NOVEL MACROCYCLES EMBEDDING *p,p'*-TERPHENYL UNITS: SYNTHESIS, CHARACTERIZATION, SINGLE CRYSTAL X-RAY MOLECULAR STRUCTURES AND THEORETICAL INVESTIGATIONS[**]

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In this study we report the design and efficient synthesis of new macrocycles containing *p,p'*-terphenyl and oxime units. The structures of the reported macrocycles were fully characterized by NMR and HRMS, as well as by single-crystal X-ray diffraction. In addition, density functional theory (DFT) calculations were performed in order to gain more information about the conformational behavior of the reported macrocycles.
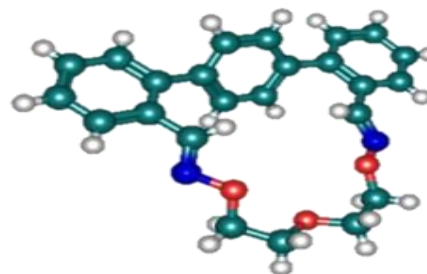
INTRODUCTION

The field of synthetic macrocycles witnessed an impressive expansion after the synthesis of the first crown ether carried out by Pederson in 1967.[1] The high interest for macrocycles is due to their ability to selectively form host-guest supramolecular systems by complexation of cations, anions or small organic molecules.[2] Aside from the classic crown ethers [(CH₂-CH₂X)ₙ; X = O] and the similar compounds exhibiting other heteroatoms (*e.g.* X = S, NH), many other macrocycles displaying specific units (usually aromatic moieties) embedded in cyclic systems by various chains were investigated.[3] However, literature data reveal few works unveiling *p,p'*-terphenyl-based macrocycles. In addition to the exciting papers of Mayor dedicated to chiral Geländer (also known as banister) compounds,[4] there are only few reports focused on highly tensioned monomeric macrocycles exhibiting diyne[5] or aliphatic bridges[6] and/or dimeric macrocycles with diyne chains.[7]

In this context and based on our previous experience in the study of macrocycles exhibiting spiro- and dispiro-1,3-dioxane,[8] bis(1,3-dioxan-2-yl)benzene,[8b,9] phenothiazine,[10] bi- and terthiophene[11] or biphenyl[12] units we considered of interest to elaborate the design of two novel macrocycles (**1** and **2**, Chart 1) embedding *p,p'*-terphenyl moieties. Thus, we report here their synthesis and characterization by NMR, HRMS, single crystal X-ray diffractometry and molecular modeling.
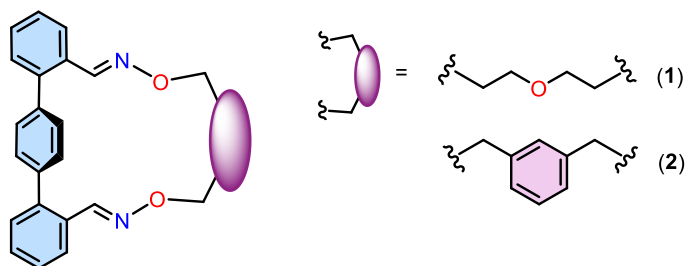
Chart 1 – Structure of the target *p,p'*-terphenyl-based macrocycles **1** and **2**.

RESULTS AND DISCUSSION

The target macrocycles **1** and **2** showing etheroxime connections of the bridges were obtained in good yields by classic alkylation reactions, under high dilution conditions, starting from *p,p'*-terphenyldioxime **3** (Scheme 1) and ditosylated diethyleneglycol (for **1**) or 1,3-bis(bromomethyl)benzene (for **2**). In these reactions *t*-BuONa was used as base.

Dioxime **3** was, in its turn, synthesized starting from *p*-dibromobenzene, which was transformed, making use of a Miyaura reaction with bis(pinacolato)diboron, in the corresponding benzene-1,4-diboronic acid, pinacol diester **4**. The

Suzuki-Miyaura cross-coupling of **4** with *o*-bromobenzaldehyde yielded the dialdehyde **5**. The classic condensation reaction of **5** with hydroxylamine gave the desired dioxime **3** (Scheme 2). All these reactions occurred in good or very good yields.

