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Novel 13-membered cyclic dioxatetraaza scaffolds – synthesis, solution and solid state characterization

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A series of three novel ligands with 1,4,8,11-tetraazacyclotridecine-2,10-dione skeleton, possessing relatively hindered amine fragment and variable substitution pattern at the aryl group in the amide moiety, was designed and obtained *via* an improved synthetic protocol. The macrocycles were analysed by NMR spectra in solution and by single crystal and powder XRD in solid state. The 13-membered ring conformation was discussed and compared with literature data.

Key words: 1,4,8,11-tetraazacyclotridecine-2,10-diones, NMR, single crystal XRD, powder XRD

INTRODUCTION

Macrocyclic polyfunctional molecules are of growing interest as they are widely applied as scaffolds in the combinatorial synthesis of artificial receptors for ions with medical and environmental potential [1–16]. Among the broad variety of synthetic macrocycles [17–26], polyaza ligands have received special attention due to their outstanding coordination abilities [27–34]. In particular, dioxatetraaza macrocycles possess unique properties due to their dual features between oligopeptides and saturated cyclic amines. The characteristics of the amide group and the hydrogen-bonding capability of both NH and C=O moieties [35] determine the amino acid like ligands' properties. The latter instigated the extraordinary research in supramolecular chemistry in last decades on the amide-based receptors for molecule and ion recognition [36–49].

The most widely studied dioxatetraaza macrocycles are built of *o*-phenylene diamine amide fragment and saturated amine unit. The usual protocol for their construction is based on subsequent acylation of *o*-phenylene diamine and reaction with bis-amine. Among the latter, unsubstituted ethylene and propylene α,ω-diamines are commonly used [42, 46, 49]. The corresponding 12- and 13-membered cyclic products are isolated in low to moderate yields and studied as ligands for metal complexes.

Herein, we report on the synthesis of three new 13-membered cyclic dioxatetraaza ligands, convenient scaffolds for synthetic protein surface receptors, *via* improved protocol and their characterization in solution and solid state.

EXPERIMENTAL

Synthesis

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography and R_f-values determination. The melting points were determined in capillary tubes on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system with heating rate 1 °C/min. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 25 °C; the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The assignment of the sig-

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nals was confirmed by applying 2D techniques. The spectra were recorded as 5×10^{-2} M solutions and were processed with Topspin 2.1 program.

Synthesis of N,N'-(1,2-phenylene)bis(2-chloroacetamides) ***2***

To a suspension of 1,2-phenylenediamine (5 mmol **1a**x2HCl, **1b**, or **1c**;) and K_2CO_3 (25 mmol for **2a**, 15 mmol for **2b** and **2c**) in dry CH_2Cl_2 (50 ml) chloroacetyl chloride (11 mmol) was added and the mixture was stirred at room temperature for 3 h. The products were partitioned between water and CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to dryness to give the crude product, which was pure enough (TLC, NMR) to be used in the next step without purification.

N,N'-(1,2-phenylene)bis(2-chloroacetamide) ***2a****:* m. p. 200.6-201.2 °C (lit. [50] 204 °C); R_f 0.53 (5% MeOH in DCM); ^{1}H NMR (DMSO-d_6) 4.284 (s, 4H, 2 x CH_2), 7.219 (AA'BB', 2H, C*H*-4,5), 7.500 (AA'BB', 2H, C*H*-3,6), 9.786 (bs, 2H, 2 x N*H*); ^{13}C 43.57 (*C*H$_2$), 125.68 (*C*H-3,6), 126.39 (*C*H-4,5), 130.59 (C_q-1,2), 165.93 (*C*=O); NOESY cross peaks 4.284/9.786, 7.219/7.500, 7.500/9.786; HSQC cross peaks 4.284/43.57, 7.219/126.39, 7.500/125.68.

N,N'-(4-Methyl-1,2-phenylene)bis(2-chloroacetamide) ***2b****:* m. p. 177.8-178.2 °C; R_f 0.55 (5% MeOH in DCM); ^{1}H NMR (DMSO-d_6) 2.285 (s, 3H, CH_3), 4.303 (s, 2H, CH_2), 4.309 (s, 2H, CH_2), 7.030 (dd, 2H, J 1.3, 8.2, C*H*-5), 7.358 (d, 2H, J 1.3, C*H*-3), 7.388 (d, 2H, J 8.2, C*H*-6), 9.625 (s, 1H, N*H*-1), 9.634 (s, 1H, N*H*-2); ^{13}C 20.62 (*C*H$_3$), 43.28 (*C*H$_2$), 43.29 (*C*H$_2$), 125.09 (*C*H-6), 125.34 (*C*H-3), 126.29 (*C*H-5), 127.59 (C_q-1), 130.14 (C_q-4), 135.11 (C_q-2), 165.15 (*C*=O), 165.17 (*C*=O); NOESY cross peaks 2.285/7.030, 2.285/7.358, 4.303, 4.309/9.625, 9.634, 7.030/7.388, 7.388/9.625, 9.634; HSQC cross peaks 2.285/20.62, 4.303, 4.309/43.28, 43.29, 7.030/126.29, 7.358/125.34, 7.388/125.09; HMBC cross peaks 2.285/125.34, 2.285/126.29, 2.285/135.11, 4.303/165.15, 165.17, 4.309/165.15, 165.17, 7.030/20.62, 7.030/125.34, 7.030/127.59, 7.358/20.62, 7.358/127.59, 7.388/130.14, 7.388/135.11, 9.625, 9.634/165.15, 165.17.

N,N'-(4-Nitro-1,2-phenylene)bis(2-chloroacetamide) ***2c****:* m. p. 145.2-145.6 °C (lit. [51] 142.5-143.5 °C); R_f 0.46 (5 % MeOH in DCM); ^{1}H NMR (DMSO-d_6) 4.381 (s, 2H, CH_2-2), 4.407 (s, 2H, CH_2-1), 7.887 (dd, 2H, J 2.7, 9.0, C*H*-5), 7.963 (d, 2H, J 9.0, C*H*-6), 8.430 (d, 2H, J 2.7, C*H*-3), 10.047 (s, 1H, N*H*-2), 10.067 (s, 1H, N*H*-1); ^{13}C 43.35 (*C*H$_2$-2), 43.43 (*C*H$_2$-1), 120.90 (*C*H-3), 123.67 (*C*H-5), 124.45 (*C*H-6), 129.73 (C_q-2), 136.53 (C_q-1), 143.58 (C_q-4), 165.63 (*C*=O-1), 165.78 (*C*=O-2); NOESY cross peaks 4.381/10.047, 4.407/10.067, 7.887/7.963, 7.963/10.067, 8.430/10.047; HSQC cross peaks 4.381/43.35, 4.407/43.43, 7.887/123.67, 7.963/124.45, 8.430/120.90; HMBC cross peaks 4.381/165.78, 4.407/165.63, 7.887/120.90, 7.887/136.53, 7.963/129.73, 7.963/143.58, 8.430/123.67, 8.430/136.53, 8.430/143.58 (weak), 10.047/120.90, 10.047/165.78, 10.067/124.45, 10.067/165.78.

Synthesis of 6,6-dimethyl-4,5,6,7,8,9-hexahydro-1H-benzo[e][1,4,7,10]tetraazacyclotridecine-2,10(3H,11H)-diones ***3***

To a solution of crude dichloride **2** (theor. 5 mmol) and Et_3N (10.7 mmol) in dry DMF (10 ml) 2,2-dimethyl-1,3-propanediamine (5 mmol) was added and the mixture was stirred at room temperature for 3–5 h. The reaction mixture was poured in water. The solid phase formed was filtered off, washed with water, and dried in air.

