prepare sophisticated polyazamacrocycles were recently developed with the focus on the optimization and widening of their properties. For cyclam, in particular, numerous methods for the synthesis of poly-*N*-functionalized derivatives have been used [3]. Tetra- and mono-*N*-functionalized cyclams are the most widely described as these types of compounds may be obtained by straightforward procedures [4]. Even though, the syntheses of mono-*N*-functionalized cyclams are non-efficient procedures concerning atomic economy requiring a large excess of cyclam. The direct preparation of *N,N'*-difunctionalized cyclam rings faces several problems mainly because the reaction of cyclam with two equivalents of alkyl or aryl halides yield mixtures of mono-, di-, tri- and even tetrasubstituted macrocycles [3b,5]. Moreover, disubstituted cyclams display several isomers depending on the relative positions of the pendant arms, namely, two different *cis*-disubstituted and one *trans*-disubstituted isomers. Guilard et al. developed a convenient three-step procedure that relies on the formation of 1,4,8,11-tetraazatricyclo [9.3.1.1^{4,8}]hexadecane, **1**, by reaction of cyclam with formaldehyde providing exclusively the *trans*-disubstituted isomer [6]. This methodology was used by us for the preparation of several *trans*-H_2(R_2Cyclam) compounds whose molecular and supramolecular structures are discussed here (Scheme 1).

In this work we also explore the solid-state molecular structure of 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane either in anhydrous and hydrated forms (**1**.4H_2O and **1**.6H_2O). The role of the stereochemical conformation on its protonation is addressed.

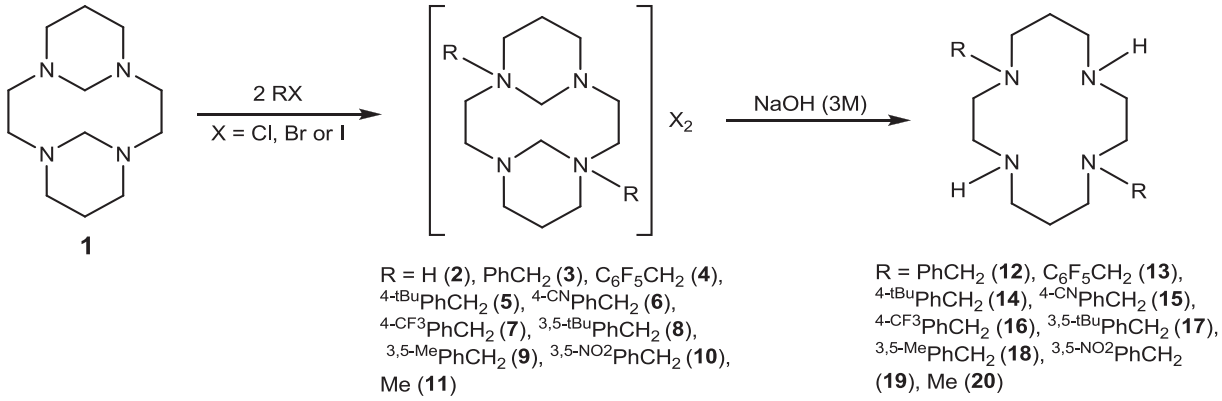
2. Experimental

2.1. General considerations

Cyclam [7], 3,5-di-*tert*-butylbenzyl bromide [8], 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane, **1** [6], 1,8-benzyl-1,4,8,11-tetraazacyclotetradecane, **12** [6], 1,8-(4-*tert*-butylbenzyl)-1,4,8,11-tetraazacyclotetradecane, **14** [9], 1,8-(4-trifluoromethylbenzyl)-1,4,8,11-tetraazacyclotetradecane, **16** [9], 1,8-(3,5-di-*tert*-butylbenzyl)-1,4,8,11-tetraazacyclotetradecane, **17** [8], 1,8-(3,5-dimethylbenzyl)-1,4,8,11-tetraazacyclotetradecane, **18** [8], and 1,8-methyl-1,4,8,11-tetraazacyclotetradecane, **20** [6], were prepared according to general described procedures. All other reagents were commercial grade and used without further purification. The NMR spectra were recorded in a Bruker AVANCE II 300 or 400 MHz spectrometers at 296 K. ^{1}H and ^{13}C NMR spectra were referenced internally to residual solvent resonances and reported relative to tetramethylsilane (0 ppm). ^{19}F NMR was referenced to external

* Corresponding author.
E-mail address: ana.martins@tecnico.ulisboa.pt (A.M. Martins).

http://dx.doi.org/10.1016/j.molstruc.2015.05.037
0022-2860/



Scheme 1. Syntheses of cyclam derivatives.

CF_3COOH (−76.55 ppm). 2D NMR experiments such as $^1H-^{13}C\{^1H\}$ HSQC and $^1H-^1H$ COSY were performed in order to make all the assignments. FT-IR spectra were recorded on a Jasco FT/IR-4100 spectrometer at IST. Elemental analyses were obtained from Instituto Tecnológico e Nuclear or Laboratório de Análises do IST.

2.2. Synthesis and characterization of the compounds

1,8-benzyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**3**): The compound was prepared according to a published procedure [6]. 1,4,8,11-tetraazatricyclo[9.3.1.14,8]hexadecane, **1**, (5.00 g, 22.3 mmol) was dissolved in acetonitrile and two equiv. of benzyl bromide (5.80 mL, 48.8 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 34% yield (4.32 g, 7.63 mmol). Crystalline material was obtained from slow evaporation of a $H_2O/(CH_3)_2CO$ solution. ^1H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 7.54–7.45 (overlapping, 10H total, *Ph*CH_2N), 5.56 (d, $^2J_{H-H} = 9$ Hz, 2H, NC*H*$_2$N), 4.76 (d, $^2J_{H-H} = 13$ Hz, 2H, PhC*H*$_2$N), 4.59–4.45 (overlapping, 4H total, 2H, [C2]C*H*$_2$N and 2H, PhC*H*$_2$N), 3.67–3.59 (overlapping, 4H total, 2H, [C2]C*H*$_2$N and 2H, NC*H*$_2$N), 3.40 (m, 2H, [C3]C*H*$_2$N), 3.28–3.17 (overlapping, 4H total, 2×[C3]C*H*$_2$N), 2.98–2.84 (overlapping, 4H total, 2×[C2]C*H*$_2$N), 2.57–2.44 (overlapping, 4H total, 2H, [C3]C*H*$_2$N and 2H, $CH_2CH_2CH_2$), 1.82 (m, 2H, $CH_2CH_2CH_2$). $^{13}C\{^1H\}$ NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 133.5 (*Ph*CH_2N), 131.2 (*p*-*Ph*CH_2N), 129.8 (*Ph*CH_2N), 126.6 (*i*-*Ph*CH_2N), 77.2 (NCH_2N), 63.3 (PhCH_2N), 60.0 ([C3]CH_2N), 51.8 ([C3]CH_2N), 48.1 (2×[C2]CH_2N), 20.0 ($CH_2CH_2CH_2$). Anal. calcd for $C_{26}H_{38}Br_2N_4$: C, 55.13; H, 6.76; N, 9.89. Found: C, 54.61; H, 6.72; N, 9.98.

1,8-perfluorobenzyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**4**): Compound **1** (2.15 g, 9.58 mmol) was dissolved in acetonitrile and two equiv. of perfluorobenzyl bromide (5.00 g, 19.2 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduce pressure. The compound was obtained as a white powder in 14% yield (2.09 g, 2.80 mmol). Anal. calcd for $C_{26}H_{28}Br_2F_{10}N_4.(H_2O)_2$: C, 41.84; H, 3.78; N, 7.51. Found: C, 39.78; H, 3.68; N, 7.62.

1,8-(4-*tert*-butylbenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**5**): Compound **1** (2.40 g, 10.7 mmol) was dissolved in acetonitrile and two equiv. of 4-*tert*-butylbenzyl bromide (5.00 g, 22.0 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 96% yield (7.00 g, 10.3 mmol). Crystalline material was obtained from slow evaporation of a $H_2O/(CH_3)_2CO$ solution. ^1H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 7.53–7.46 (overlapping, 8H total, *Ph*CH_2N), 5.61 (d, $^3J_{H-H} = 10$ Hz, 2H, NC*H*$_2$N), 4.79 (d, $^2J_{H-H} = 13$ Hz, 2H, PhC*H*$_2$N), 4.61–4.47 (overlapping, 4H total, 2H, [C2]C*H*$_2$N and 2H, PhC*H*$_2$N), 3.66–3.61 (overlapping, 4H total, 2H, [C2]C*H*$_2$N and 2H, NC*H*$_2$N), 3.42 (m, 2H, [C3]C*H*$_2$N), 3.29–3.18 (overlapping, 4H total, 2×[C3]C*H*$_2$N), 3.00–2.86 (overlapping, 4H total, 2×[C2]C*H*$_2$N), 2.60–2.43 (overlapping, 4H total, 2H, [C3]C*H*$_2$N and 2H, $CH_2CH_2CH_2$), 1.84 (m, 2H, $CH_2CH_2CH_2$), 1.22 (s, 18H, C(C*H*$_3$)$_2$). $^{13}C\{^1H\}$ NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 154.4 (*Ph*CH_2N), 133.5 (*Ph*CH_2N), 126.6 (*Ph*CH_2N), 124.0 (*Ph*CH_2N), 82.4 (*C*(CH$_3$)$_2$), 77.3 (NCH_2N), 63.0 (PhCH_2N), 60.1 ([C3]CH_2N), 51.8 ([C3]CH_2N), 48.2 (2×[C2]CH_2N), 34.9 (C(*C*H$_3$)$_2$, 20.1 ($CH_2CH_2CH_2$). Anal. calcd for $C_{34}H_{54}Br_2N_4.(H_2O)_4$: C, 54.40; H, 8.32; N, 7.46. Found: C, 53.83; H, 8.66; N, 7.45.

1,8-(4-cyanobenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**6**): Compound **1** (2.86 g, 12.7 mmol) was dissolved in acetonitrile and two equiv. of 4-cyanobenzyl bromide (5.00 g, 25.5 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 65% yield (5.09 g, 8.26 mmol). Anal. calcd for $C_{28}H_{36}Br_2N_6$: C, 54.56; H, 5.89; N, 13.63. Found: C, 53.24; H, 5.88; N, 13.48. FT-IR (KBr, cm^{-1}): 2230 ($\nu_{C\equiv N}$).