The NMR spectra of **1** and **2** showed the expected pattern of signals for symmetric structures (see for example ^{1}H-NMR spectrum of **2** in Figure 1 and Supporting Information). The HRMS investigations confirmed the molecular formula, while more structural insights could be obtained from solid-state molecular structures and by theoretical calculations.
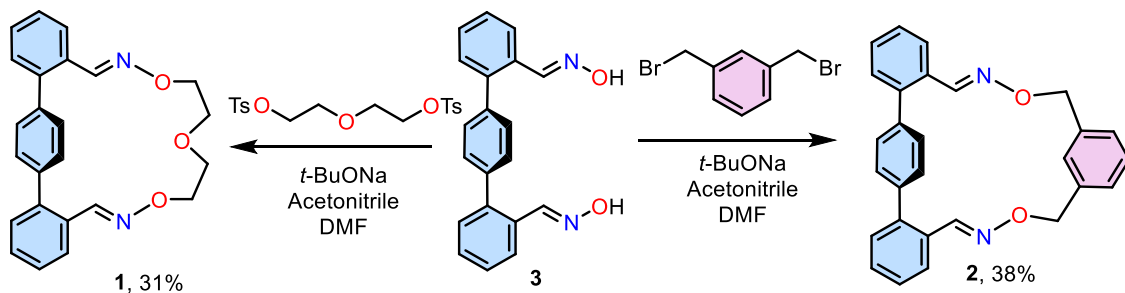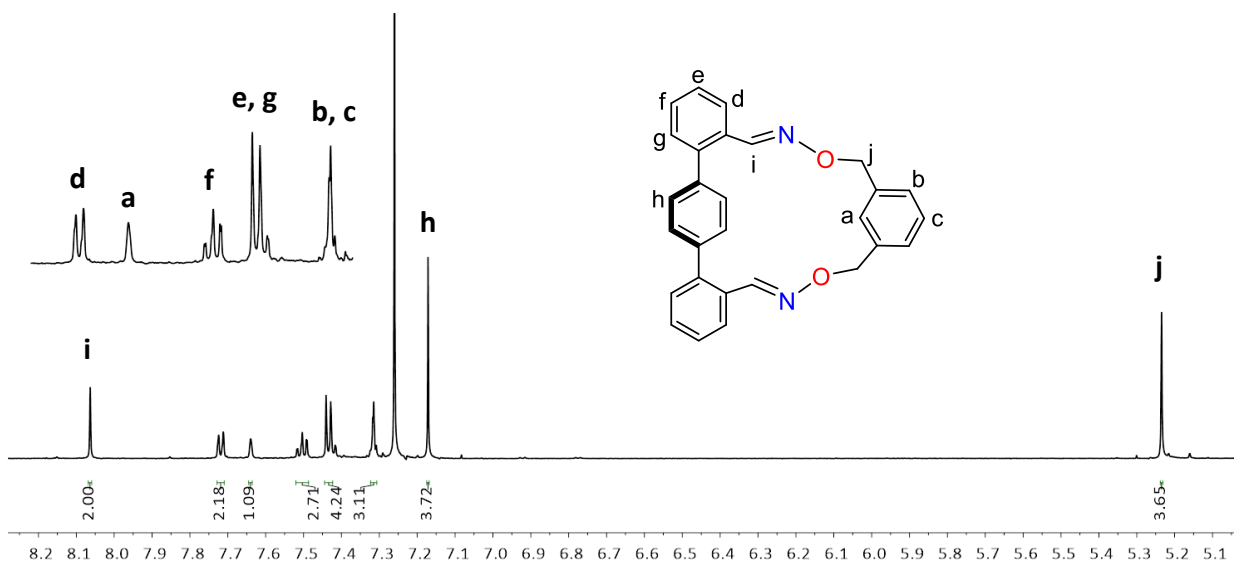