6,6-dimethyl-4,5,6,7,8,9-hexahydro-1H-benzo[e][1,4,7,10]tetraazacyclotridecine-2,10-dione ***3a****:* 64% overall yield; m. p. 283.6-283.9 °C (*i*-PrOH); R_f 0.36 (5% MeOH in DCM); ^{1}H NMR ($CDCl_3$) 0.960 (s, 6H, 2 x CH_3-6), 1.688 (bs, 2H, N*H*-4,8), 2.668 (bs, 4H, CH_2-5,7), 3.416 (bs, 4H, CH_2-3,9), 7.185 (AA'BB', 2H, C*H*-13,14), 7.861 (AA'BB', 2H, C*H*-12,15), 9.506 (bs, 2H, N*H*-1,11); ^{13}C 24.59 (2 x *C*H$_3$-6), 34.61 (C_q-6), 53.00 (*C*H$_2$-3,9), 56.74 (*C*H$_2$-5,7), 123.00 (*C*H-12,15), 125.32 (*C*H-13,14), 128.16 (C_q-11a,15a), 169.44 (C_q-2,10); NOESY cross peaks 0.960/1.688, 0.960/2.668, 0.960/9.506 (weak), 1.688/2.668 (weak), 1.688/3.416, 1.688/9.506 (exchange), 2.668/3.416, 2.668/9.506, 3.416/9.506, 7.185/7.861, 7.861/9.506; HSQC cross peaks 0.960/24.59, 2.668/56.74, 3.416/53.00, 7.185/ 125.32, 7.861/123.00; HMBC cross peaks 0.960/24.59, 0.960/34.61, 0.960/56.74, 7.185/123.00, 7.185/128.16, 7.861/125.32, 7.861/128.16, 9.506/123.00, 9.506/128.16 (weak).

6,6,13-trimethyl-4,5,6,7,8,9-hexahydro-1H-benzo[e][1,4,7,10]tetraazacyclotridecine-2,10-dione ***3b****:* 70% overall yield; m. p. 252.4-252.7 °C (EtOH); R_f 0.38 (5% MeOH in DCM); ^{1}H NMR ($CDCl_3$) 0.942 (s, 6H, 2 x CH_3-6), 1.672 (bs, 2H, N*H*-4,8), 2.332 (s, 3H, CH_3-13), 2.642 (bs, 4H, CH_2-5,7), 3.386 (bs, 4H, CH_2-3,9), 6.980 (dd, 1H, J. 1.3, 8.2, C*H*-14), 7.671 (d, 1H, J 1.3, C*H*-12), 7.701 (d, 1H, J. 8.2, C*H*-15), 9.388 (bs, 1H, N*H*-1), 9.444 (bs, 1H, N*H*-11); ^{13}C 21.38 (*C*H$_3$-13), 24.68 (2 x *C*H$_3$-6), 34.70 (C_q-6), 53.10, 53.12 (*C*H$_2$-3,9), 56.79, 56.84 (*C*H$_2$-5,7), 122.96 (*C*H-15), 123.43 (*C*H-12), 125.60 (C_q-11a), 126.08 (*C*H-14), 128.13 (C_q-15a), 135.36 (C_q-13), 169.53 (C_q-2,10); NOESY cross peaks 0.942/1.672, 0.942/2.642, 1.672/2.642 (weak), 1.672/9.388, 9.444 (exchange), 1.672/3.386, 2.332/6.980, 2.332/7.671, 2.642/3.386, 6.980/7.701, 7.671/9.444, 7.701/9.388; HSQC cross

peaks 0.942/24.68, 2.332/21.38, 2.642/56.79, 56.84, 3.386/53.10, 53.12, 6.980/126.08, 7.671/123.43, 7.701/122.96; HMBC cross peaks 0.942/24.68, 0.942/34.70, 0.942/56.79, 56.84, 2.332/123.43, 2.332/126.08, 2.332/135.36, 6.980/21.38, 6.980/123.43, 6.980/125.60, 7.671/126.08, 7.671/128.13, 7.701/125.60, 7.701/135.36, 9.388/122.96, 9.444/123.43.

6,6-dimethyl-13-nitro-4,5,6,7,8,9-hexahydro-1-H-benzo[e][1,4,7,10]tetraazacyclotridecine-2,10-dione ***3c****:* 61% overall yield; m. p. 284.1-284.3 °C (*i*-PrOH-acetone); R_f 0.40 (5% MeOH in DCM); ^{1}H NMR (DMSO-d_6) 0.879 (s, 6H, 2 x CH_3-6), 2.549 (bs, 2H, CH_2-5,7), 2.585 (bs, 2H, CH_2-5,7), 3.269 (bs, 4H, CH_2-3,9), 3.341 (bs, 2H, N*H*-4,8), 6.530 (bs, >2H, N*H*-1,11; mixed with H_2O in the solvent), 8.053 (d, 1H, J. 8.9, C*H*-15), 8.086 (dd, 1H, J. 2.5, 8.9, C*H*-14), 8.532 (d, 1H, J 2.5, C*H*-12); ^{13}C 24.92 (2 x *C*H_3-6), 34.54 (C_q-6), 52.68, 52.77 (*C*H_2-3,9), 56.31, 56.39 (*C*H_2-5,7), 117.82 (*C*H-12), 120.31 (*C*H-14), 121.58 (*C*H-15), 128.85 (C_q-11a), 135.87 (C_q-15a), 142.77 (C_q-13), 170.50 (C_q-2,10), 170.63 (C_q-2,10); NOESY cross peaks 0.879/2.549, 0.879/2.585, 0.879/3.341 (weak), 2.549/3.269, 2.549/3.341, 2.585/3.269, 2.585/3.341, 3.341/6.530 (exchange), 8.053/8.086; HSQC cross peaks 0.879/24.92, 2.549/56.31, 2.585/56.39, 3.269/52.68, 52.77, 8.053/121.58, 8.086/120.31, 8.532/117.82; HMBC cross peaks 0.879/24.92, 0.879/34.54, 0.879/56.39, 2.549/24.92, 2.549/34.54, 2.585/24.92, 2.585/34.54, 3.269/56.39, 3.269/170.50, 3.269/170.63, 3.341/56.39, 8.053/128.85, 8.053/142.77, 8.086/135.87, 8.532/120.31, 8.532/128.85, 8.532/135.87, 8.532/ 142.77.

Crystallography

The crystals of **3a** and **3b** were mounted of on a glass capillary and all geometric and intensity data were taken from these crystals. Crystallographic measurements were taken on an Agilent SupernovaDual diffractometer equipped with an Atlas CCD detector and on an Enraf Nonius CAD4 diffractometer using micro-focus Mo Kα radiation (λ = 0.71073 Å) at room temperature. The determinations of the unit cell parameters, data collection and reduction were performed with Crysalispro software [52]. The structures were solved by direct methods and refined by the full-matrix least-squares method on F^2 with ShelxS and ShelxL 2013 programs [53]. All non-hydrogen atoms, including solvent molecules, were located successfully from Fourier maps and were refined anisotropically. Hydrogens adjoining N atoms were positioned from difference Fourier map while H atoms on C atoms were generated geometrically. The methyl moiety of **3b** shows a disorder over two positions and the refinement model revealed that the major component is 65%. Most important crystallographic and refinement indicators are listed in Table 1. Complete crystallographic data for the structure reported in this paper, **3a** and **3b**, have been deposited in the CIF format with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 1037064 and 1037065, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (44) 1223336-033; e-mail: deposit@ccdc.cam.ac.uk).

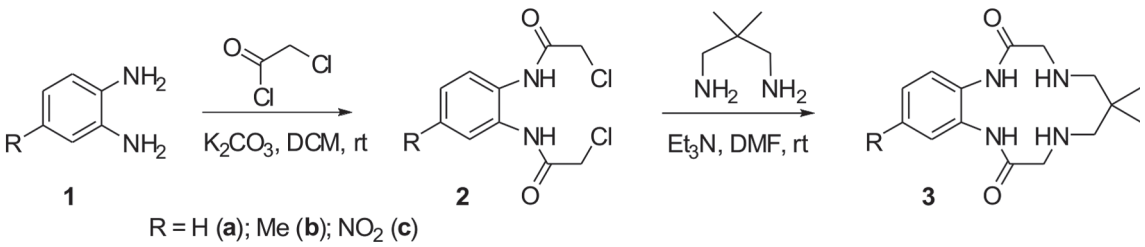
Powder X-ray diffraction data were collected at room temperature on Bruker D2 Phaser diffractometer (Ni-filtered Cu Kα radiation, 30 kV, 10 mA). Data collection was performed in the range 5 to 50° 2θ, step size of 0.02° 2θ with counting time of 10 s per step.

RESULTS AND DISCUSSION

The novel 13-membered benzodioxatetraaza cyclic compounds, 1,4,8,11-tetraazacyclotridecine-2,10-diones **3**, were designed by following two main concepts. First, to replace the flexible propylenediamine unit of an existing scaffold [42, 46] with its 2,2-dimethyl analogue in order to hinder partially the amine fragment, which is expected to have an important impact on our further studies. Second, to obtain the symmetric product **3a** and non-symmetric compounds, possessing either an electron donating (Me, **3b**) or an electron withdrawing (NO_2, **3c**) substituent at position 13, which will enable to examine the influence of the latter on the amide proton properties.