1,8-(4-trifluoromethylbenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**7**): Compound **1** (2.57 g, 11.5 mmol) was dissolved in acetonitrile and two equiv. of 4-(trifluoromethyl)benzyl bromide (5.77 g, 24.1 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 35% yield (2.80 g, 3.99 mmol). Crystalline material was obtained from slow evaporation of a $H_2O/(CH_3)_2CO$ solution. ^{19}F NMR ($D_2O/(CD_3)_2CO$), 282.4 MHz, 296 K): δ (ppm) −62.7 (s, C*F*$_3$). Anal. calcd for $C_{28}H_{36}Br_2F_6N_4$: C, 47.88; H, 5.17; N, 7.98. Found: C, 47.60; H, 5.18; N, 7.99.

1,8-(3,5-di-*tert*-butylbenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**8**): Compound **1** (2.35 g, 10.5 mmol) was dissolved in acetonitrile and two equiv. of 3,5-di-*tert*-butylbenzyl bromide (6.54 g, 23.1 mmol) were rapidly added. The solution was stirred at room temperature and the white

precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 58% yield (4.82 g, 6.09 mmol). Crystalline material was obtained from slow evaporation of a $H_2O/(CH_3)_2CO$ solution. Anal. calcd for $C_{42}H_{70}Br_2N_4.(H_2O)$: C, 62.37; H, 8.97; N, 6.93. Found: C, 62.81; H, 9.15; N, 7.03.

1,8-(3,5-dimethylbenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dibromide (**9**): Compound **1** (5.00 g, 22.3 mmol) was dissolved in acetonitrile and two equiv. of 3,5-dimethylbenzyl bromide (9.32 g, 46.8 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 33% yield (4.59 g, 7.37 mmol). Anal. calcd for $C_{30}H_{46}Br_2N_4.(H_2O)$: C, 56.25; H, 7.55; N, 8.75. Found: C, 55.77; H, 7.46; N, 9.23.

1,8-(3,5-dinitrobenzyl)-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium dichloride (**10**): Compound **1** (2.59 g, 11.5 mmol) was dissolved in acetonitrile and two equiv. of 3,5-dinitrobenzyl chloride (5.00 g, 23.1 mmol) were rapidly added. The solution was stirred at room temperature and the brown precipitate formed was then separated by filtration, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a brownish powder in 20% yield (1.49 g, 2.27 mmol). Anal. calcd for $C_{26}H_{34}Cl_2N_8O_8$: C, 47.49; H, 5.21; N, 17.04. Found: C, 47.38; H, 5.28; N, 16.97. FT-IR (KBr, cm^{-1}): 1558, 1533 and 1365, 1346 (ν_{NO2}).

1,8-dimethyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium diiodide (**11**): The compound was prepared according to a published procedure [6]. Compound **1** (3.50 g, 15.6 mmol) was dissolved in acetonitrile and two equiv. of methyl iodide (2.14 mL, 34.3 mmol) were rapidly added. The solution was stirred at room temperature and the white precipitate formed was then filtered, washed with a small quantity of CH_3CN and dried under reduced pressure. The compound was obtained as a white powder in 86% yield (6.79 g, 13.4 mmol). Crystalline material was obtained from slow evaporation of a $H_2O/(CH_3)_2CO$ solution. ^{1}H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 5.42 (d, $^2J_{H-H}$ = 10 Hz, 2H, NCH_2N), 4.55 (m, 2H, [C3]CH_2N), 3.68 (m, 2H, [C3]CH_2N), 3.55 (m, $^2J_{H-H}$ = 10 Hz, 2H, NCH_2N), 3.49–3.40 (overlapping, 4H total, 2H, [C3]CH_2N and 2H, [C2]CH_2N), 3.23–3.18 (overlapping, 8H total, 6H, CH_3 and 2H, [C2]CH_2N), 3.04 (m, 2H, [C2]CH_2N), 2.94 (m, 2H, [C2]CH_2N), 2.70–2.51 (overlapping, 4H total, 2H, [C3]CH_2N and 2H, $CH_2CH_2CH_2$), 1.93 (m, 2H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 78.0 (NCH_2N), 65.0 ([C3]CH_2N), 52.0 ([C3]CH_2N and [C2]CH_2N), 49.2 (CH_3), 48.4 ([C2]CH_2N), 21.0 ($CH_2CH_2CH_2$). Anal. calcd for $C_{14}H_{30}I_2N_4(H_2O)$: C, 31.95; H, 6.13; N, 10.65. Found: C, 31.59; H, 6.07; N, 10.40.

1,8-perfluorobenzyl-1,4,8,11-tetraazacyclotetradecane (**13**): Compound **5** (1.40 g, 1.86 mmol) was hydrolyzed in an aqueous NaOH solution (3 M) and the product was extracted with small portions of $CHCl_3$. The organic phases were collected and dried with $MgSO_4$ anhydrous. The compound was obtained as an off-white solid after solvent evaporation and successive freeze-trituration-pump-thaw cycles in 82% yield (0.85 g, 1.52 mmol). Crystalline material was obtained from slow evaporation of a $CHCl_3$ solution. ^{1}H NMR ($CDCl_3$, 300.1 MHz, 296 K): δ (ppm) 3.82 (s, 4H, PhCH_2N), 2.71 (m, 4H, [C3]CH_2N), 2.66 (m, 4H, [C2]CH_2N), 2.57–2.44 (overlapping, 10H total, 4H, [C3]CH_2N, 4H, [C2]CH_2N and 2H, N*H*), 1.83 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.5 MHz, 296 K): δ (ppm) 144.2 (m, *Ph*CH_2N), 141.6 (m, *Ph*CH_2N), 139.1 (m, *Ph*CH_2N), 110.0 (t, J_{C-F} = 20 Hz, *i-Ph*CH_2N), 53.8 ([C3]CH_2N or [C2]CH_2N), 52.0 ([C3]CH_2N or [C2]CH_2N), 50.1 ([C3]CH_2N), 47.7 ([C2]CH_2N), 44.6 (PhCH_2N), 26.3 ($CH_2CH_2CH_2$). ^{19}F NMR ($CDCl_3$, 282.4 MHz, 296 K): δ (ppm) −139.7 ($^3J_{C-F}$ = 21 Hz, $^4J_{C-F}$ = 6 Hz, *o-Ph*CH_2N), −154.5 (t, $^3J_{C-F}$ = 21 Hz, *p-Ph*CH_2N), −162.0 (td, $^3J_{C-F}$ = 21 Hz, $^4J_{C-F}$ = 6 Hz, *m-Ph*CH_2N). ^{1}H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 4.03 (s, 4H, PhCH_2N), 3.45 (m, 4H, [C2]CH_2N), 3.40 (m, 4H, [C3]CH_2N), 2.84 (m, 4H, [C2]CH_2N), 2.76 (m, 4H, [C3]CH_2N), 2.11 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 52.4 ([C3]CH_2N), 49.9 ([C2]CH_2N), 48.0 ([C3]CH_2N), 45.8 ([C2]CH_2N), 43.6 (PhCH_2N), 23.9 ($CH_2CH_2CH_2$). The clear identification of the carbon resonances for the pentafluorophenyl groups was not possible due to their weak intensities. ^{19}F NMR ($D_2O/(CD_3)_2CO$, 282.4 MHz, 296 K):δ (ppm) −138.0 (m, $^3J_{C-F}$ = 18 Hz, *o-Ph*CH_2N), −151.4 (t, $^3J_{C-F}$ = 21 Hz, *p-Ph*CH_2N), −159.3 (td,$^3J_{C-F}$ = 18 Hz, $^4J_{C-F}$ = 4 Hz, *m-Ph*CH_2N). Anal. calcd for $C_{24}H_{26}F_{10}N_4$: C, 51.43; H, 4.68; N, 10.00. Found: C, 51.39; H, 4.88; N, 9.90.FT-IR (KBr, cm^{-1}): 3316 (ν_{N-H}).

1,8-(4-cyanobenzyl)-1,4,8,11-tetraazacyclotetradecane (**15**): Compound **6** (4.00 g, 6.48 mmol) was hydrolyzed in an aqueous NaOH solution (3 M) and the product was extracted with small portions of $CHCl_3$. The organic phases were collected and dried with $MgSO_4$ anhydrous. The compound was obtained as an off-white solid after solvent evaporation and successive freeze-trituration-pump-thaw cycles in 78% yield (2.98 g, 5.05 mmol). Crystalline material was obtained from slow evaporation of a $CHCl_3$ solution. ^{1}H NMR ($CDCl_3$, 400.1 MHz, 296 K): δ (ppm) 7.56 (d, $^3J_{H-H}$ = 8 Hz, 4H, *Ph*CH_2N), 7.40 (d, $^3J_{H-H}$ = 8 Hz, 4H, *Ph*CH_2N), 3.70 (s, 4H, PhCH_2N), 2.70–2.69 (overlapping, 8H total, 4H, [C3]CH_2N and 4H, [C2]CH_2N), 2.55–2.51 (overlapping, 10H total, 4H, [C3]CH_2N, 4H, [C2]CH_2N and 2H, N*H*), 1.80 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz, 296 K): δ (ppm) 143.6 (*C*N), 132.1 (*o-Ph*CH_2N or *m-Ph*CH_2N), 129.9 (*o-Ph*CH_2N or *m-Ph*CH_2N), 118.9 (*i-Ph*CH_2N or *p-Ph*CH_2N), 111.0 (*i-Ph*CH_2N or *p-Ph*CH_2N), 57.7 (PhCH_2N), 54.5 ([C3]CH_2N or [C2]CH_2N), 51.2 ([C3]CH_2N or [C2]CH_2N), 49.6 ([C3]CH_2N or [C2]CH_2N), 47.6 ([C3]CH_2N or [C2]CH_2N), 26.0 ($CH_2CH_2CH_2$). ^{1}H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 7.92 (d, $^3J_{H-H}$ = 8 Hz, 4H, *Ph*CH_2N), 7.66 (d, $^3J_{H-H}$ = 8 Hz, 4H, *Ph*CH_2N), 3.93 (s, 4H, PhCH_2N), 3.51 (overlapping, 8H total, 4H, [C3]CH_2N and 4H, [C2]CH_2N), 2.97 (m, 4H, [C2]CH_2N), 2.82 (m, 4H, [C3]CH_2N), 2.17 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 141.2 (*C*N), 134.1 (*o-Ph*CH_2N or *m-Ph*CH_2N), 132.6 (*o-Ph*CH_2N or *m-Ph*CH_2N), 120.4 (*i-Ph*CH_2N or *p-Ph*CH_2N), 112.2 (*i-Ph*CH_2N or *p-Ph*CH_2N), 56.6 (PhCH_2N), 52.5 ([C3]CH_2N), 50.9 ([C2]CH_2N), 48.5 ([C3]CH_2N or [C2]CH_2N), 45.8 ([C3]CH_2N or [C2]CH_2N), 23.6 ($CH_2CH_2CH_2$). Anal. calcd for $C_{26}H_{34}N_6.(H_2O)$: C, 69.61; H, 8.09; N, 18.73. Found: C, 69.57; H, 8.10; N, 18.79. FT-IR (KBr, cm^{-1}): 3314 (ν_{N-H}) and 2222 ($\nu_{C\equiv N}$).