Scheme 1
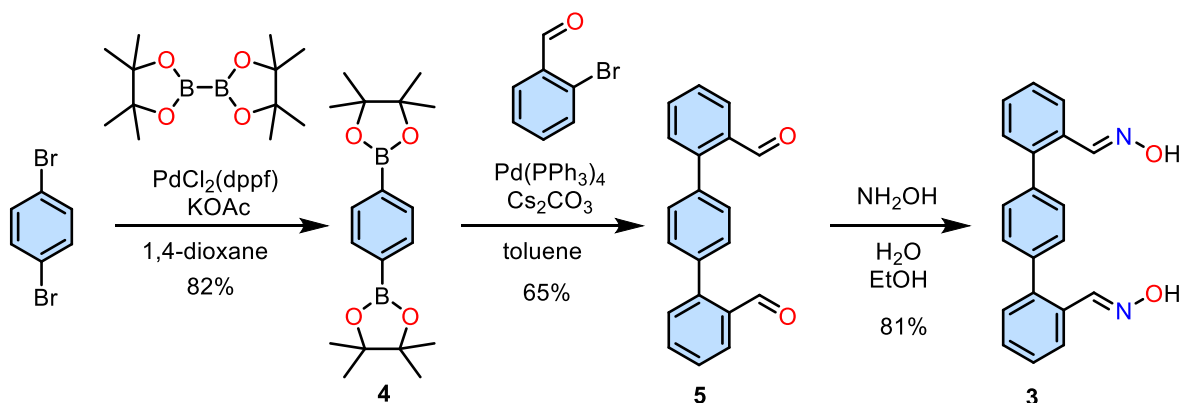
Scheme 2

Fig. 1 – ^{1}H-NMR spectrum (CDCl$_3$, 600 MHz) of **2**.

Crystals of **1** and **2** suitable for single crystal X-ray diffraction were obtained by slow evaporation from CDCl$_3$.

Solid state molecular structures of **1** and **2** revealed the torsion of benzene rings in *p,p'*-terphenyl unit (Figures 2a and 3a). Thus, the crystal of **1** contains two types of molecules that differ by the torsion angles defined by central phenylene ring and terminal ones of 50° / 49° and 51° / 53°, respectively (Figure 2b). The torsion angles of the central and the terminal phenyl units in compound **2** are about 45° (Figure 3a).

In the lattice of **1**, the organization of the molecules is ensured by N···H–C contacts involving the H atoms at the *para* positions of the peripheral benzene ring ($d_{N···H}$ = 2.625 Å) or of a methylene unit ($d_{N···H}$ = 2.592 Å) and by C–H···Ph contacts involving aromatic ring (C–H) in one molecule and a phenyl unit (Ph) in a neighbor molecule (H···centroid distances are $d_{H–centroid}$ = 2.952 and 2.828 Å) as well as C–H···Ph between N=C–H of a macrocycle and a terminal phenyl unit in an adjacent macrocycle (Figure 2b). The view along the b crystallographic axis reveal chains of molecules with parallel orientation of the *p,p'*-terphenyl moieties, the molecules within a chain are stacked with the formation of columns (Figure 2c).
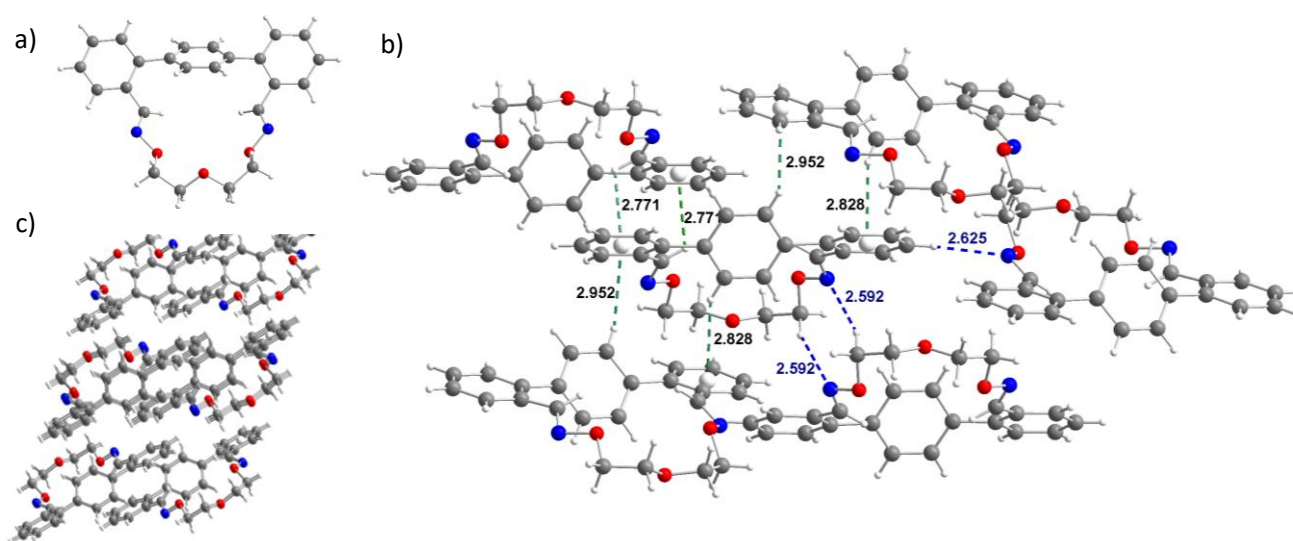