The target molecules were obtained *via* improved two-step protocol from the cheap commercial sources, *o*-phenylenediamines (**1**), as shown on Scheme 1.

The intermediates **2** were synthesised *via* a standard protocol and were isolated in high to quantitative yields. The compounds were pure enough, as indicated by TLC and NMR, and were submitted to the second step without purification. The conversion of **2** into the target heterocyclic products **3** was performed *via* a modified literature procedure for analogues molecules [42]; the reaction was carried out in DMF instead of acetonitrile, due to the limited solubility of the dichlorides **2**, in the presence of triethylamine as a base instead of heterogeneous potassium carbonate. The macrocyclic compounds **3** were isolated in good yields, 61–70% overall for two steps *vs* 52% for the second step [42], after short reaction times, 3–5 h, at room temperature *vs* 24 h at 40 °C, and simple work-up, water treatment and filtration. Products structures were assigned by 1D and 2D NMR experiments and were confirmed by X-ray diffraction.



Scheme 1. Synthesis of the novel 1,4,8,11-tetraazacyclotridecine-2,10-dione scaffolds **3**.

NMR spectra showed that the symmetrical molecule **3a** gives sharp and well defined signals for aromatic and methyl group protons and broad signals for methylene groups (Fig. 1). This pattern is valid for **3b**, while all signals are sharp in the spectra of **3c**. From the other side, the symmetrical signals in the non-symmetrical analogues **3b** and **3c**, CH-12,15, CH_2-3,9, CH_2-5,7, NH-1,11, and NH-4,8, are distinguished each other; the effect being more significant in nitro group containing compound **3c**.

Compound **3a** was recrystallized from *iso*-propanol and was analyzed by single crystal diffraction. It crystalized in monoclinic *C*2/c space group (Table 1). Only half of the molecule is observed in the asymmetric unit (ASU) of **3a**. The whole molecule is obtained (e.g the other half of the molecule)

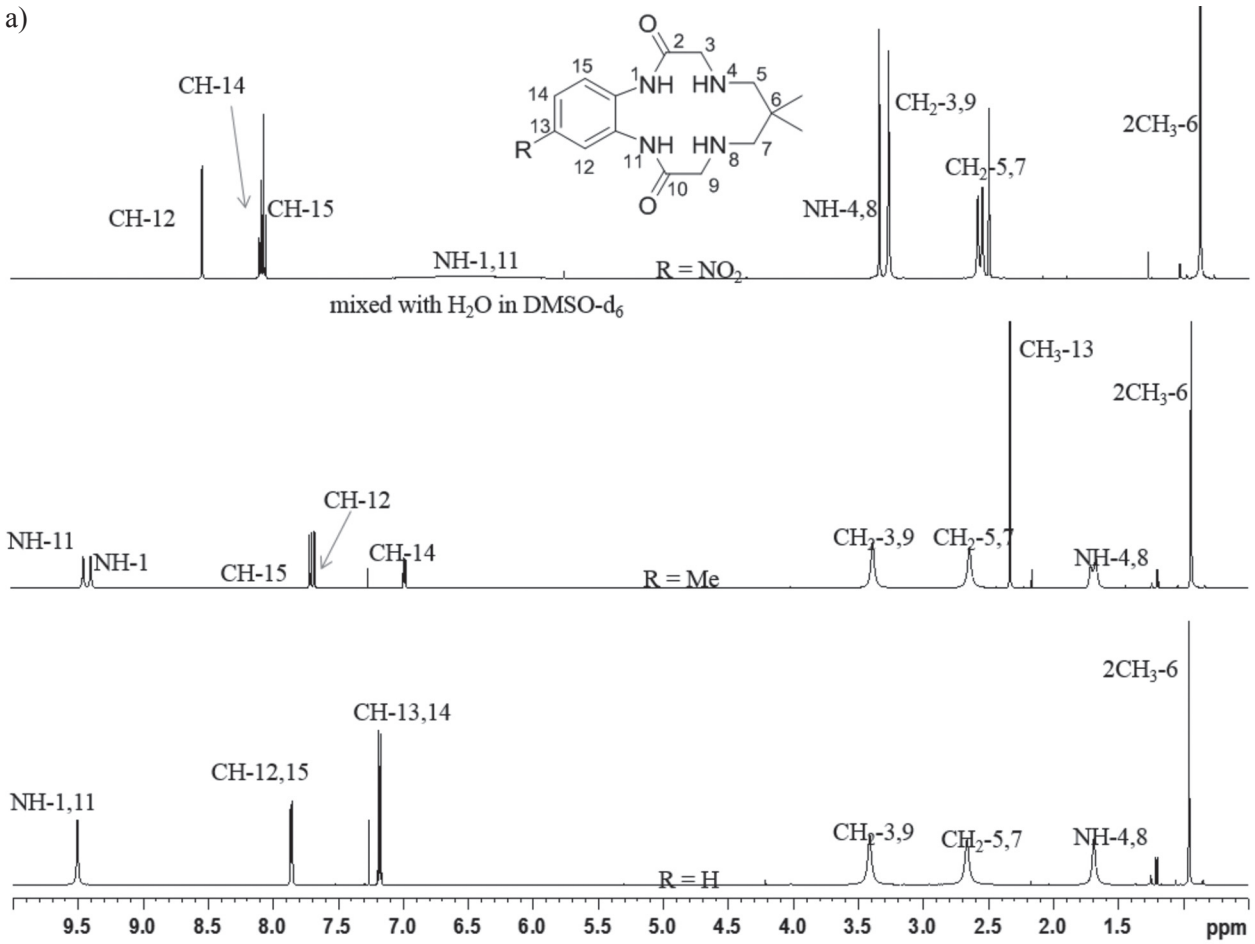


Fig. 1. ^{1}H NMR spectra of **3a** in $CDCl_3$ (down), **3b** in $CDCl_3$ (middle) and **3c** in DMSO-d_6 (up): a) full spectra; b) aromatic protons area

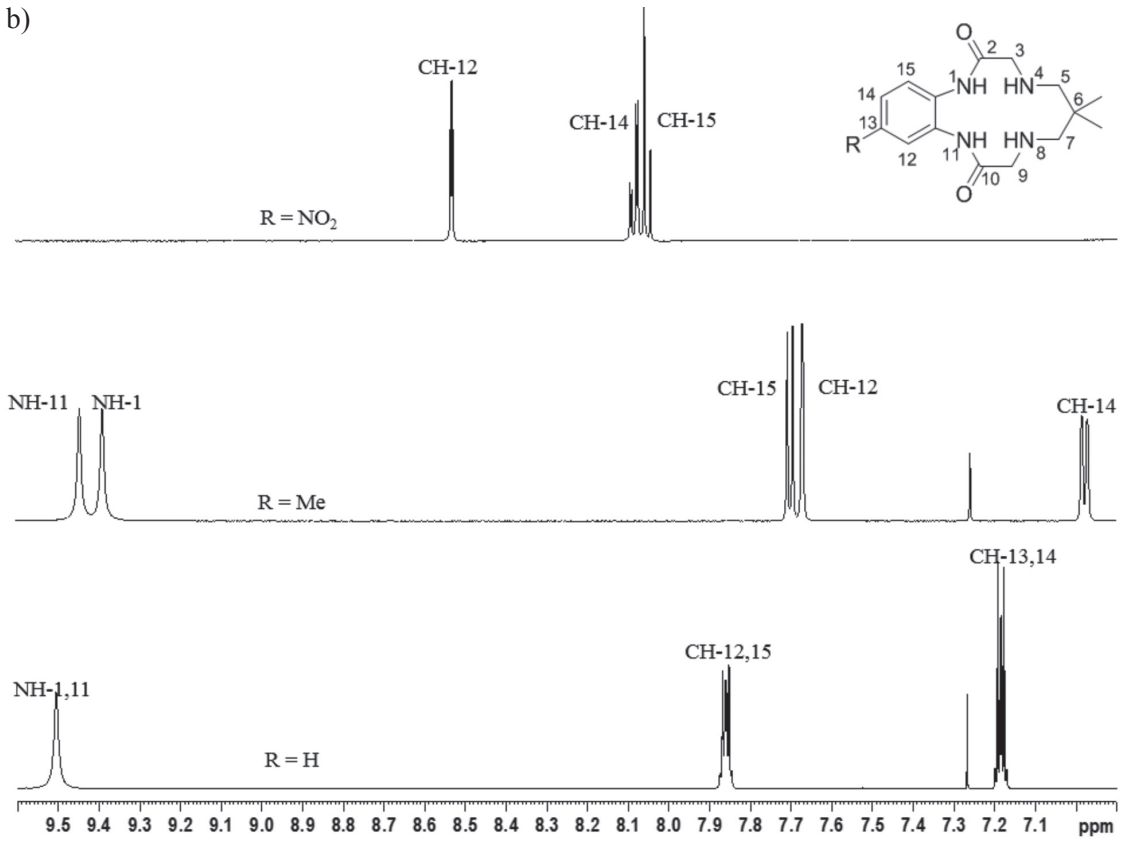


Fig. 1. (continued)

through a 2-fold rotation axis (with direction [0, 1, 0] at 0, y, 1/4) (Fig. 2a). Quality single crystals of compound **3b**, suitable for data collection, were obtained by the vapor diffusion technique using acetonitrile and diethyl ether. Compound **3b** crystallizes in the triclinic space group $P\bar{1}$, with one molecule per asymmetric unit (for additional details see Table 1 and Fig. 2b). The majority of bond lengths and angles are comparable for **3a** and **3b** (Table 2 and Fig. 3).