1,8-(3,5-dinitrobenzyl)-1,4,8,11-tetraazacyclotetradecane (**19**): Compound **10** (1.35 g, 2.05 mmol) was hydrolyzed in an aqueous NaOH solution (3 M) and the product was extracted with small portions of $CHCl_3$. The organic phases were collected and dried with $MgSO_4$ anhydrous. The compound was obtained as a red solid after solvent evaporation and successive freeze-trituration-pump-thaw cycles in 63% yield (0.72 g, 1.29 mmol). ^{1}H NMR ($CDCl_3$, 400.1 MHz, 296 K): δ (ppm) 8.86 (s, 2H, *p-Ph*CH_2N), 8.65 (s, 4H, *o-Ph*CH_2N), 3.77 (s, 4H, PhCH_2N), 2.83 (m, 4H, [C2]CH_2N), 2.76 (m, 4H, [C3]CH_2N), 2.68–2.65 (overlapping, 8H total, 4H, [C3]CH_2N and 4H, [C2]CH_2N), 1.88 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz, 296 K): δ (ppm) 148.6 (*m-Ph*CH_2N), 145.3 (*i-Ph*CH_2N), 128.5 (o-*Ph*CH_2N), 117.5 (*p-Ph*CH_2N), 56.3 (PhCH_2N), 54.5 ([C3]CH_2N or [C2]CH_2N), 49.6 ([C3]CH_2N), 47.9 ([C3]CH_2N or [C2]CH_2N), 47.4 ([C2]CH_2N), 26.1 ($CH_2CH_2CH_2$). ^{1}H NMR ($D_2O/(CD_3)_2CO$, 300.1 MHz, 296 K): δ (ppm) 8.94 (s, 2H, *p-Ph*CH_2N), 8.58 (s, 4H, *o-Ph*CH_2N), 4.03 (s, 4H, PhCH_2N), 3.43 (m, 4H, [C2]CH_2N), 3.34 (m, 4H, [C3]CH_2N), 2.95 (m, 4H, [C2]CH_2N), 2.69 (m, 4H, [C3]CH_2N), 2.03 (m, 4H, $CH_2CH_2CH_2$). ^{13}C{^{1}H} NMR ($D_2O/(CD_3)_2CO$, 75.5 MHz, 296 K): δ (ppm) 149.7 (*m-Ph*CH_2N), 142.0 (*i-Ph*CH_2N), 131.3 (o-*Ph*CH_2N),

Table 1
Crystallographic data of compounds **1**–**3, 5, 7, 8, 11**–**13, 15** and **16**.

Compound	**1.4H$_2$O**	**2**	**3**
Empirical formula	C12 H32 N4 O4	C12 H26 Cl2 N4	C26 H38 Br2 N4
Formula weight	296.42	297.27	566.40
Temperature (K)	150	150	150
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	P −1	C2/c	P −1
Unit cell dimensions:			
a (Å)	6.2557(9)	12.891(2)	8.2052(3)
b (Å)	6.668(1)	14.743(3)	11.1548(5)
c (Å)	10.212 (1)	9.682 (2)	17.1566 (7)
α(°)	95.164 (9)	90	92.369 (2)
β(°)	105.49 (1)	98.60 (1)	98.603 (2)
γ(°)	98.213 (9)	90	105.315 (3)
Volume (Å^3)	402.6 (1)	1819.4 (5)	1492.1 (1)
Z	1	4	2
Calculated density (g m^{-3})	1.223	1.085	1.261
Absorption coefficient (mm^{-1})	0.091	0.349	2.735
F (000)	164	640	584
Crystal size (mm)	0.02 × 0.10 × 0.20	0.02 × 0.05 × 0.40	0.20 × 0.20 × 0.20
Theta range for data collection (°)	3.43–25.68	2.11–27.54	2.94–25.68
Limiting indices	$-7\leq h\leq 7$, $-8\leq k\leq 8$, $-12\leq l\leq 12$	$-16\leq h\leq 16$, $-18\leq k\leq 19$, $-12\leq l\leq 12$	$-10\leq h\leq 8$, $-13\leq k\leq 13$, $-20\leq l\leq 20$
Reflections collected/unique [R$_{int}$]	3796/1503 [0.0206]	10236/2091 [0.1065]	17893/5602 [0.0311]
Completeness to θ (%)	98.2 (θ = 25.68)	99.8 (θ = 27.54)	99.1 (θ = 25.68)
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	1503/0/103	2091/0/86	5602/0/307
Goodness-of-fit on F^2	1.062	0.976	1.080
Final *R* indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0389$, $wR_2 = 0.0995$	$R_1 = 0.0627$, $wR_2 = 0.1249$	$R_1 = 0.0842$, $wR_2 = 0.2597$
R indices (all data)[a]	$R_1 = 0.0506$, $wR_2 = 0.1043$	$R_1 = 0.1097$, $wR_2 = 0.1389$	$R_1 = 0.1128$, $wR_2 = 0.2792$
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Largest diff. peak/hole (e Å^{-3})	0.257 and −0.163	0.409–0.293	1.914 and −0.557

Compound	**5**	**7**	**8**
Empirical formula	C34 H54 Br2 N4	C28 H36 Br2 F6 N4	C42 H70 Br2 N4
Formula weight	678.61	702.41	790.82
Temperature (K)	150	150	150
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Triclinic	Triclinic	Orthorhombic
Space group	P −1	P −1	Pbca
Unit cell dimensions:			
a (Å)	8.9852 (6)	7.879 (1)	8.950 (1)
b (Å)	20.611 (1)	8.1794 (8)	11.512 (1)
c (Å)	20.752 (1)	12.572 (1)	40.085 (6)
α(°)	78.485 (3)	77.808 (3)	90
β(°)	89.970 (4)	87.573 (4)	90
γ(°)	79.869 (3)	74.562 (3)	90
Volume (Å^3)	3704.7 (4)	763.3 (1)	4130.1 (9)
Z	4	1	4
Calculated density (g m^{-3})	1.217	1.528	1.272
Absorption coefficient (mm^{-1})	2.214	2.716	1.996
F (000)	1424	356	1680
Crystal size (mm)	0.10 × 0.10 × 0.40	0.01 × 0.05 × 0.20	0.01 × 0.20 × 0.20
Theta range for data collection (°)	2.56–25.50	2.64–27.12	2.49–25.39
Limiting indices	$-10\leq h\leq 10$, $-24\leq k\leq 24$, $-25\leq l\leq 24$	$-9\leq h\leq 10$, $-10\leq k\leq 10$, $-15\leq l\leq 16$	$-9\leq h\leq 10$, $-10\leq k\leq 13$, $-48\leq l\leq 44$
Reflections collected/unique [R$_{int}$]	64402/13494 [0.0726]	9541/3293 [0.0460]	22314/3769 [0.0776]
Completeness to θ (%)	98.0 (θ = 25.50)	97.4 (θ = 27.12)	99.2 (θ = 25.39)
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	13494/36/706	3293/0/177	3769/0/223
Goodness-of-fit on F^2	1.105	1.060	1.082
Final *R* indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0834$, $wR_2 = 0.2341$	$R_1 = 0.0514$, $wR_2 = 0.1331$	$R_1 = 0.0568$, $wR_2 = 0.1077$
R indices (all data)[a]	$R_1 = 0.1380$, $wR_2 = 0.2545$	$R_1 = 0.0687$, $wR_2 = 0.1395$	$R_1 = 0.1000$, $wR_2 = 0.1159$
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Largest diff. peak/hole (e Å^{-3})	1.824 and −2.268	1.748 and −2.351	0.704 and −0.703

Compound	**11.2H$_2$O**	**12**	**13**
Empirical formula	C14 H34 I2 N4 O2	C24 H36 N4	C24 H26 F10 N4
Formula weight	544.25	380.57	560.49
Temperature (K)	150	150	150
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	P2$_1$/n	C2/c	P −1
Unit cell dimensions:			
a (Å)	7.6735 (2)	24.828 (3)	7.3089 (6)
b (Å)	15.1331 (5)	8.3866 (8)	7.7185 (6)
c (Å)	8.9944 (3)	21.039 (2)	11.997 (1)

Table 1 (*continued*)

Compound	**11.2H$_2$O**	**12**	**13**
α(°)	90	90	79.295 (5)
β(°)	106.142 (1)	91.801 (4)	81.375 (6)
γ(°)	90	90	62.341 (4)
Volume (Å^3)	1003.29 (5)	4378.6 (8)	587.42 (9)
Z	2	8	1
Calculated density (g m^{-3})	1.802	1.155	1.584
Absorption coefficient (mm^{-1})	3.147	0.069	0.151
F (000)	536	1664	288
Crystal size (mm)	0.10 × 0.22 × 0.24	0.08 × 0.16 × 0.18	0.06 × 0.08 × 0.28
Theta range for data collection (°)	2.69–34.99	2.50–25.74	3.01–27.95
Limiting indices	$-12 \le h \le 12$, $-24 \le k \le 24$, $-14 \le l \le 14$	$-30 \le h \le 30$, $-10 \le k \le 10$, $-25 \le l \le 17$	$-9 \le h \le 9$, $-10 \le k \le 10$, $-15 \le l \le 15$
Reflections collected/unique [R$_{int}$]	22531/4402 [0.0326]	18956/4165 [0.0802]	7023/2797 [0.0320]
Completeness to θ (%)	99.5 (θ = 34.99)	99.6 (θ = 25.74)	99.0 (θ = 27.95)
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	4402/0/109	4165/0/261	2797/0/176
Goodness-of-fit on F^2	1.084	0.944	1.058
Final *R* indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0191$, $wR_2 = 0.0440$	$R_1 = 0.0491$, $wR_2 = 0.0923$	$R_1 = 0.0462$, $wR_2 = 0.1065$
R indices (all data)[a]	$R_1 = 0.0244$, $wR_2 = 0.0454$	$R_1 = 0.1051$, $wR_2 = 0.1056$	$R_1 = 0.0804$, $wR_2 = 0.1154$
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Largest diff. peak/hole (e Å^{-3})	0.539 and −0.602	0.192 and −0.205	0.269 and −0.287