Fig. 2 – Molecular structure of **1** (a); Representation of the non-covalent interactions within the lattice of **1** (b); and crystal packing – view along *b*-crystallographic axis.
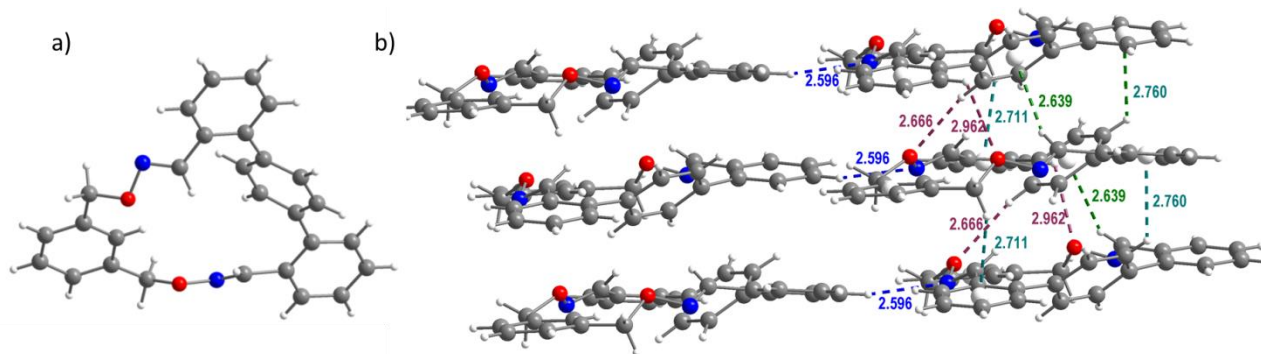
Fig. 3 – Molecular structure of **2** (a); Representation of the non-covalent interactions within the lattice of **2** (b).

In the lattice of **2**, there are two groups of *p,p'*-terphenyl units (Figure 3b). The members of one group are parallel to each other and the two types of planes which contain the two groups of parallel *p,p'*-terphenyl units are perpendicular. The stability of the lattice is ensured by O (oxime)···H (CH$_2$) (d = 2.666 Å), O(oxime)···H (*o*-H of a terminal Ph ring) (d = 2.962 Å), N···H (*m*-H of a terminal Ph ring), (d$_{N-H}$ = 2.569 Å), C–H (central Ph)---Ph (terminal Ph) (d$_{H-centroid}$ = 2.760 Å), C–H (oxime)---Ph (central) (d$_{H-centroid}$ = 2.639 Å), C–H (CH$_2$)---Ph (terminal) (d$_{Hcentroid}$ = 2.711 Å) contacts.