The 13 membered ring, [1,4,7,10]tetraazacyclotridecine-2,10-dione, common for **3a-c** is decorated

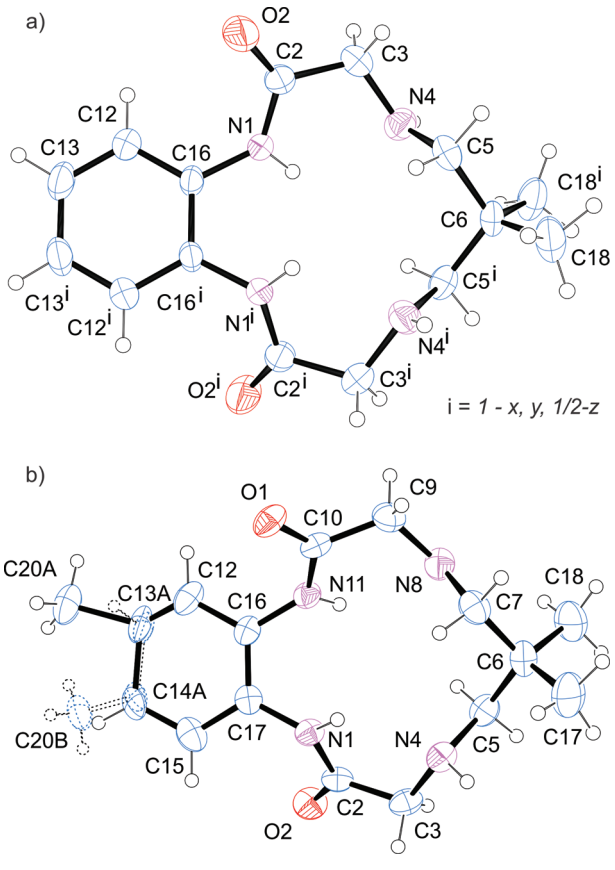


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Fig. 2. ORTEP (ORTEP-3, v. 2.02) drawing of **3a** (a) and **3b** (b) with the atomic numbering scheme (ellipsoids are at 50% probability), the hydrogen atoms areshown as small sphere of arbitrary radii (Color figure available online). The minor disorder component (33%) in **3b** is shown as dotted lines (atoms C20B, C13B, C14B). The ASU of **3a** contains only half of the molecule while the complete molecule is generated through a 2-fold rotation axis (symmetry operation: *1-x, y, 1/2-z*).

Table 1. Most important crystallographic and refinement details for compounds **3a** and **3b**

Compound reference	**3a**	**3b**
Chemical formula	$C_{15}H_{22}N_4O_2$	$C_{16}H_{24}N_4O_2$
Formula Mass	290.36	304.39
Crystal system	Monoclinic	Triclinic
a/Å	11.584(6)	8.7532(13)
b/Å	12.475(7)	8.960(2)
c/Å	10.089(6)	11.210(7)
α/°	90	101.80(5)
β/°	93.20(3)	91.76(5)
γ/°	90	108.567(19)
Unit cell volume/Å^3	1455.6(14)	811.5(6)
Temperature/K	290(2)	290(2)
Space group	*C*2/*c*	$P\bar{1}$
No. of formula units per unit cell, *Z*	4	2
Radiation type	MoKα	MoKα
Absorption coefficient, μ/mm^{-1}	0.091	0.084
No. of reflections measured	2718	9358
No. of independent reflections	1435	4502
R_{int}	0.2218	0.0282
Final R_1 values ($I > 2\sigma(I)$)	0.093	0.0666
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.2098	0.2067
Final R_1 values (all data)	0.2321	0.0881
Final $wR(F^2)$ values (all data)	0.2701	0.2261
Goodness of fit on F^2	0.984	0.949
CCDC number	1037064	1037065

with an aromatic moiety (benzene, toluene and nitrobenzene) and two methyl groups. The aliphatic diamine and aromatic diamide fragments are opposite to each other. The aromatic ring in **3b** is nearly planar [with *rmsd* of 0.00217(2)] while in **3a** it is obtained from three atoms which always lie on a plane. The angle between the mean planes of the aromatic ring and the 13-membered ring system is 5.6(1.1) and 11.7(3)° in **3a** and **3b** respectively.

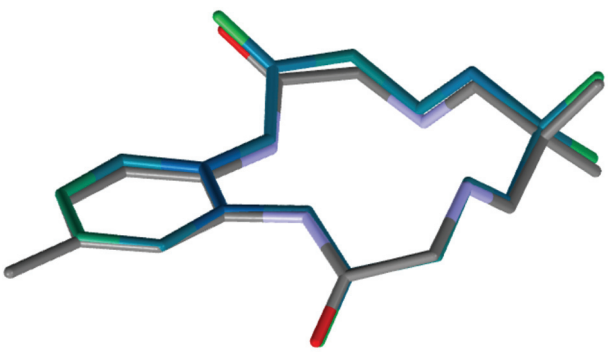

Fig. 3. Relative orientation of the 13-cycle fragment in **3a** *vs* **3b**.

In **3b**, the Me substituent at position 13 produces a disorder over two positions with major component occupancy of 65% (C20A-C13A-C14A) and 35% (almost one third) for the minor component (C20B-C13B-C14B). The superposition of the molecules **3a** and **3b** shows that the molecular features (bond length and angles) are very similar (Table 2). In the CSD the data base (v.5.35) forty seven structures with the 13-membered cyclic fragment are present (AHUCAI [55], BAYZIL [56], BAYZOR [56], DIGFUW [57], FENMOA [58], FEZMEE [57], FUNPEJ [59], FUNPIN [59], ICUDUG [60], ICUFAO [60], IXISUE [61], JEDZIB [62], JETBUF [63], KAJBIH [64], KAJBON [64], KAPPUO [65], KAPQAV [65], KELXUW [66], KELYAD [66], KELYEH [66], KUXJAP [67], KUXJIX [67], LUGSOW [68], LUGSUC [68], LUGTAJ [68], MOCMAT [69], MTAZNI [70], PUJGIK [71], RASSAF [72], SICVAC [68], UYOVUA [73], UYOWAH [73], VASSOY [74], VASSUE [74], VASTAL [74], VIXTOM [75], VIXTUS [75], VOKFAC [76], VOKFEG [76], WIMVEU [77], XATXIB [78], XATXOH [78], XOWWUB [79], YUTHAW [80], YUTHEA [80], ZUFFIP [81]). From the 47 structures, only in three structures