Compound	**15**	**16.NaBr**
Empirical formula	C26 H34 N6	C26 H34 Br F6 N4 Na
Formula weight	430.59	619.46
Temperature (K)	150	150
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	P −1	P −1
Unit cell dimensions:		
a (Å)	8.2348 (6)	7.805 (1)
b (Å)	12.2201 (8)	9.289 (2)
c (Å)	13.769 (1)	20.268 (4)
α(°)	113.966 (3)	93.073 (8)
β(°)	95.313 (2)	95.166 (7)
γ(°)	103.161 (2)	98.258 (7)
Volume (Å^3)	1205.9 (2)	1445.0 (4)
Z	2	2
Calculated density (g m^{-3})	1.186	1.424
Absorption coefficient (mm^{-1})	0.073	1.498
F (000)	464	636
Crystal size (mm)	0.10 × 0.16 × 0.20	0.02 × 0.15 × 0.25
Theta range for data collection (°)	1.65–25.43	2.02–25.78
Limiting indices	$-9 \le h \le 9$, $-14 \le k \le 14$, $-16 \le l \le 16$	$-9 \le h \le 9$, $-11 \le k \le 11$, $-24 \le l \le 24$
Reflections collected/unique [R$_{int}$]	9635/4346 [0.0386]	10881/5393 [0.1155]
Completeness to θ (%)	97.5 (θ = 25.43)	96.9 (θ = 25.78)
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	4346/0/297	5393/72/344
Goodness-of-fit on F^2	0.982	1.128
Final *R* indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0522$, $wR_2 = 0.1389$	$R_1 = 0.1679$, $wR_2 = 0.3830$
R indices (all data)[a]	$R_1 = 0.1019$, $wR_2 = 0.1760$	$R_1 = 0.2076$, $wR_2 = 0.4074$
Absorption correction	Multi-scan	Multi-scan
Largest diff. peak/hole (e Å^{-3})	0.208 and −0.204	1.322 and −1.261

[a] $R_1 = \sum||F_0| - |F_c||/\sum|F_0|$; $wR_2 = \{\sum[w(F_0^2 - F_c^2)^2]/\sum[w(F_0^2)^2]\}^{1/2}$.

119.6 (*p-Ph*CH_2N), 56.3 (PhCH_2N), 51.7 ([C3]CH_2N), 48.3 ([C2]CH_2N), 46.4 ([C3]CH_2N), 44.9 ([C2]CH_2N), 24.6 ($CH_2CH_2CH_2$). Anal. calcd for $C_{24}H_{32}N_8O_8$: C, 51.42; H, 5.75; N, 19.99. Found: C, 50.80; H, 5.99; N, 18.48. FT-IR (KBr, cm^{-1}): 3107 ($\nu_{N\text{-}H}$), 1540 and 1343 (ν_{NO2}).

2.3. X-ray crystallography

Crystallographic and experimental details of data collection and crystal structure determinations are available in Table 1. Suitable crystals of compounds **1**.4H$_2$O, **2**, **3**, **5**, **7**, **8**, **11**, **12**, **13**, **15** and **16** were coated and selected in Fomblin® oil. Data were collected using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all observed reflections [10]. Absorption corrections were applied using SADABS [11]. The structures were solved by direct methods using SIR92 [12], SIR97 [13] or SIR2004 [14]. Structure refinement was done using SHELXL-97 [15]. These programs are part of the WinGX software package version 1.80.05 [16]. The hydrogen atoms bonded to nitrogen were located in the difference map and refined freely. The hydrogen atoms bonded to carbon were included in fixed positions and allowed to refine riding on the parent atom. Torsion angles, mean square planes and other geometrical parameters were calculated using SHELX [15]. Illustrations of the molecular structures were made with Mercury 3.0 [17] or ORTEP-3 [18] for Windows.

Compounds **2**, **3** and **5** crystallize with a disordered molecule of solvent. As all attempts to model the disorder did not lead to acceptable solutions, the Squeeze/PLATON [19] sequence was applied. The poor diffracting power and quality of the crystals of compounds **3**, **5** and **16** led to high R$_{int}$ values. Restraints were

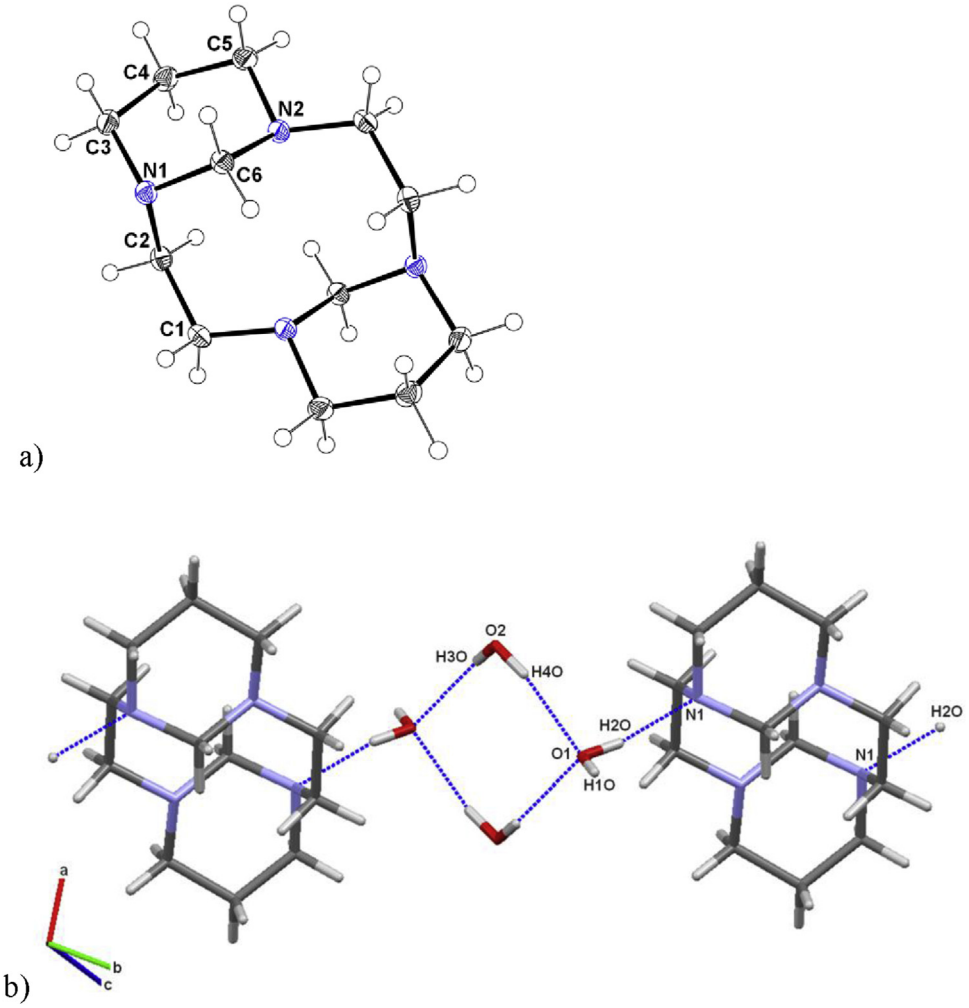


Fig. 1. a) ORTEP diagram of 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane, **1**, showing thermal ellipsoids at 40% probability level. Co-crystallized water molecules are omitted for clarity; b) Best view of **1** showing hydrogen bonds as blue dashed lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Hydrogen bond distances (Å) and angles (°) in compounds **1**.4H_2O, **2**, **7**, **12**, **13**, **15** and **16**.

	D-H···A	d(D-H)	d(H···A)	d(D···A)	(DĤA)	Symmetry operation
1.4H_2O	O(1)-H(2O)···N(1)	0.86 (2)	1.93(2)	2.776 (2)	169 (2)	–
	O(2)-H(3O)···O(1)	0.66 (3)	2.17(3)	2.818 (2)	166 (3)	–
	O(2)-H(4O)···O(1)	0.85 (3)	2.04(3)	2.876 (2)	169 (2)	−x,−y,−z
2	N(1)-H(1N)···Cl(1)	0.91 (3)	2.16(3)	3.064 (3)	174 (3)	–
7	C(4)-H(4B)···F(2)	0.99	2.66	3.379	129	1−x,−y,1−z
11	O(1)-H(1O)···I(1)	0.89 (2)	2.69(2)	3.561 (1)	167(1)	$^{3}/_{2}$−x, ½+y, ½−z
	O(1)-H(2O)···I(1)	0.84 (2)	2.82(3)	3.657 (1)	176(2)	2−x,1−y,1−z
	C(3)-H(3B)···O(1)	0.99	2.59	3.233 (2)	123	1−x,1−y,1−z
	C(6)-H(6A)···O(1)	0.99	2.70	3.503	138	2−x,1−y,1−z
	C(6)-H(6B)···I(1)	0.99	3.13	3.953	141	2−x,1−y,1−z
	C(7)-H(7B)···I(1)	0.98	3.06	4.003	161	1−x,1−y,1−z
12	N(2)-H(2N)···N(3)	0.89 (2)	2.46 (2)	3.130 (2)	133 (1)	–
	N(4)-H(4N)···N(1)	0.92 (2)	2.46(2)	3.177 (2)	135 (2)	–
13	C(1)-H(1A)···F(5)	0.99	2.47	3.025 (3)	115	–
	C(4)-H(4A)···F(1)	0.99	2.35	3.184 (3)	141	1−x,1−y,1−z
	C(1)-H(1B)···F(3)	0.99	2.63	3.560 (3)	157	2−x,1−y,2−z
	C(2)-H(2A)···F(5)	0.99	2.67	3.636 (3)	168	−1+x,y,z
	C(5)-H(5B)···F(2)	0.99	2.63	3.489 (3)	146	2−x,−y,2−z
15	C(22)-H(22)···N(2)	0.95	2.38	3.244 (3)	151	–
16	N(4)-H(4N)···N(2)	0.8 (1)	2.2 (1)	2.99 (1)	157 (12)	–
	C(22)-H(22)···F(3)	0.953	2.572	3.464	156	–
	C(2)-H(2N)···Br(1)	1.0 (1)	2.8 (1)	3.673 (8)	150 (8)	–