As inferred from crystallographic data, the bridges match exactly between the *orto*, *orto''* positions of *p,p'*-terphenyl unit and, as a consequence, the terminal phenylene rings are almost coplanar. However, due to the possibilities of rotation around C–C single bonds, many conformers can exist in solution. The symmetry of each macrocycle can be broken in some conformers by increasing the dihedral angle (θ) defined by terminal aromatic rings. In order to determine the geometry of several helical geometries, their relative energies and the maximum value of θ, Density Functional Theory (DFT) studies were performed using *Gaussian 09* package.[13] M06-2X exchange-correlation functional has been chosen as DFT method[14] due to its widespread applicability on a broad range of organic compounds.[15] Thus, employing this Minnesota functional along with valence triple-zeta Def2-TZVP[16] basis set, all structures were optimized in gas phase without any symmetry constraints. Moreover, optimization criteria were set to tight. In order to characterize the nature of the stationary points and to determine the zero-point energy and the thermal corrections, analytic second derivative calculations were performed on the optimized structures. Also, within all calculations, the integration grid used was of

99 radial shells and 950 points for each shell (99, 950), representing the ultrafine grid in *Gaussian 09*.

Starting optimization from the XRD structures, converged geometries of both macrocycles are close to the initial guess. The θ maintains its value to 0.0° in case of **1**, while in the case of **2** decrease from 0.5° to 0.0°. A more significant difference is the increase of dihedral angle defined by central phenylene ring and terminal ones of macrocycle **2**, from 43.3° to 49.5°. Noteworthy, although with an energetical cost, an increase of θ value induces a helical arrangement of bridge around *p*-terphenyl backbone (Figure 4). More exactly, a maximum deviation from coplanarity (θ=65.7°) destabilizes **1-C4** conformer with 9.8 kcal mol^{-1}, relative to symmetrically **1-C1**. Although the 1,3-bis(methylene)benzene bridge is more rigid, it allows a higher helical twist in macrocycle **2** (**2-C4**, θ=69.1°) with a lower relative enthalpy (3.8 kcal mol^{-1} relative to **2-C1**). **1-C4** is less stabilized than **2-C4** as result of extra steric repulsion between sp^3 hybridized atoms from diethyleneoxide bridge and central ring of *p*-terphenyl backbone. Moreover, the π···H interaction between phenylene ring of bridge and central aromatic unit of *p*-terphenyl balance the strain energy induced in **2-C4**.