Table 2. Selected bond lengths, angles and torsions

Compound **3a**		Compound **3b**	
Bond length			
C13—C12	1.365 (8)	C12—C17	1.395 (3)
C13—C13^{i}	1.387 (13)	C12—C13B	1.30 (3)
C12—C16	1.380 (8)	C12—C13A	1.430 (12)
C16—C16^{i}	1.394 (11)	C17—C16	1.385 (3)
C16—N1	1.412 (7)	C17—N11	1.415 (3)
C2—O2	1.201 (7)	C16—C15	1.390 (3)
C2—N1	1.335 (7)	C16—N1	1.418 (3)
C2—C3	1.506 (9)	C10—O2	1.220 (2)
C3—N4	1.462 (8)	C10—N11	1.347 (3)
C5—N4	1.452 (7)	C10—C9	1.518 (3)
C5—C6	1.516 (7)	C9—N8	1.464 (3)
C6—C17	1.508 (8)	C7—N8	1.465 (3)
C6—C5^{i}	1.516 (7)	C2—O1	1.233 (3)
N1—H1	0.8599	C2—N1	1.347 (3)
Bond angle			
C12—C13—C13^{i}	120.1 (4)	C16—C17—C12	119.2 (2)
C13—C12—C16	120.4 (6)	C16—C17—N11	118.96 (18)
C12—C16—C16^{i}	119.5 (4)	C12—C17—N11	121.8 (2)
C12—C16—N1	122.8 (5)	C17—C16—C15	119.8 (2)
C16i—C16—N1	117.6 (3)	C17—C16—N1	118.24 (18)
O2—C2—N1	126.0 (6)	C15—C16—N1	121.9 (2)
O2—C2—C3	120.8 (6)	O2—C10—N11	124.5 (2)
N1—C2—C3	113.1 (5)	O2—C10—C9	120.65 (19)
N4—C3—C2	113.9 (5)	N8—C9—C10	113.79 (18)
N4—C5—C6	114.4 (4)	N8—C7—C6	113.48 (19)
C17—C6—C17^{i}	108.3 (7)	C7—C6—C5	111.64 (18)
C17—C6—C5i	110.5 (4)	C7—C6—C18	107.9 (2)
C2—N1—H1	116.4	C5—C6—C18	110.7 (2)
C16—N1—H1	117	C7—C6—C19	110.1 (2)
C5—N4—C3	113.7 (5)	N4—C5—C6	114.24 (18)
C5—N4—H4	122.8	N4—C3—C2	114.62 (17)
C2—N1—H1	116.4	O1—C2—N1	124.0 (2)
C16—N1—H1	117	O1—C2—C3	121.45 (19)
Torsion angle			
C13^{i}—C13—C12—C16	−0.5 (12)	C12—C17—C16—C15	0.8 (3)
C13—C12—C16—C16^{i}	−0.2 (11)	N11—C17—C16—C15	−177.93 (18)
C13—C12—C16—N1	175.4 (6)	C12—C17—C16—N1	−178.60 (18)
O2—C2—C3—N4	163.8 (6)	N11—C17—C16—N1	2.7 (3)
N1—C2—C3—N4	−17.7 (8)	O2—C10—C9—N8	159.8 (2)
N4—C5—C6—C17	172.2 (5)	N11—C10—C9—N8	−21.8 (3)
N4—C5—C6—C17^{i}	53.8 (7)	N8—C7—C6—C5	−67.2 (3)
N4—C5—C6—C5	−66.3 (4)	N8—C7—C6—C18	171.0 (2)
O2—C2—N1—C16	−1.7 (10)	N8—C7—C6—C19	52.1 (3)
C3—C2—N1—C16	−180.0 (5)	C7—C6—C5—N4	−65.6 (3)
C12—C16—N1—C2	42.2 (9)	C18—C6—C5—N4	54.6 (3)
C16^{i}—C16—N1—C2	−142.1 (7)	C19—C6—C5—N4	173.5 (2)
C6—C5—N4—C3	−180.0 (5)	N4—C3—C2—O1	165.35 (19)
C2—C3—N4—C5	−93.0 (6)	N4—C3—C2—N1	−17.2 (3)

Symmetry code: (i)*1−x*, *y*, *−z*+1/2.

(KUXJAP, KUXJIX and RASSAF) no metal ion is trapped by the 13-membred ring. Nevertheless the structural variations of the dioxatetraaza scaffolds are conserved and the changes are not significant as one can see from figure Fig. 4.

Thus, one can expect that the metal coordination ability of the cycle will not be significantly affected by the various substituents. On the other hand, specific interactions and/or properties can be achieved by the selection of the 13-cycle "opposite" and

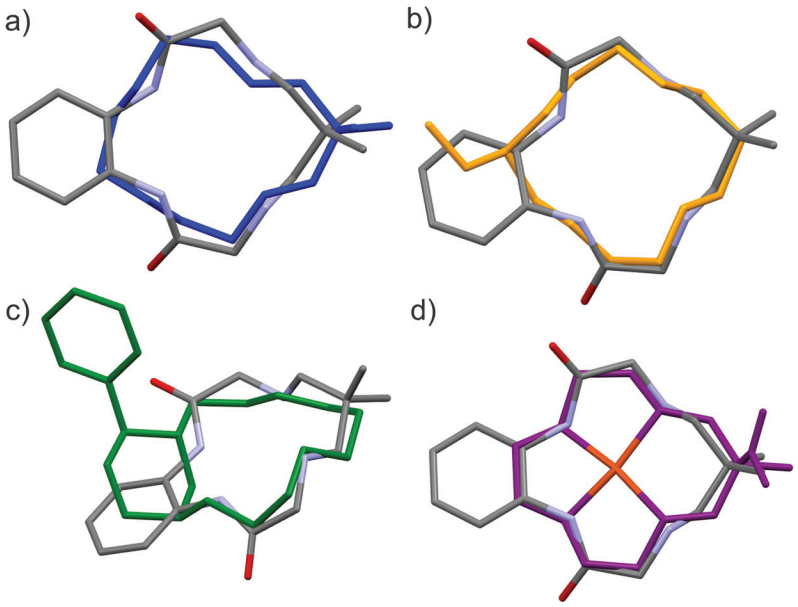

Fig. 4. Fig. XRD3. Relative orientation of the 13-cycle fragment in **3a** vs RASSAF (a), **3a** vs KUXJAP (b), **3a** vs KUXJIH (c) and **3a** vs FUNPEJ (d).

"side" substituents. Undeniably, the obtained scaffolds are very promising building blocks allowing various functionalizations.

The crystal packing of **3a** and **3b** showed that adjacent molecules are alternately oriented; the amide area of one molecule is on the side of the amine fragments of the neighboring molecules.

Thus they are connected by N—H…O=C hydrogen bonds producing identical $R_2^2(14)$ hydrogen bonding topology (Table 3). One should note that amine nitrogen atoms (N4 and N8) are not participating in intermolecular hydrogen bonding interactions. Interestingly the molecular arrangement produces a relatively short distances between the carbonyl atom from different molecules that are somewhat close to the limit distances e.g. O2…O2 3.235 and O1…O1 of 3.511 Å in **3b** and 3.991 Å for O1…O1 in **3a**. Contrary, a similar 12-membered dioxatetraaza compound [42] has shown packing of identically oriented molecules (Fig. 5) with both intra and intermolecular H-bonding. This substantial difference is most probably due to the steric hindrance of the CMe_2 fragment of **3**.

The NOESY experiments showed tree unexpected features: weak interaction between CH_3 and NH-1,11, which seemed rather distant each other, and weak interactions between NH-1,11 and CH-12,15 and CH_2-3,9, which were expected to be stronger. Moreover, this pattern, which is illustrated on Fig. 6 for **3a**, was valid for all compounds. So, we decided to compare NOESY interactions with crystal structure data (Fig. 7) and found that the distances in the single crystal structure of **3a**, CH_3… NH-1,11 of 4.234 Å, CH-12,15… NH-1,11 of 3.376 Å, and CH_2-3,9…NH-1,11 of 2.907 Å, are in full agreement with the observed cross peaks in

Table 3. Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Compound **3a**				
N1—H1···N4	0.86	2.19	2.655 (7)	114
N1—H1···O2^{i}	0.86	2.43	3.153 (7)	142
Symmetry codes: (i) *x*, −*y*, *z*+1/2.				
Compound **3b**				
N11—H11···N8	0.83	2.32	2.721 (3)	110
N11—H11···O1^{i}	0.83	2.37	3.089 (3)	145
N1—H1···N4	0.87	2.17	2.709 (3)	120
N1—H1···O2^{ii}	0.87	2.42	3.046 (2)	130
Symmetry codes: (i) −*x*+2, −*y*+1, −*z*; (ii) −*x*+1, −*y*, −*z*.				

