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

A R T I C L E I N F O

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

A B S T R A C T

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

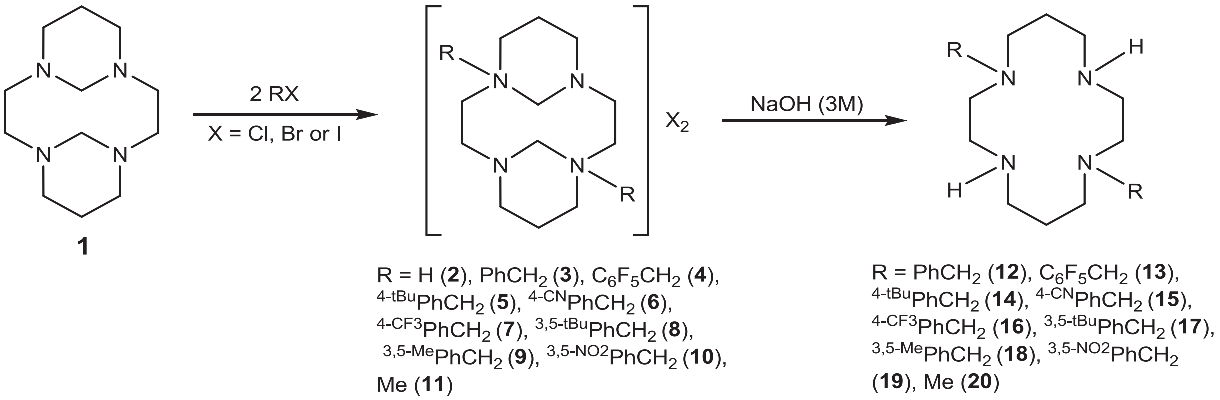
2.1. General considerations

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. ^1H 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, NCH_2N), 4.76 (d, $^2J_{H-H} = 13$ Hz, 2H, $PhCH_2N$), 4.59–4.45 (overlapping, 4H total, 2H, [C2]CH_2N and 2H, $PhCH_2N$), 3.67–3.59 (overlapping, 4H total, 2H, [C2]CH_2N and 2H, NCH_2N), 3.40 (m, 2H, [C3]CH_2N), 3.28–3.17 (overlapping, 4H total, 2×[C3]CH_2N), 2.98–2.84 (overlapping, 4H total, 2×[C2]CH_2N), 2.57–2.44 (overlapping, 4H total, 2H, [C3]CH_2N 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, NCH_2N), 4.79 (d, $^2J_{H-H} = 13$ Hz, 2H, $PhCH_2N$), 4.61–4.47 (overlapping, 4H total, 2H, [C2]CH_2N and 2H, $PhCH_2N$), 3.66–3.61 (overlapping, 4H total, 2H, [C2]CH_2N and 2H, NCH_2N), 3.42 (m, 2H, [C3]CH_2N), 3.29–3.18 (overlapping, 4H total, 2×[C3]CH_2N), 3.00–2.86 (overlapping, 4H total, 2×[C2]CH_2N), 2.60–2.43 (overlapping, 4H total, 2H, [C3]CH_2N and 2H, $CH_2CH_2CH_2$), 1.84 (m, 2H, $CH_2CH_2CH_2$), 1.22 (s, 18H, $C(CH_3)_2$). $^{13}C\{^1H\}$ 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 ($C(CH_3)_2$, 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, CF_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