Others noticeable unsymmetrical conformers are **1-C2** and **1-C3**, **2-C2** and **2-C3**, respectively. Concerning the structures of these local minima, the bridges do not cross the *p*-terphenyl backbone, resulting in a decrease of strain energies. However, **1-C2**, displaying an ether oxime group rotated around C(Ar)–C(oxime) bond, has a relative enthalpy of about 6 kcal·mol^{-1}, while **1-C3** with larger torsion angle, but not rotated oxime group, is with almost 3 kcal mol^{-1}·more stable. On the other hand, even though the torsion angle increases with *cca.* 10.0° from **2-C2** to **2-C3**, the relative enthalpies are kept around 3 kcal mol^{-1}.
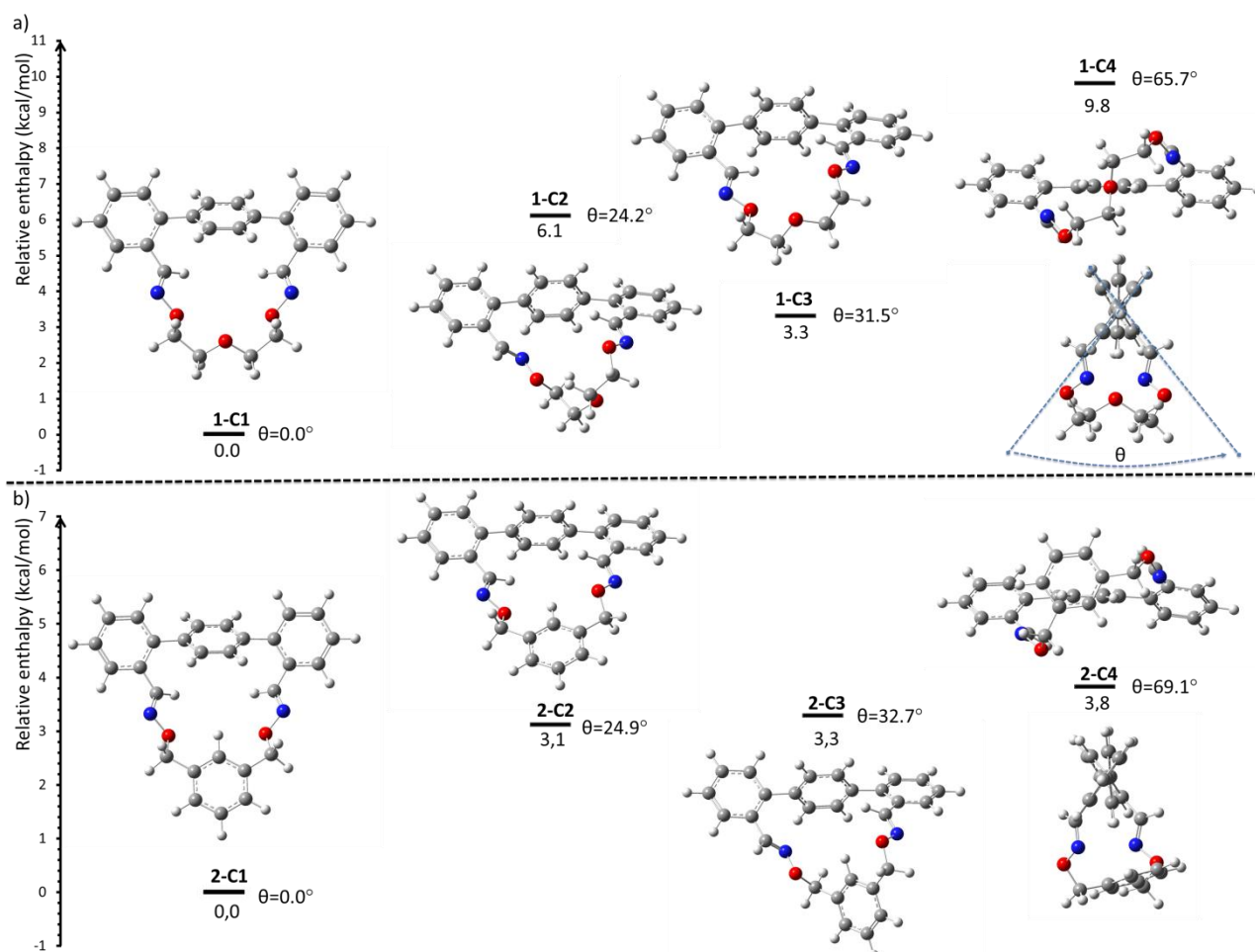
Fig. 4 – Equilibrium geometries, relative enthalpies and the dihedral angles (θ) for several conformers of macrocycle **1**(a) and **2**(b).

EXPERIMENTAL PART

General experimental data. ¹H and ¹³C NMR spectra were recorded at room temperature (*rt*) on Bruker Avance 600 or Bruker Avance 400 spectrometers. High resolution mass spectra were recorded in positive mode, on a ThermoScientific spectrometer equipped with Orbital Ion Trap mass analyzer using electrospray (ESI) or atmospheric pressure chemical ionization (APCI) techniques. Thin-layer chromatography was performed on Merck 60F 254 silica gel sheets, while Merck silica gel (40-60 µm) was used for preparative column chromatography. All chemicals of commercial grade were used without further purification. The crystals of **1** and **2** were mounted on MiTe GenmicroMounts cryo loops and data were collected on a Bruker D8 VENTURE diffractometer using Mo-Kα radiation (λ = 0.71073 Å) from a IμS 3.0 microfocus source with multilayer optics, at low temperature (100 K). The structures were refined with anisotropic thermal parameters for non-H atoms. Hydrogen atoms were placed in fixed, idealized positions and refined with a riding model and a mutual isotropic thermal parameter. For structure solving and refinement the Bruker APEX3 Software Packages were used.[17] The drawings were created using the Diamond program.[18] Intermolecular contacts were found in Platon[19]. CCDC 2119430 and 2119431 contain the supplementary crystallographic data for compounds **1** and **2**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via *www.ccdc.cam.ac.uk/ data_request/cif.* Theoretical calculations were performed using the high-performance computational facility at Babeş-Bolyai University.