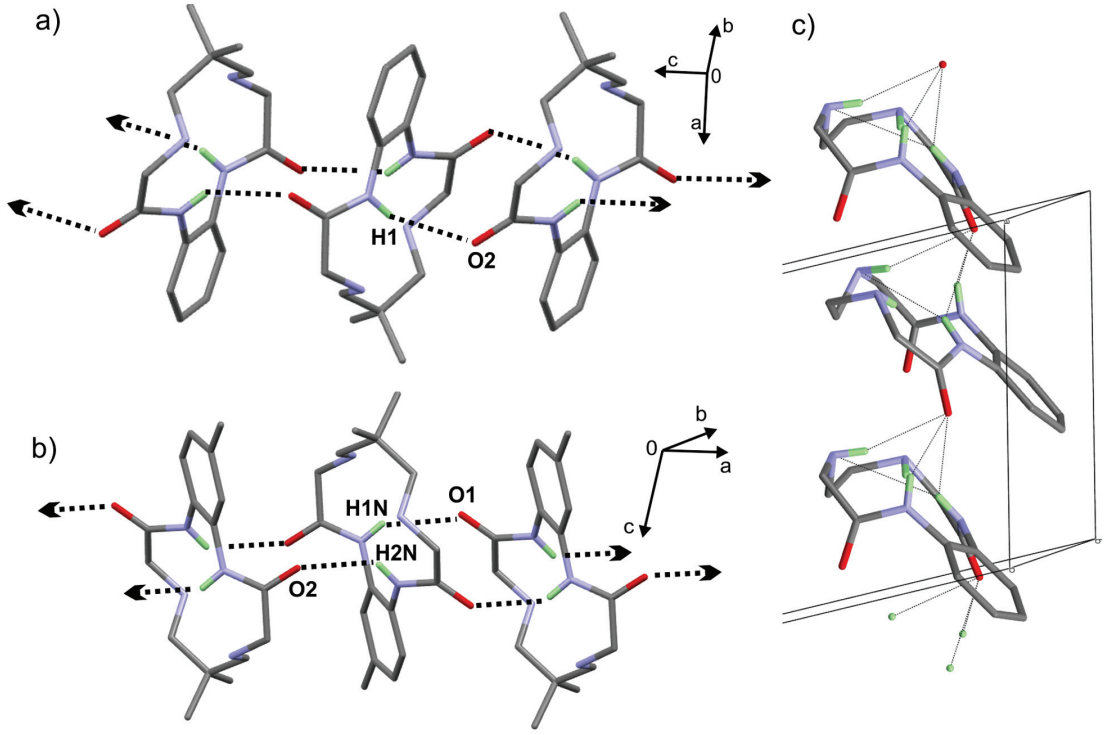

Fig. 5. Relative orientation of the molecules (amide area of one molecule is on the side of the amine fragments) and hydrogen bonding interactions in a) **3a**, b) **3b**and**c)** ref. 43.

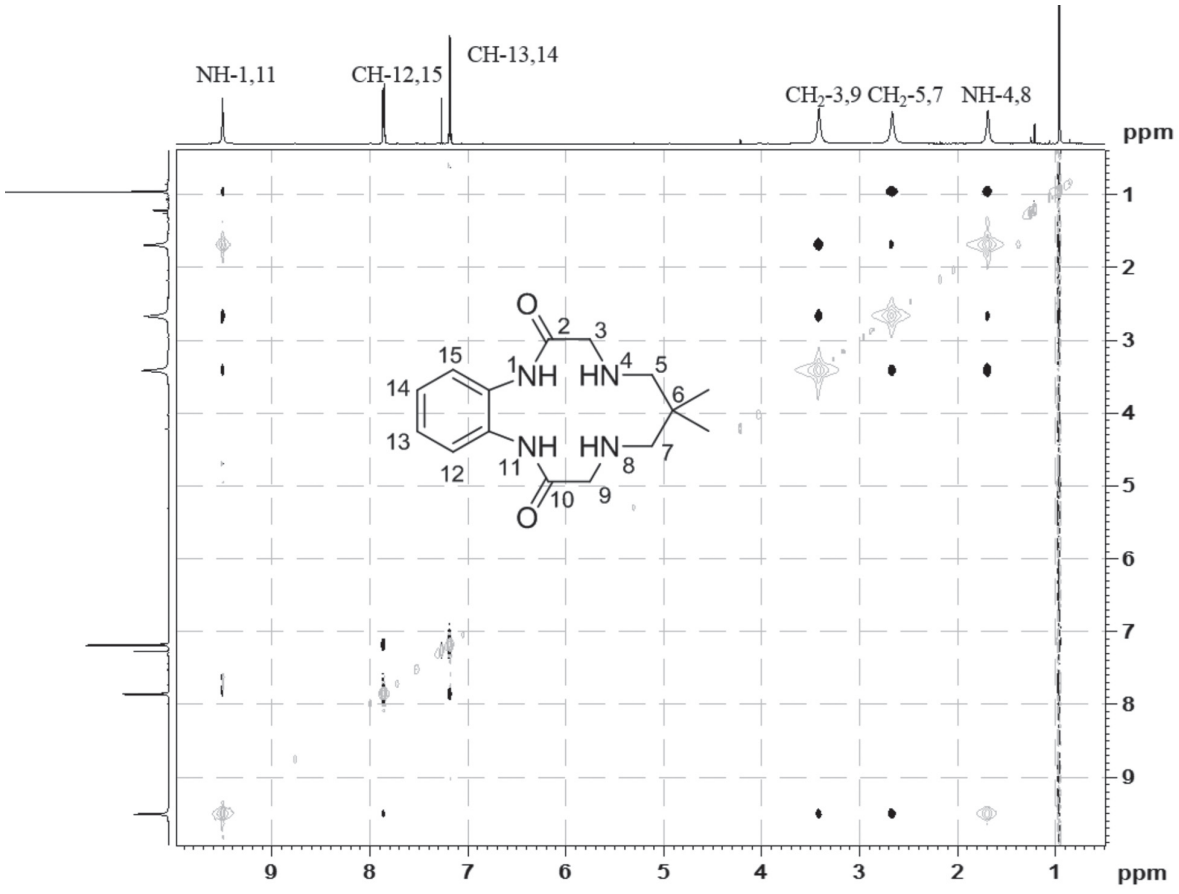

Fig. 6. ^{1}H-^{1}H NOESY spectrum of **3a** in $CDCl_3$.

NOESY experiment. Similarly, the unsymmetrical ligand **3b** showed CH_3…NH-1of 4.280 Å, CH_3… NH-11 of 4.213 Å, CH-12… NH-11 of 3.269 Å, CH-15… NH-1of 3.308 Å, CH_2-3…NH-1of 2.946 Å, and CH_2-9…NH-11 of 2.902 Å distances in the crystal phase. These results indicate that the ligands possess similar conformations in solution and in solid state.

As well as in NMR spectra the powder X-ray diffraction data of the three new compounds (Fig. 8) show that no parasite phases are present and that they crystallize with different unit cell parameters. In addition one can speculate that the crystal packing of **3b** and **3c** is comparable. While suitable single crystals were obtained for **3a** and **3b**, large crystals could not be grown for **3c**. Thus indexing, structure solution and refinement were attempted from powder diffraction data.

CONCLUSIONS

Three new ligands with 1,4,8,11-tetraazacyclotridecine-2,10-dione skeleton, a symmetric product **3a** and non-symmetric compounds possessing either an electron donating (Me, **3b**) or an electron withdrawing (NO_2, **3c**) substituent at position 13, were obtained *via* an improved two-steps protocol in good overall yields, 61–70%. The products were fully characterized by 1D and 2D NMR spectra and

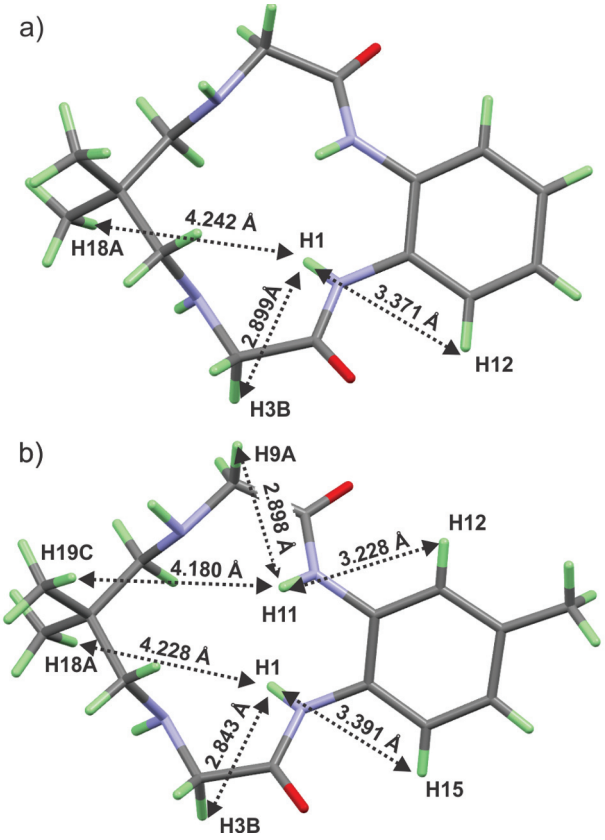

Fig. 7. Weak intramolecular interaction observed in NOESY experiments and the distances for molecules of (a) **3a** and (b) **3b** from X-ray.