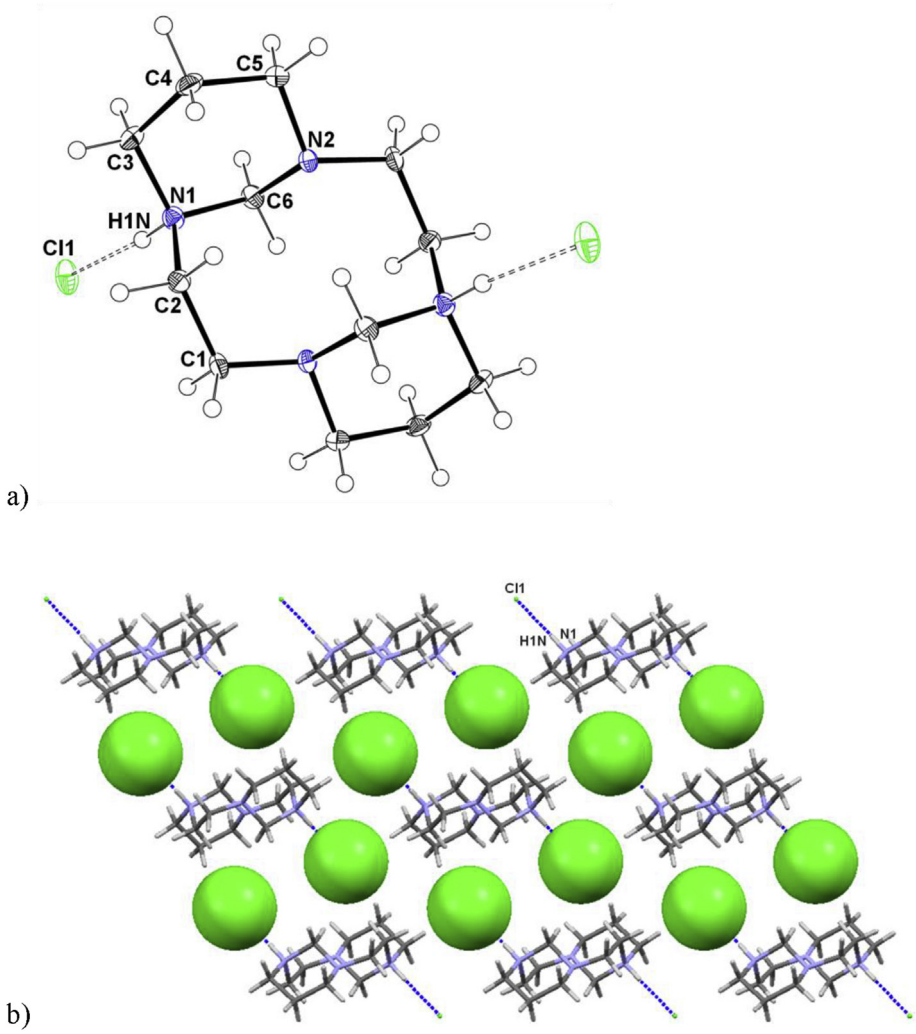


Fig. 2. a) ORTEP diagram of 1,8-diazonia-4,11-triazatricyclo[9.3.1.1^{4,8}]hexadecane dichloride, **2**, showing thermal ellipsoids at 40% probability level. Hydrogen bonds are represented as dashed lines. b) View, along the *b*-axis, of the supramolecular structure. Chloride anions are represented using the space filling model.

applied to compounds **5** and **16** in order to model the disorder observed in the ^{t}Bu and CF_3 groups, respectively.

3. Results and discussion

1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane, **1**, shown in Fig. 1a, was prepared according to a published procedure [6] and obtained as a tetrahydrate by slow evaporation of a concentrated solution in a THF/H_2O mixture. The molecular structure of **1** reveals the presence of one ten-membered and two six-membered rings with internal angles around the nitrogen atoms of approximately 109.5° in agreement with their sp_3 hybridization. Each six-membered ring adopts a distorted chair conformation with the [C2] chains attached to nitrogen atom N(1) occupying an equatorial and an axial position of each ring. The methylene cross-bridges between the nitrogens of the latter rings point to opposite faces of the macrocycle. The molecular parameters obtained for the macrocycle frame of **1**.4H_2O are analogous to those reported for **1** (CSD refcode BOBHOP [20]) and **1**.6H_2O (CSD refcode PUHPOX [6]) and do not deserve further discussion.

The reactions of **1** with electrophiles lead to the selective formation of *trans*-disubstituted compounds. Molecular Electrostatic Potential calculations have shown that the deepest negative potentials in the cyclam frame are located on one pair of *trans* nitrogen atoms (N(1) in Fig. 1a) that simultaneously display non-bonding electron pairs pointing out of the macrocycle backbone

Table 3
Selected bond lengths (Å) and angles (°) for **2**, **3**, **5**, **7** and **8**.

	2	**3a**	**3b**	**5a**	**5b**	**5c**	**7**	**8**	**11**
N^+–C_{aminal}	1.505 (4)	1.540 (7)	1.522 (6)	1.499 (9)	1.519 (8)	1.526 (8)	1.523 (5)	1.511 (5)	1.515 (1)
N^+–C	1.502 (4)	1.492 (7)	1.515 (6)	1.501 (8)	1.521 (9)	1.513 (9)	1.528 (5)	1.513 (5)	1.520 (2)
	1.495 (4)	1.536 (7)	1.504 (6)	1.514 (9)	1.504 (9)	1.522 (9)	1.522 (5)	1.527 (5)	1.518 (2)
N–C_{aminal}	1.445 (3)	1.416 (7)	1.441 (6)	1.440 (9)	1.448 (9)	1.445 (9)	1.440 (5)	1.438 (5)	1.439 (1)
N–C	1.462 (3)	1.462 (6)	1.456 (6)	1.453 (9)	1.474 (8)	1.478 (9)	1.472 (5)	1.468 (5)	1.461 (2)
	1.474 (4)	1.475 (7)	1.471 (6)	1.456 (9)	1.430 (9)	1.450 (10)	1.472 (5)	1.466 (5)	1.473 (2)

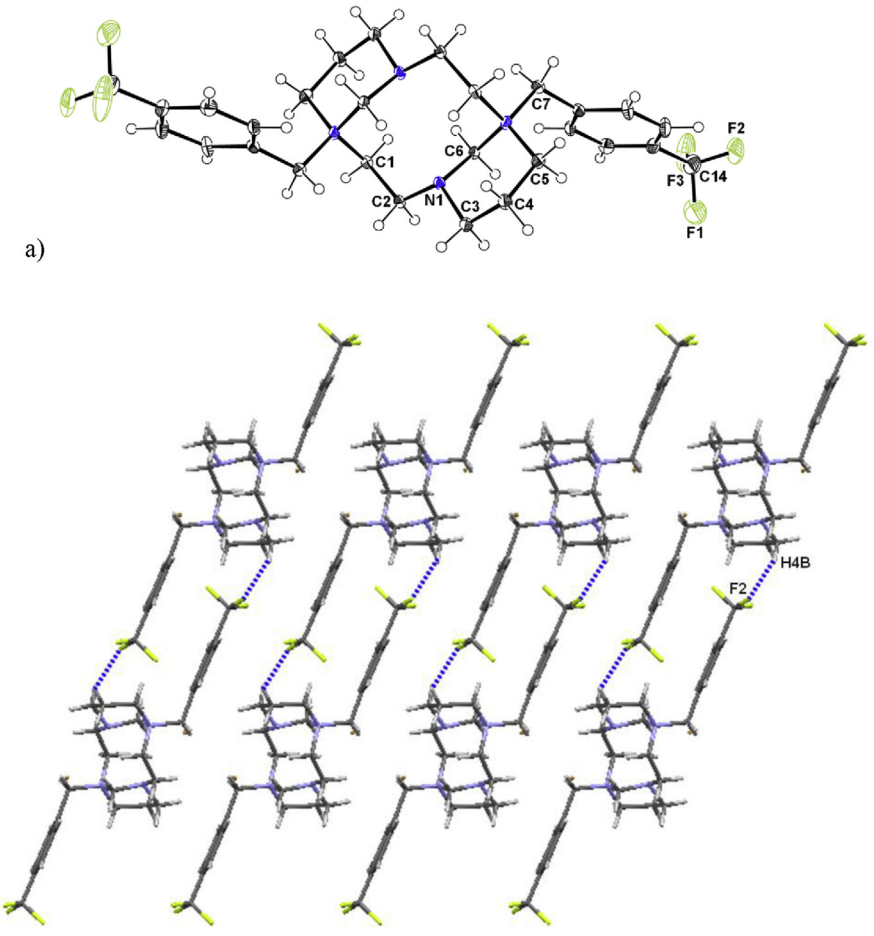


Fig. 3. a) ORTEP diagram of **7** showing thermal ellipsoids at 40% probability level. Bromide counter-ions are omitted for clarity. b) View, along the *a*-axis, of the supramolecular structure of **7**. Intermolecular C–H···F bonds between molecules are shown as blue dashed lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[6]. This circumstance is responsible for the establishment of a hydrogen bond between the N(1) atom of the cyclam ring and the H(2O) atom of one co-crystallized water molecule with a distance of 1.93(2) Å (Fig. 1b). Detailed information about the hydrogen bonds is given in Table 2. The four water molecules in **1**.4H_2O create tetrameric clusters arranged in a coplanar square-like fashion with internal angles of *ca* 91° and 108°. In the $(H_2O)_4$ cluster the O···O distances are 2.818(2) and 2.876(2) Å. The supramolecular structure consists of unidimensional infinite chains of **1** and $(H_2O)_4$ clusters growing in the *b* direction linked to each other by $N_{cyclam}\cdots H_{water}$ hydrogen bonds (see Fig. SM1). This assembly differs from the one displayed by the hexahydrated compound where the water molecules define hexameric clusters that are intercalated between two 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane units [6]. The hydrogen bonds established between the nitrogen atom N(2) and the water molecules are in **1**.4H_2O slightly longer (1.93(2) Å *vs.* 1.840 Å) than in the structure of the hexahydrated of **1** described in the literature [6]. In the anhydrous form of **1**, the supramolecular arrangement is based on the establishment of hydrogen interactions between the two most electronegative *trans*-nitrogen atoms of the cyclam framework and the hydrogens belonging to the macrocyclic [C2] chains of parent molecules [20].

Compound **1** undergoes diprotonation in acidic media to give 1,8-diazonia-4,11-diazatricyclo[9.3.1.1^{4,8}]hexadecane salts as the dichloride, [**1**H_2]Cl_2, **2**, which was obtained as a white crystalline material suitable for single crystal X-ray diffraction from a diluted aqueous solution [21]. An ORTEP depiction of the molecular structure is shown in Fig. 2a. Both protons in **2** are selectively located on the two *trans*-nitrogen atoms that in **1** display the most negative charges. The N(1)-H(1N) bond length of 0.91(3) Å is in agreement with values reported, the hydrogens being located from the electron density map [21,22]. Both nitrogen atoms show sp_3 hybridization and (*R*,*R*) configuration. The distances N(1)-C(2), N(1)-C(3) and N(1)-C(6) are similar and slightly longer than N(2)-C(i) bonds reflecting, in a first instance, the positive charge on N(1) (see Table 3). On the other hand, the distance between N(2) and the aminal carbon C(6) is the shortest of all N–C bonds possibly as a consequence of an anomeric effect involving the non-bonding electron pair (lp) in N(1) [21]. This explains N(2) and N(1) aminal carbon C(6) shortening/lengthening of the distances, respectively, due to the overlap of the sp_3 orbitals across lp-N(1)-C(6)-N(2). This is maximised if the dihedral angle defined is close to antiperiplanar (180°) or eclipsed (0°), as observed in the structure of the cation [**1**H_2]$^{2+}$ in **2** that displays a torsion angle of 168°. Relevant bond lengths and angles for **2** are presented in Table 3. Intermolecular hydrogen bonds are established between the N(1)-H(1N) group of the macrocycle and the Cl(1) anions with an interaction distance of 2.16(3) Å (see Table 2). These interactions are responsible for the supramolecular arrangement of **2** that show 2D grid networks of cyclam cations (**2**$^+$) and chloride anions (Cl^-) as depicted in Fig. 2b.