*General procedure for the synthesis of macrocycles **1** and **2***. A dry solution of dioxime **3** (0.80 g, 0.252 mmol) and t-BuONa (53.3 mg, 0.556 mmol) in anhydrous DMF (6 mL) and anhydrous acetonitrile (50 mL) was stirred at 80°C under argon for one hour. To this mixture, ditosylated diethyleneglycol (135 mg, 0.328 mmol, for macrocycle **1**) or 1,3-bis(bromomethyl)benzene (86.78 mg, 0.328 mmol, for macrocycle **2**) solved in anhydrous acetonitrile (5 mL) were added dropwise under argon at 80°C during 10 h. The reaction mixture was stirred at reflux for 6 days. The reaction mixture was brought at *rt*, the solvents were removed *in vacuum*, the residue was dissolved in CH₂Cl₂ (30 mL) and washed with H₂O (3x25 mL). The organic phase was dried over anhydrous MgSO₄ and the solvent was removed *in vacuum*. Pure macrocycles **1** and **2** were isolated after column chromatography using silica gel as stationary phase and a mixture of pentane / acetone 8 / 2 as elution system.

3,11-diaza-4,7,10-trioxatetracyclo[21,4,2¹⁹,²²,0¹,²³, 0¹³,¹⁸] nonacosan-1(23),2,11, 13,15,17,19,21,24,26,28-undecaene (**1**). White solid (30.2 mg, η = 31 %). Rf = 0.5 (silica gel, pentane/acetone 8/2). **¹H-NMR** (400 MHz, CDCl₃), δ (ppm):

8.08 (s, 2H), 7.70 (d, ^3J= 7.5 Hz, 2H), 7.51–7,47 (overlapped peaks, 4H), 7.45–7.39 (overlapped peaks, 6H), 4.41–4.36 (overlapped peaks, 4H), 3.71–3.67 (overlapped peaks, 4H). **^{13}C(APT)-NMR** (150 MHz, CDCl₃), δ (ppm): 152.3, 141.4, 139.0, 130.8, 129.8, 129.7, 129.1, 127.9, 127.7, 73.2, 70.4. **HRMS (ESI+)** (m/z): calculated for C₂₄H₂₂N₂O₃ [M+Na]⁺=409.15226; found:409.15463.

3,13-diaza-4,12-dioxapentacyclo[23,4,2²¹,²⁴,1⁶,¹⁰,0¹⁵,²⁰,0¹,²⁵] dotricosan-1(25),2,6,8,10(30),13,15,17,19,21,23,26,28,31-tetradecaene (**2**). White solid (40 mg, η = 38 %). R_f = 0.62 (silica gel, pentane/acetone 8/2). **^{1}H-NMR** (600 MHz, CDCl₃), δ (ppm): 8.06 (s, 2H), 7.72 (d, ^3J = 7.3 Hz, 2H), 7.64 (s, 1H), 7.50 (t, ^3J= 7.5 Hz, 2H), 7.45 – 7.41 (overlapped peaks, 4H), 7.33–7.29 (overlapped peaks, 3H), 7.17 (s, 4H), 5.23 (s, 4H). **^{13}C(APT)-NMR** (100 MHz, CDCl₃), δ (ppm): 154.0, 141.0, 138.5, 138.5, 130.5, 130.3, 130.0, 129.6, 129.5, 128.3, 128.2, 128.0, 127.8, 75.8. **HRMS (APCI+)** (m/z): calculated for C₂₈H₂₂N₂O₂ [M+H]⁺=419.17540; found:419.17587.