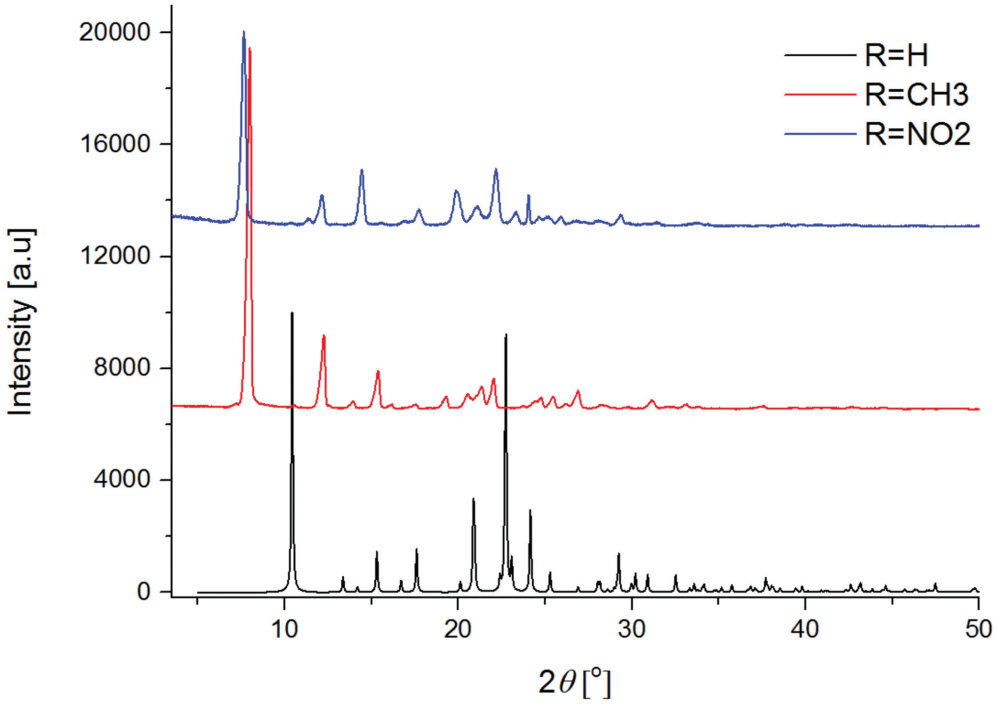

Fig. 8. Powder XRD of **3a** (black), **3b** (red) and **3c** (blue).

single crystal and powder X-ray diffraction. The crystal packing of **3a** and **3b** showed that adjacent molecules are alternately oriented; the amide area of one molecule is on the side of the amine fragments of the neighboring molecules. A juxtaposition with literature data indicated that the metal coordination ability of the cycle is not significantly affected by the substitution pattern in aryl unit. From the other side, specific interactions and/or properties can be achieved by the selection of the 13-cycle "opposite" and "side" substituents. A comparison between NOESY interactions and distances in crystal phases was performed and was found that the ligands possess similar conformations in solution and in solid state.

The obtained products **3** offer unlimited possibilities for derivatization. The preparation of a series of compounds, possessing variable spacers and type of substituents at N-4,8, and investigation of their efficiency as protein surface receptors is in progress.

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REFERENCES

1. Co-ordination Chemistry of Macrocyclic Compounds, G. A. Melson (Ed.), Plenum, New York, 1979.
2. J.-M. Lehn, Supramolecular Chemistry, VCH, Weinheim, 1995.
3. Supramolecular Chemistry of Anions, E. Bianchi, K. Bowman-James, E. García-España (Eds.), Wiley-VCH, New York, 1997.
4. J. P. Desvergne, A. W. Czarnik, Chemosensors for Ion and Molecule Recognition; NATO Asi Series, Series C, Kluwer Academic Publishers, London, 1997.
5. F. P. Schmitdchen, M. Berger, *Chem. Rev.,* **97**, 1609 (1997).
6. K. P. Wainwright, *Coord. Chem. Rev.*, **166**, 35 (1997).
7. P. A. Gale, *Coord. Chem. Rev*., **199**,181 (2000).
8. P. D. Beer, P. A. Gale, *Angew. Chem., Int. Ed.*, **40**, 486 (2001).
9. P. A. Gale, *Coord. Chem. Rev.*, **213**, 79 (2001).
10. R. Martínez-Máñez, F. Sancenón, *Chem. Rev.*, **103**, 4419 (2003).
11. C. Suksai, T. Tuntulani, *Chem. Soc. Rev*., **32**, 192 (2003).
12. Anion Receptor Chemistry, J. F. Stoddart (Ed.), RSC Publishing, 2006.
13. T. Gunnlaugsson, M. Glynn, G. M. Tocci, P. E. Kruger, F. M. Pfeffer, *Coord. Chem. Rev*., **250**, 3094 (2006).
14. J. W. Steed, J. L. Atwood, Supramolecular Chemistry, Second Edition, John Wiley & Sons, Ltd, Chichester, UK, 2009.
15. P. J. Cragg, Supramolecular Chemistry, From Biological Inspiration to Biomedical Applications, Springer Science+Business Media B.V., 2010.
16. Applications of Supramolecular Chemistry, H.-J. Schneider (Ed.), CRC Press, Boca Raton, 2012.
17. V. Alexander, *Chem. Rev.*, **95**, 273 (1995).
18. Macrocycle Synthesis, A Practical Approach, D. Parker (Ed.), Oxford University Press, 1996.
19. J. A. Semlyen, *Large Ring Molecules*; John Wiley & Sons, Chichester, 1996.
20. Z. R. Laughrey, B. C. Gibb, *Top. Curr. Chem.*, **249**, 67 (2005).
21. Modern Supramolecular Chemistry: Strategies for Macrocycle Synthesis, F. Diederich, P. J. Stang, R. R. Tykwinski (Eds.), Wiley-VCH Verlag GmbH & Co. KGaA, 2008.
22. N. K. Terrett, *Drug Discovery Today: Technologies*, **7**, e97 (2010).
23. F. Davis, S. Higson, Macrocycles, John Wiley & Sons, Ltd., 2011.
24. J. C. Collins, K. James, *Med. Chem. Commun.*, **3**, 1489 (2012).
25. X. Yu, D. Sun, *Molecules*, **18**, 6230 (2013).
26. L. Xu, Y. Li, Y. Li, *Asian J. Org. Chem.*, **3**, 582 (2014).
27. J. S. Bradshaw, K. E. Krakowiak, R. M. Izatt, Aza-crown Macrocycles, The Chemistry of Heterocyclic Compounds Series, Volume 51, E. C. Taylor, A. Weissberger (Eds.), John Wiley&Sons, Inc., 1993.
28. A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.*, **97**, 1515 (1997).
29. L. Cronin, *Annu. Rep. Prog. Chem., Sect. A*, **101**, 319 (2005).
30. K. Bowman-James, Macrocyclic Ligands. Encyclopedia of Inorganic and Bioinorganic Chemistry, John Wiley & Sons, Ltd., 2006.
31. A. Chaudhary, R.V. Singh, *Rev. Inorg. Chem.*, **28**, 35 (2008).
32. T.-B. Lu, in: Macrocyclic Chemistry: New Research Developments, D. W. Fitzpatrick, H. J. Ulrich (Eds.), Nova Science Publishers, Inc., 2009, Chapter 15.
33. K. Bowman-James, Macrocyclic Ligands. Encyclopedia of Inorganic and Bioinorganic Chemistry, John Wiley & Sons, Ltd., 2006.
34. Rajni, L. Singh, *Int. J. Adv. Eng. Appl.*, **6**, 74 (2013).
35. L. Pauling, The Nature of the Chemical Bond, 3rd ed., Cornell University Press, New York, 1960.
36. Molecular Recognition: Receptors for Molecular Guests, F. Vögtle (Ed.), Comprehensive Supramolecular Chemistry, Vol. 2, Pergamon, New York, 1996.
37. L. Fabbrizzi, M. Licchelli, G. Rabaioli, A. Taglietti, *Coord. Chem. Rev.*, **205**, 85 (2000).
38. M. B. Inoue, L.Machi, I. C. Muñoz, S. Rojas-Rivas, M. Inoue, Q. Fernando, *Inorg. Chim. Acta*, **324**, 73 (2001).
39. G. Cooke, V. M. Rotello, *Chem. Soc. Rev.*, **31**, 275 (2002).
40. R. Martinez-Manez, F. Sancenon, *Chem. Rev.*, **103**, 4419 (2003).
41. J. L. Sessler, P. A. Gale, W. S. Cho, Anion Receptor Chemistry, J. F. Stoddart (Ed.), Royal Society of Chemistry, Cambridge, 2006.