Trans-*N*,*N*′-dibenzylcyclam, **3**–**10**, and *trans*-*N*,*N*′-dimethylcyclam, **11**, were obtained by reactions of **1** with two equivalents of appropriate benzyl halides (bromide or chloride) or methyl iodide, respectively, as shown in Scheme 1. These products are the result of

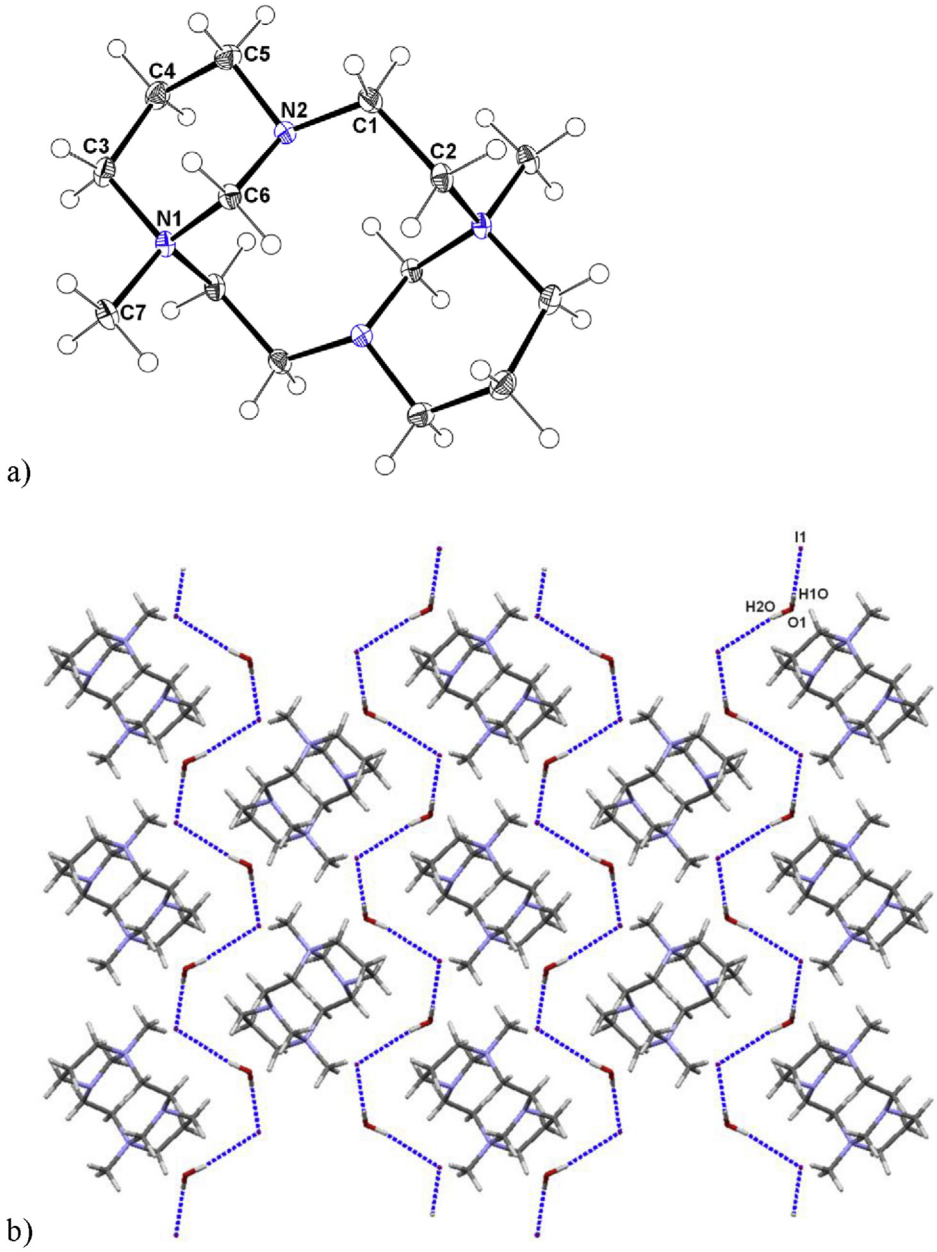


Fig. 4. a) ORTEP diagram of compound **11** showing thermal ellipsoids at 40% probability level. Co-crystallized water molecules and iodide anions are omitted for clarity. b) View, along the *a*-axis, of the supramolecular structure of **11**. Water molecules and iodide anions zigzag chain is depicted. Intermolecular O–H···I interactions are shown as blue dashed lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

electrophilic attack of the benzyl halides or methyl iodide to the most negative nitrogen atoms of **1**. Compounds **3**–**11** are hygroscopic solids that can hydrolyze in air depending on the nature of the substituent groups of the aromatic rings. Compounds having electron withdrawing groups such as F, **4**, CN, **6**, CF_3, **7** or NO_2, **10**, slowly hydrolyse in the presence of moisture originating the corresponding *trans*-dibenzyl cyclams **13**, **15**, **16** and **19**. These reactions are immediate for **4**, **6** and **10** in acetone/water solutions; compound **7** is relatively more resistant to hydrolysis and, although pure NMR spectra could not be recorded (the sample showed already some hydrolysis product, **16**), crystals suitable for X-ray structure determination grew from acetone/water solution. It was also observed that compounds having more than one alkyl group in the aromatic rings, as **8** (^{t}Bu) and **9** (Me), are fairly soluble in water or mixtures of water with polar organic solvents as acetone or dimethyl sulfoxide. The characterization of compounds **4** and **6**–**10** by NMR spectroscopy was therefore hampered by their solubility/stability properties.

The ^{1}H and ^{13}C NMR spectra of compounds **3**, **5** and **11** reveal that all compounds display C_i symmetry in solution. The proton NMR spectra reveal ten multiplets corresponding to the methylene protons of the macrocycle backbone, integrating to two protons each. Additionally, two AB systems corresponding to the bridging methylene protons ($^2J_{H\text{-}H}$ = 9–10 Hz) and to the benzylic protons of the pendant arms ($^2J_{H\text{-}H}$ = 12–13 Hz) are observed in **3** and **5**. In **11** the pendant methyl groups appear in the region 3.23–3.18 ppm, overlapping with proton resonances of the macrocyclic [C2] chain. The carbon NMR spectra show seven resonances assigned to the

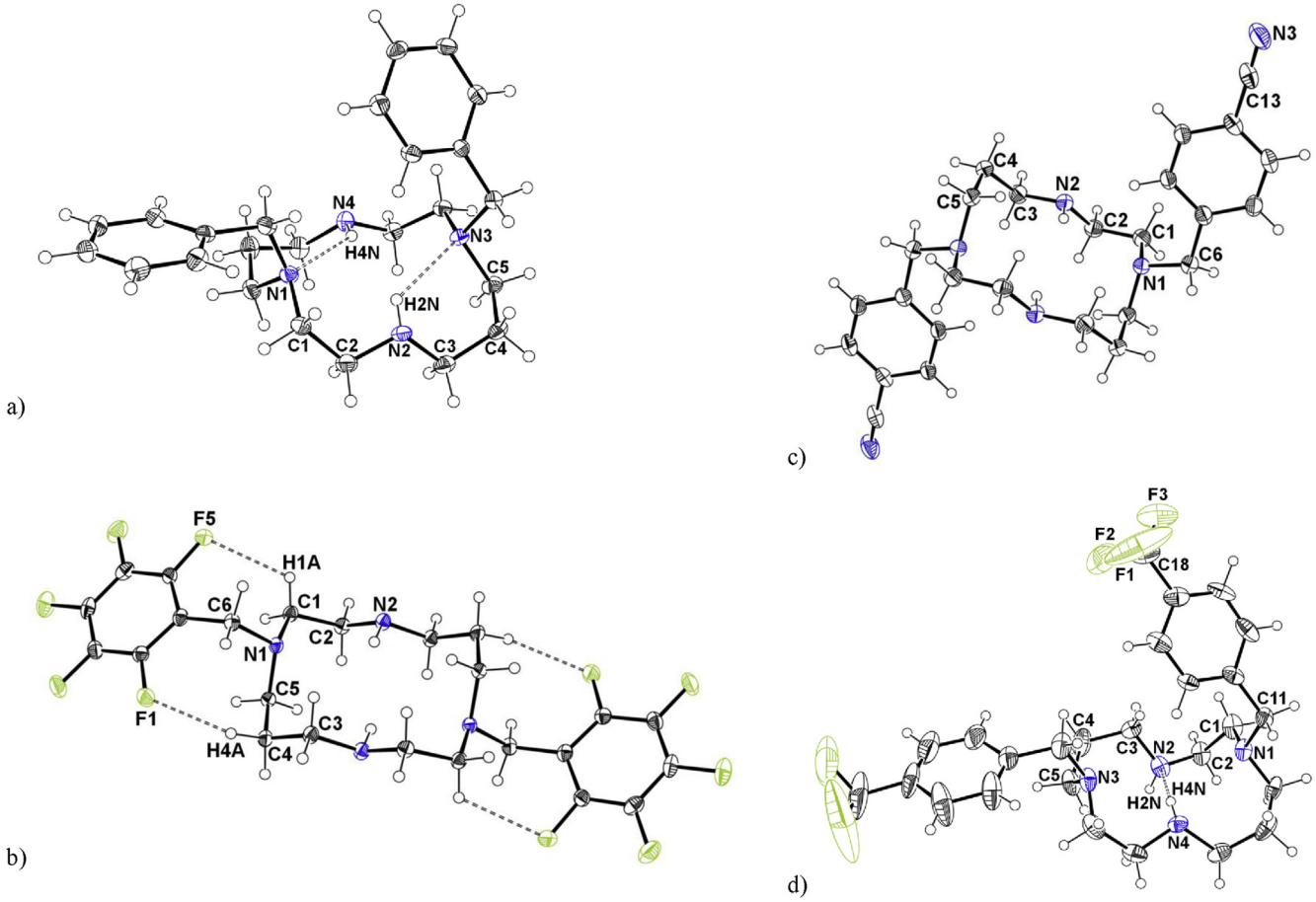


Fig. 5. ORTEP diagrams of compounds **12** (a), **13** (b), **15** (c) and **16** (d) showing thermal ellipsoids at 40% probability level. In **16**, the co-crystallized NaBr molecule was omitted for clarity. The dashed lines represent hydrogen bonds.

methylene carbons and one set of resonances belonging to the phenyl or methyl groups.