1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**4**).[20] 1,4-Dibromobenzene (1.5 g, 6.36 mmol), bis(pinacolato) diboron (3.23 g, 12.72 mmol) and sodium acetate (3.92 g, 47.8 mmol) were dissolved in dioxane (30 mL). The solution was purged with argon for 30 min. and PdCl₂(dppf) x CH₂Cl₂ (0.322 g, 0.44 mmol) was added. The reaction mixture was refluxed for 40 h, then the solvent was removed *in vacuum*, the residue was solved in DCM and filtered over celite. The filtrate was washed with water (3x50 mL) and the organic phase was dried over MgSO₄. The solvent was removed in vacuum and the crude of reaction was purified by trituration with pentane. White solid, (1,7 g, η =82%). R_f: 0.37 (silica gel, pentane/ethyl acetate 16/1). **^{1}H-NMR** (400 MHz, CDCl₃), δ (ppm): 7.80 (s, 4H), 1.35 (s, 24H).

[1,1':4',1''-terphenyl]-2,2''-dicarbaldehyde (**5**).[21] Compound **4** (0.410 g, 1.242 mmol), 2-bromobenzldehyde (0.662 g, 3.578 mmol) and Cs₂CO₃ (2.332 g, 7.157 mmol) were dissolved in a mixture of 1,2-dimethoxyethane (30 mL) and water (15 mL). The solution was purged with argon for 30 minutes, Pd(PPh₃)₄ (0.331 g, 0.286 mmol) was added and the reaction mixture was stirred at reflux for 16 hours. After evaporation of the solvents, the residue was dissolved in DCM (50 mL), filtered over celite and the filtrate was washed with water (3 x 50 mL). The organic phase was dried over MgSO₄ and the solvent was evaporated *in vacuum*. The crude of reaction was purified by column chromatography. White solid (0.238, g η =67 %), R_f: 0.33, (silica gel, pentane/ethyl acetate 8/1). **^{1}H-NMR** (600 MHz, CDCl₃), δ (ppm): 10.10 (s, 2H), 8.10 (dd, ^3J = 7.8, ^4J =1.1 Hz, 2H), 7.72 (td, ^3J = 7.5, ^4J =1.4 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.56–7.53 (overlapped peaks, 6H).

(1E,1'E)-[1,1':4',1''-terphenyl]-2,2''-dicarbaldehyde dioxime (**3**). Compound **5** (0.210 g, 0.733 mmol) and NH₂OH x HCl (0.407 g, 5.867 mmol) were dissolved in a mixture of ethanol (75 mL) and water (15 mL). The solution was cooled at 0 ℃ and an aqueous solution of KOH (0.35 g, 6.234 mmol, dissolved in 75 mL water) was added dropwise. Then, the reaction mixture was stirred at reflux for 36 hours. After cooling at room temperature, the pH was adjusted to 6 with HCl 10% and the precipitate was filtered and dried. White solid, (0.192 g, η=83%). R_f: 0.29 (silica gel, toluene/acetone 9/1). **^{1}H-NMR** (600 MHz, DMSO-*d6*), δ_H (ppm): 11.35 (s, 2H), 7.99 (s, 2H), 7.90 (d, ^3J = 7.7 Hz, 2H), 7.50 (t, ^3J = 7.1 Hz, 2H), 7.47–7. 42 (overlapped signals,

10H). **^{13}C-NMR** (150 MHz, DMSO-*d6*), δ (ppm): 147.0, 141.0, 138.9, 130.7, 130.6, 130.0, 129.9, 128.3, 126.0.

CONCLUSIONS

In summary, we described here the synthesis and structural analysis of new *p,p'*-terphenyl based macrocycles displaying etheroxime connections of the diethyleneoxide and 1,3-bis(methylene) benzene bridge, respectively. The synthetic strategy used allowed the obtaining of the monomer macrocycles in good yields. NMR spectra and single crystal X-ray diffraction data show symmetrical structures for the macrocycles both in solution and in solid state. Higher stability of the symmetrical structures as compared to asymmetrical helical conformers was also confirmed by DFT calculations.

Supporting Information Available. Copies of NMR spectra as well as details of theoretical calculations and X-ray diffraction data (PDF)

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