42. P. Antunes, R. Delgado, M. G. B. Drew, V. Félix, H. Maecke, *Inorg. Chem.*, **46**, 3144 (2007).
43. S. Carvalho, R. Delgado, M. G. B. Drew, V. Calisto, V. Félix, *Tetrahedron*, **64**, 5392 (2008).
44. H. M. Betts, P. J. Barnard, S. R. Bayly, J. R. Dilworth, A. D. Gee, J. P. Holland, *Angew. Chem., Int. Ed.*, **47**, 8416 (2008).
45. R. E. Navarro, D. Aguilera-Márquez, C. Virués, M. Inoue, *Supramol.Chem.*, **20**, 737 (2008).
46. P. J. Barnard, J. P. Holland, S. R. Bayly, T. J. Wadas, C. J. Anderson, J. R. Dilworth, *Inorg. Chem.*, **48**, 7117 (2009).
47. S. Kumar, S. Vaidya, M. Pissas, Y. Sanakis, R. Gupta, *Eur. J. Inorg. Chem*., 5525 (2012).
48. S. K. Sharma, R. Gupta, *Inorg. Chim. Acta*, **376**, 95 (2011).
49. P. Comba, M. Kubeil, J. Pietzsch, H. Rudolf, H. Stephan, K. Zarschler, *Inorg. Chem.*, **53**, 6698 (2014).
50. J. L. Everett, W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949).
51. W. Ozegowski, D. Krebs, M. Wunderwald, *J. Prakt. Chem.*, **20**, 166 (1963).
52. CrysAlis PRO, Agilent Technologies, UK Ltd, Yarnton, England, 2011.
53. G. M. Sheldrick, *Acta Cryst. A*, **64**, 112 (2008).
54. L. Farrugia, *J. Appl. Crystallogr.*, **45**, 849 (2012).
55. J. Annaraj, J. Cho, Y.-M. Lee, S. Y. Kim, R. Latifi, S. P. de Visser, W. Nam, *Angew. Chem. Int. Ed.*, **48**, 4150 (2009).
56. X. Zhou, A. I. Day, A. C. Willis,W. G. Jackson, *Chem. Commun.*, 2386 (2003).
57. J. Cho, H. Y. Kang, L. V. Liu, R. Sarangi, E. I. Solomon,W. Nam, *Chem. Sci.*, **4**, 1502 (2013).
58. C. G. Miller, S. W. Gordon-Wylie, C. P. Horwitz, S. A. Strazisar, D. K. Peraino, G. R. Clark, S. T. Weintraub,T. J. Collins, *J. Am. Chem. Soc.*, **120**, 11540 (1998).
59. P. Comba, N. F. Curtis, G. A. Lawrance, M. A. O'Leary, B. W. Skelton,A. H. White, *J. Chem Soc, Dalton Trans*, 2145 (1988).
60. J. Notni, H. Görls,E. Anders, *Eur. J. Inorg. Chem.*, **2006**, 1444 (2006).
61. A. Ghosh, P. Ramidi, S. Pulla, S. Sullivan, S. Collom, Y. Gartia, P. Munshi, A. Biris, B. Noll,B. Berry, *Catal. Lett.*, **137**, 1 (2010).
62. T. J. Collins, R. D. Powell, C. Slebodnick, E. S. Uffelman, *J. Am. Chem. Soc.*, **112**, 899 (1990).
63. T. J. Collins, C. Slebodnick,E. S. Uffelman, *Inorg. Chem.*, **29**, 3433 (1990).
64. A. Ghosh, F. Tiago de Oliveira, T. Yano, T. Nishioka, E. S. Beach, I. Kinoshita, E. Münck, A. D. Ryabov, C. P. Horwitz, T. J. Collins, *J. Am. Chem. Soc.*, **127**, 2505 (2005).
65. S. Kumar, R. Gupta, *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.*, **50**, 1369 (2011).
66. S. Kumar, S. Vaidya, M. Pissas, Y. Sanakis,R. Gupta, *Eur. J. Inorg. Chem.*, **2012**, 5525 (2012).
67. Y. Rousselin, N. Sok, F. Boschetti, R. Guilard, F. Denat, *Eur. J. Org. Chem.*, **2010**, 1688 (2010).
68. P. J. Barnard, J. P. Holland, S. R. Bayly, T. J. Wadas, C. J. Anderson, J. R. Dilworth, *Inorg. Chem.*, **48**, 7117 (2009).
69. V. Polshin, D.-L. Popescu, A. Fischer, A. Chanda, D. C. Horner, E. S. Beach, J. Henry, Y.-L. Qian, C. P. Horwitz, G. Lente, I. Fabian, E. Münck, E. L. Bominaar, A. D. Ryabov,T. J. Collins, *J. Am. Chem. Soc.*, **130**, 4497 (2008).
70. J. M. Waters K. R. Whittle, *J. Inorg. Nucl. Chem.*, **34**, 155 (1972).
71. R. E. Patterson, S. W. Gordon-Wylie, C. G. Woomer, R. E. Norman, S. T. Weintraub, C. P. Horwitz, T. J. Collins, *Inorg. Chem.*, **37**, 4748 (1998).
72. O. P. Gladkikh, N. F. Curtis,M. M. Turnbull, *Acta Crystallogr. Sect. C*, **53**, 586 (1997).
73. S. K. Sharma R. Gupta, *Inorg. Chim. Acta*, **376**, 95 (2011).
74. A. Ghosh, A. D. Ryabov, S. M. Mayer, D. C. Horner, D. E. Prasuhn, S. Sen Gupta, L. Vuocolo, C. Culver, M. P. Hendrich, C. E. F. Rickard, R. E. Norman, C. P. Horwitz, T. J. Collins, *J. Am. Chem. Soc.*, **125**, 12378 (2003).
75. J. Notni, S. Schenk, H. Görls, H. Breitzke, E. Anders, *Inorg. Chem.*, **47**, 1382 (2008).
76. T. J. Collins, R. D. Powell, C. Slebodnick, E. S. Uffelman, *J. Am. Chem. Soc.*, **113**, 8419 (1991).
77. G. Berggren, F. B. Kaynak, M. F. Anderlund, L. Eriksson, B. Akermark, *Acta Crystallogr. Sect. E*, **63**, m2672 (2007).
78. J. Cho, R. Sarangi, H. Y. Kang, J. Y. Lee, M. Kubo, T. Ogura, E. I. Solomon, W. Nam, *J. Am. Chem. Soc.*, **132**, 16977 (2010).
79. C. P. Horwitz, S. W. Gordon-Wylie, Y. Leychkis, D. M. Flynn, S. T. Weintraub, G. R. Clark, T. J. Collins, *J. Phys. Chem. B*, **105**, 8821 (2001).
80. M. J. Bartos, C. Kidwell, K. E. Kauffmann, S. W. Gordon-Wylie, T. J. Collins, G. C. Clark, E. Münck, S. T. Weintraub, *Angew. Chem. Int. Ed.*, **34**, 1216 (1995).
81. E. Joseph Billo, P. J. Connolly, D. J. Sardella, J. P. Jasinski, R. J. Butcher, *Inorg. Chim. Acta*, **230**, 19 (1995).

НОВИ 13-ЧЛЕННИ ЦИКЛИЧНИ ДИОКСАТЕТРААЗА ПЛАТФОРМИ – СИНТЕЗ И ОХАРАКТЕРИЗИРАНЕ В РАЗТВОР И ТВЪРДО СЪСТОЯНИЕ

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(Резюме)

Серия от три нови лиганда с 1,4,8,11-тетраазациклотридецин-2,10-дионов скелет, притежаващи относително запречен аминен фрагмент и разнообразен модел на заместване в ароматното ядро на амидната единица, са моделирани и получени по подобрен синтетичен протокол. Макроциклите са анализирани с ЯМР спектри в разтвор и с монокристална и прахова рентгенова дифракция в твърдо състояние. Дискутирана е конформацията на 13-членния пръстен и е сравнена с литературни данни.