Crystals of **3**, **5**, **7**, **8** and **11** suitable for single crystal X-ray diffraction were obtained from concentrated water/acetone mixtures. The asymmetric unit of **3** displays two molecules (**3a** and **3b**) and the asymmetric unit of **5** contains three different molecules (**5a**-**5c**). The molecular structures of these compounds show the pendant arms in mutually *trans* positions pointing to opposite sides of the macrocycle, which cause the nitrogen atoms in **3**, **7**, **8** and **11** to adopt (*R*,*R*) or (*S*,*S*) configurations. Diverse nitrogen configurations ((*R*,*R*), (*S*,*S*) and (*R*,*S*)) were observed for the molecular structures of **5**. Interestingly, the bonds between the aminal carbons and the neutral nitrogens in **3a**, **5a**, **7**, **8** and **11** are significantly shorter than the two other C—N bonds to that nitrogen atom as observed in **2** (see Table 2). However, in **3b**, **5b** and **5c** this effect is almost negligible, raising the question about the importance of anomeric effect in this class of compounds. ORTEP representations of the solid-state molecular structures of **7** and **11** are shown in Figs. 3a and 4a, respectively (for **3**, **5** and **8**, see Fig. SM2).

At the supramolecular level the disordered bromine counterions in **3** preclude any packing consideration. In compounds **5** and **8** there are no relevant intermolecular interactions but in **7** the

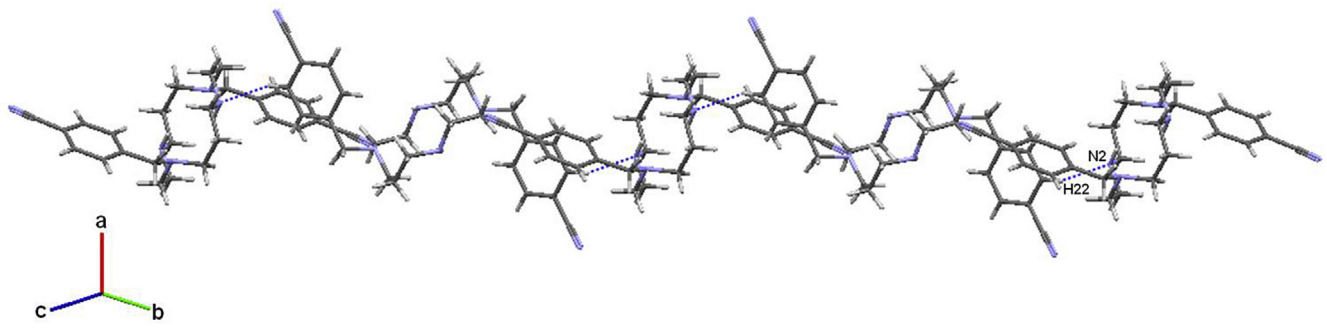


Fig. 6. Best view of the supramolecular structure of **15** revealing the intermolecular hydrogen bonds as blue dashed lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

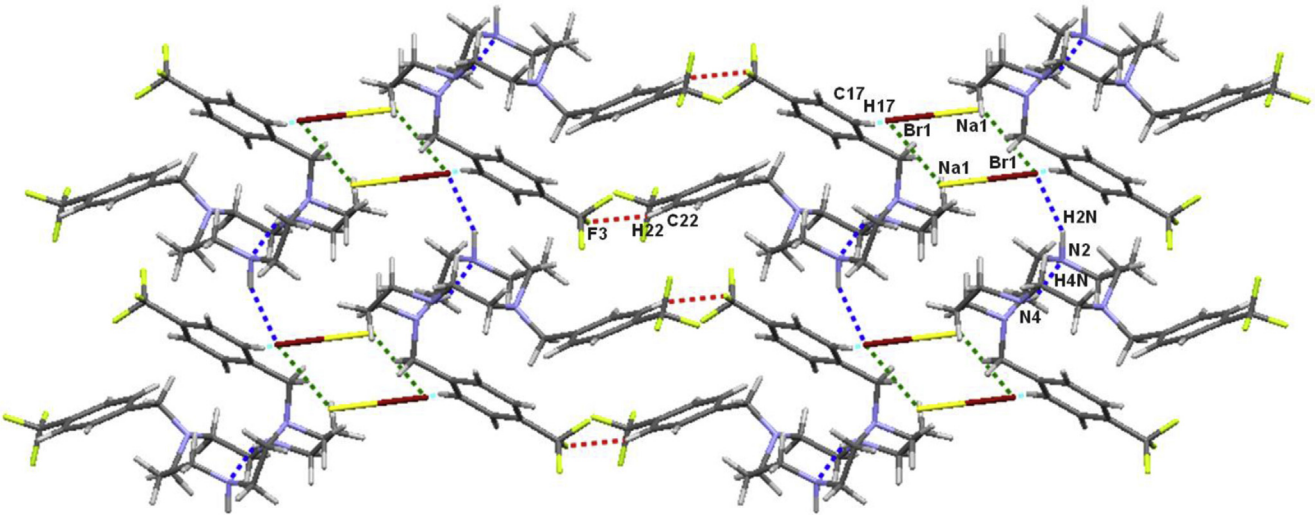


Fig. 7. View, along the *b*-axis, of **16** revealing the interaction between macrocycles and co-crystallized NaBr. Intermolecular bonds are shown as dashed lines: Na···Br interactions (*green*), N–H···Br (*blue*), C–H···Br (*cyan*) and C–H···F (*red*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

X-ray crystal analysis reveals the presence of C–H···F halogen bonds, C(4)-H(4B) and F(2) with a distance of 2.664 Å that promotes the formation of unidimensional chains as shown in Fig. 3b. The average distance of 1.316 (8) Å for the C–F bonds in **7** are within the ranges usually observed [23].

In compound **11** the co-crystallized water molecules display hydrogen bonds with the iodide anions that alternate in a zigzag motif with distances of 2.69(2) and 2.82(3) Å. These interactions create water/iodine parallel chains that intercalate cations $\mathbf{11}^{+}$ as shown in Fig. 4b and Fig. SM3. The interactions of the hydrogen atoms belonging to the [C3] chains, methylene cross-bridges and methyl groups of the cyclam framework with the oxygens and iodides determine the tridimensional arrangement (see details in Table 2).

Basic hydrolysis of compounds **3**–**11** gave the correspondent H_2(R_2Cyclam) products, **12**–**20**, in variable yields (41–100%) (see Scheme 1) [8,9]. These compounds are hygroscopic and, under air, give rise to colorless oils which can be converted to white solids after various freeze-thaw-pump cycles under nitrogen.

The comparison of the NMR spectra of salts **3**–**11** with those of **12**–**20** reveals that the molecular symmetry changed from C_i to C_{2v} upon hydrolysis. In compounds **12**–**20** the macrocycle geminal protons are equivalent, giving rise to the emergence of only five signals integrating to four protons each. The benzylic protons of the cyclam pendant arms in **12**–**19** show up as singlets in accordance with allowed nitrogen inversion.

Crystals of **12**, **13**, **15** and **16** suitable for single crystal X-ray diffraction were obtained from chloroform solutions. ORTEP representations of **12, 13, 15** and **16** solid-state molecular structures are shown in Fig. 5.

In **12** the two benzyl pendant arms are located at the same side of the macrocyclic ring. The structural arrangement of the macrocycle framework is determined by the establishment of intramolecular hydrogen bonds between N(2)-H(2N) and N(4)-H(4N), and N(3) and N(1), respectively (see Table 2). These interactions form two 6-membered heterocycles and impel both N_{Bn} atoms to adopt a tetrahedral geometry with (*R,R*) configuration. Intramolecular N–H···N hydrogen bonds with comparable bond lengths and angles are responsible for the stabilization of crystal structures in other reported *trans*-disubstituted cyclams [24].

In compounds **13** and **15** the two benzyl pendant arms are located at opposite sides of the macrocyclic ring. Despite the structural arrangement of the cyclam ring, one can not consider intramolecular hydrogen bonds between N(2)-H(2N) and N(1) as the corresponding angles are narrower than 110° [25]. In **13**, intramolecular hydrogen bonds are established between hydrogen atoms of the macrocycle ring and the fluorine atoms of the C_6F_5 moieties ($d_{C(1)\text{-}H(1A)\cdots F(5)} = 2.47$ Å and $d_{C(4)\text{-}H(4A)\cdots F(1)} = 2.35$ Å). At a supramolecular level, C(1)-H(1B)···F(3), C(2)-H(2A)···F(5) and C(5)-H(5B)···F(2) intermolecular hydrogen bonds are established with distances of 2.63, 2.67 and 2.63 Å, respectively (see Table 2 and Fig. SM4).

In compound **15** the X-ray crystal analysis reveals C(22)-H(22)···N(2) that the hydrogen bonding ($d_{C(22)\text{-}H(22)\cdots N(2)} = 2.38$ Å) create a unidimensional chain shown in Fig. 6. The average planes defined by two consecutive cyclam rings of molecules **15a** and **15b** define dihedral angles of 25.97° leading to a helicoidal motif.

In compound **16** the two benzyl pendant arms point to one side of the macrocyclic ring as observed in **12**. However, the structural arrangement of the macrocycle framework in **16** results from the establishment of one intramolecular hydrogen bond between N(4)-H(4N) and N(2) that forms two 9-membered rings (see details in Table 2). The nitrogen atom involved in the hydrogen bond displays tetrahedral geometry but does not constitute a stereogenic center. The structural differences between **16** and the molecules described above might be due to the presence of co-crystallized NaBr in a 1:1 ratio. The supramolecular structure of **16** is constructed by units of two organic molecules and two Na^+ and Br^- ions that form a square with Na–Br distances of 3.34(1) and 3.47(1) Å and internal angles of 108.9(3)° and 71.1(3)° (Fig. 7). This pair is linked to two cyclam moieties by a hydrogen bridge between C(2)-H(2N) and Br(1) with a distance of 2.8(1) Å. Each of these supramolecular structures are linked to another by a hydrogen bridge between C(22)-H(22) and F(3) with a bond length of 2.572 Å (see Table 2 and Fig. 7 for details).

4. Concluding remarks

In 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane, **1**, the deepest negative potential of the cyclam ring corresponds only to one pair of *trans* nitrogen atoms due to the stereochemical conformation imposed by the methylene cross-bridges. These two nitrogen atoms are not only the less sterically hindered but they also have the electron lone pair pointing out of the macrocycle backbone. In

consequence, hydrogen bonds are established between those nitrogen atoms of the cyclam ring and the hydrogen atoms of co-crystallized water molecules. The formation of such interactions may ultimately end up in the protonation of the nitrogen atoms of the cyclam ring in acidic media with formation of dicationic species. Similarly, the formation of *trans-N,N'*-dibenzyl and *trans-N,N'*-dimethyl cationic derivatives can be achieved by reaction of **1** with two equivalents of the appropriate benzyl or methyl halides. These reactions follow a similar route as the protonation reactions, where the aryl or alkyl halides suffer a nucleophilic attack by the most negative nitrogen atoms of **1**. In these compounds, the bond between the aminal carbon and the neutral nitrogen is significantly shorter than the two other C–N bonds to that nitrogen atom as observed in the protonated species. This observation reveals that cations of the type 1,8-R_2-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane-1,8-diium display a N-C_{aminal} bond shortening effect if R = H, Me or Bn'. In some cases this effect is minimized by charge delocalization. The comparison of the NMR spectra of salts with those of neutral compounds reveals that the molecular symmetry changed from C_i to C_{2v} upon hydrolysis. The NMR spectra of all compounds of the same family display the same pattern, revealing that the solid-state molecular arrangements are not kept in solution. The supramolecular architectures created in the solid state crystalline forms are determined by the establishment of intermolecular hydrogen bonds that are broken upon dissolution in polar solvents.

In the cyclam families studied herein it can be said that the supramolecular arrangement depends on the nature of the substituents of the aromatic ring of the macrocyclic pending groups (^{t}Bu, CN, CF_3, C_6F_5) but it is mainly dictated by their relative positioning in the ring. In general, *para*-substituted benzyl groups are not significantly involved in intramolecular or intermolecular interactions except when the substituents are fluorinated groups. Thus, compounds **7** and **16**, displaying CF_3 groups, reveal supramolecular C–H···F interactions originating unidimensional chains in the former and 2D sheets in the latter case. The overall packing's obtained are the result of an energetic interplay between strongly directed hydrogen bonds and a large number of C–H···F weaker interactions.

Acknowledgements

The authors are grateful to Fundação para a Ciência e a Tecnologia, Portugal, for funding (UID/QUI/00100/2013, RECI/QEQ-QIN/0189/2012, SFRH/BD/44295/2008, SFRH/BPD/86815/2012) and to the Portuguese NMR Network (IST-UTL Centre).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.205.03715.0. Figures SM1–4 are presented as Supporting Information. CCDC 1054086-1054096 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

References

[1] (a) X.Y. Liang, J.A. Parkinson, S. Parsons, M. Weishaupl, P.J. Sadler, Inorg. Chem. 41 (2002) 4539–4547;
(b) E. Kimura, Y. Kurogi, T. Takahashi, Inorg. Chem. 30 (1991) 4117–4121;
(c) A. Chaudhary, R. Swaroop, R.V. Singh, Bol. De. Soc. Chil. De. Quim. 47 (2002) 203–211;
(d) P. Mahato, A. Ghosh, S. Saha, S. Mishra, S.K. Mishra, A. Das, Inorg. Chem. 49 (2010) 11485–11492;
(e) B. Bosnich, M.L. Tobe, G.A. Webb, Inorg. Chem. 4 (1965) 1109–1112;
(f) B. Bosnich, C.K. Poon, M.L. Tobe, Inorg. Chem. 4 (1965) 1102–1108;
(g) S.A. Zuckman, G.M. Freeman, D.E. Troutner, W.A. Volkert, R.A. Holmes, D.G. Vanderveer, E.K. Barefield, Inorg. Chem. 20 (1981) 2386–2389.
[2] (a) E. Kimura, Top. Curr. Chem. 128 (1985) 113–141;
(b) K.R. Adam, M. Antolovich, I.M. Atkinson, A.J. Leong, L.F. Lindoy, B.J. McCool, R.L. Davis, C.H.L. Kennard, P.A. Tasker, J. Chem. Soc. Chem. Commun. (1994) 1539–1540;
(c) A. Bencini, A. Bianchi, E. Garcia-Espana, M. Micheloni, J.A. Ramirez, Coord. Chem. Rev. 188 (1999) 97–156.
[3] (a) F. Denat, S. Brandes, R. Guilard, Synlett (2000) 561–574;
(b) I.M. Helps, D. Parker, J. Chapman, G. Ferguson, J. Chem. Soc. Chem. Commun. (1988) 1094–1095;
(c) R. Guilard, A.G. Bessmertnykh, I.P. Beletskaya, Synlett (1997) 1190–1192;
(d) C.M. Madeyski, J.P. Michael, R.D. Hancock, Inorg. Chem. 23 (1984) 1487–1489;
(e) P.J. Davies, M.R. Taylor, K.P. Wainwright, P. Harriott, P.A. Duckworth, Inorg. Chim. Acta 246 (1996) 1–6.
[4] (a) M. Hediger, T.A. Kaden, Helv. Chim. Acta 66 (1983) 861–870;
(b) T.A. Kaden, Top. Curr. Chem. 121 (1984) 157–179;
(c) M. Ciampolini, M. Micheloni, N. Nardi, P. Paoletti, P. Dapporto, F. Zanobini, J. Chem. Dalt. Trans. (1984) 1357–1362.
[5] (a) C. Bucher, G. Royal, J.M. Barbe, R. Guilard, Tetrahedron Lett. 40 (1999) 2315–2318;
(b) J. Chapman, G. Ferguson, J.F. Gallagher, M.C. Jennings, D. Parker, J. Chem. Dalt. Trans. (1992) 345–353;
(c) W. Schibler, T.A. Kaden, J. Chem. Soc. Chem. Commun. (1981) 603–604;
(d) I.M. Helps, D. Parker, J.R. Morphy, J. Chapman, Tetrahedron 45 (1989) 219–226;
(e) P.J. Davies, M.R. Taylor, K.P. Wainwright, Chem. Commun. (1998) 827–828;
(f) F. Denat, S. Lacour, S. Brandes, R. Guilard, Tetrahedron Lett. 38 (1997) 4417–4420.
[6] G. Royal, V. Dahaoui-Gindrey, S. Dahaoui, A. Tabard, R. Guilard, P. Pullumbi, C. Lecomte, Eur. J. Org. Chem. (1998) 1971–1975.
[7] E.K. Barefield, F. Wagner, K.D. Hodges, Inorg. Chem. 15 (1976) 1370–1377.
[8] R.F. Munhá, L.G. Alves, N. Maulide, M.T. Duarte, I.E. Markó, M.D. Fryzuk, A.M. Martins, Inorg. Chem. Commun. 11 (2008) 1177–1179.
[9] L.G. Alves, M.A. Antunes, I. Matos, R.F. Munhá, M.T. Duarte, A.C. Fernandes, M.M. Marques, A.M. Martins, Inorg. Chim. Acta 363 (2010) 1823–1830.
[10] SAINT. Version 7.03A, Bruker AXS Inc, Madison. Wisconsin, USA, 1997-2003.
[11] G.M. Sheldrick, SADABS, Program for Empirical Absorption Corrections, University of Göttingen, Göttingen, Germany, 1996.
[12] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, J. Appl. Crystallogr. 26 (1993) 343–350.
[13] A. Altomare, M.C. Burla, M. Camalli, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, A.G.G. Moliterni, G. Polidori, R. Spagna, J. Appl. Crystallogr. 32 (1999) 115–119.
[14] M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, J. Appl. Crystallogr. 38 (2005) 381–388.
[15] G.M. Sheldrick, Acta Crystallogr. Sect. A. Found. Crystallogr. 64 (2008) S112–S122.
[16] L.J. Farrugia, J. Appl. Crystallogr. 32 (1999) 837–838.
[17] C.F. Macrae, I.J. Bruno, J.A. Chisholm, P.R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P.A. Wood, J. Appl. Cryst. 41 (2008) 466–470.
[18] L.J. Farrugia, J. Appl. Crystallogr. 30 (1997) 565.
[19] P.V.D. Sluis, A.L. Spek, Acta Crystallogr. Sect A 46 (1990) 194–201.
[20] E.J. Gabe, Y. Lepage, L. Prasad, G.R. Weisman, Acta Crystallogr. Sect. B Struct. Sci. 38 (1982) 2752–2754.
[21] R.W. Alder, T.M.G. Carniero, R.W. Mowlam, A.G. Orpen, P.A. Petillo, D.J. Vachon, G.R. Weisman, J.M. White, J. Chem. Soc. Perkin Trans. 2 (1999) 589–599.
[22] (a) J. Kotek, P. Hermann, P. Vojtisek, J. Rohovec, I. Lukes, Collect. Czechoslov. Chem. Commun. 65 (2000) 243–266;
(b) T.J. Hubin, J.M. McCormick, N.W. Alcock, H.J. Clase, D.H. Busch, Inorg. Chem. 38 (1999) 4435–4446.
[23] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, R. Taylor, J. Chem. Soc. Perkin Trans. 2 (1987) S1–S19.
[24] (a) R.I. Haines, D.R. Hutchings, Molecules 8 (2003) 243–250;
(b) T.G. Roy, S.K.S. Hazari, B.K. Dey, H.A. Miah, F. Olbrich, D. Rehder, Inorg. Chem. 46 (2007) 5372–5380;
(c) K.Y. Choi, H.H. Lee, I.H. Suh, J.G. Kim, U.S. Shin, Inorg. Chim. Acta 321 (2001) 221–227;
(d) J.H. Choi, W. Clegg, R.W. Harrington, H.M. Yoon, Y.P. Hong, Acta Crystallogr. Sect. E Struct. Rep. Online 62 (2006) O644–O646;
(e) H.T. He, G. Yin, G. Hiler, D. Kitko, J.D. Carter, W.M. Scheper, V. Day, D.H. Busch, J. Coord. Chem. 61 (2008) 45–59.
[25] E. Arunan, G.R. Desiraju, R.A. Klein, J. Sadlej, S. Schneider, I. Alkorta, D.C. Clary, R.H. Crabtree, J.J. Dannenberg, P. Hobza, H.G. Kjaergaard, A.C. Legon, B. Mennucci, D.J. Nesbitt, Pure Appl. Chem. 83 (2011) 1637–1641.