

MACROCYCLIC COMPOUNDS FORMED IN THE REACTION OF 3,7-BIS(ORTHO-, META- OR PARA-FORMYLPHENYL)PHENOTHIAZINES WITH META-BIS(AMINOMETHYL)BENZENE: EXPERIMENTAL AND THEORETICAL INVESTIGATIONS

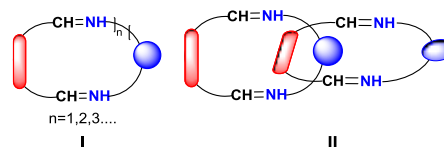
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The competition among oligomeric macrocycles and mechanically interlocked structures ([2]catenanes) in imine formation cyclization reactions of isomeric 3,7-bis(*ortho*-, *meta*- or *para*-formylphenyl)phenothiazines with *meta*-bis(aminomethyl)benzene is experimentally revealed and investigated by detailed DFT calculations.



INTRODUCTION

10*H*-Phenothiazine derivatives are largely investigated¹ mainly due to their multiple applications in exciting fields such as pharmaceutical and biological chemistry, as well as optoelectronic devices.² Phenothiazine exhibits a flattened “butterfly” structure, but the radical-cation formed by its oxidation is planar³ and fulfills the requested conditions for the obtaining of outstanding electroactive compounds as polymers,⁴ dyads and triads,⁵ cruciform fluorophores,⁶ molecular wires⁷ or ligands for surface modifications.⁸

The investigation of macrocycles is a continuous developing field due to the ability of these systems to selectively complex cations, anions or organic molecules.⁹ Besides the classic crown ethers [(CH₂-CH₂X)_n; X = O, S, NR] other macrocycles

embedding various aromatic units connected by different chains were obtained and investigated.¹⁰

In our previous studies we synthesized and characterized macrocycles having spiro- and dispiro-1,3-dioxane,¹¹ bis(1,3-dioxan-2-yl)benzene,¹² phenothiazine,¹³ ter- and bithiophene¹⁴ or biphenyl¹⁵ units. These macrocycles were obtained by etherification, esterification or cross-coupling procedures. We considered of interest to investigate the outcome of the imine formation macrocyclization reactions considering the position isomers of 3,7-bis(formylbenzen-1-yl)phenothiazine **1** (4-formyl-1-yl), **2** (3-formyl-1-yl), **3** (2-formyl-1-yl), and *meta*-bis(aminomethyl)benzene **4** (Chart 1). The imine formation reactions take place under equilibrium conditions (thermodynamic control) and the most probable cyclic products are macrocycles of type **I** or [2]catenanes of type **II**, Chart 1).

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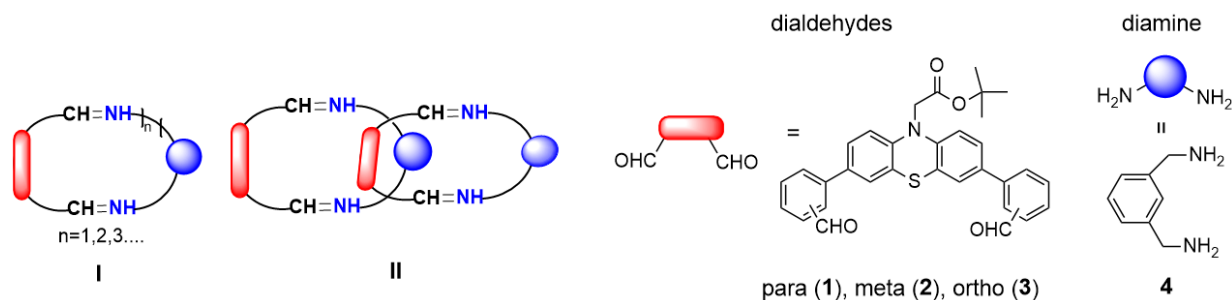


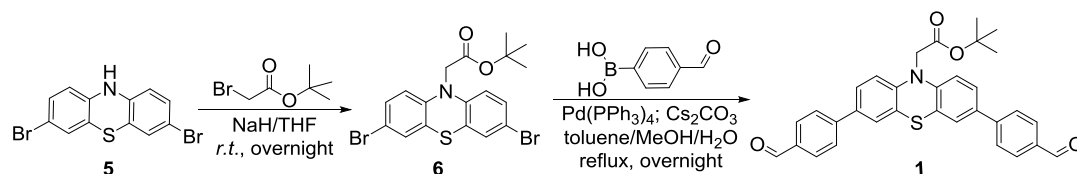
Chart 1 – Possible cyclic products resulted from the reactions of 1-3 with 4: macrocycles (I; monomers $n = 1$, dimers $n = 2$, trimers $n = 3$) or [2]catenanes (II).

Therefore, we set to study macrocyclization reactions using imine formation, as one of the most studied reaction in dynamic constitutional chemistry and to determine the equilibrium compositions. To this end, after the equilibrium was reached, we froze the exchange reactions by the reduction of imine groups to stable secondary amines and investigated the structure of the stable products in order to deduce the preferences of the reactions towards one of the oligomeric

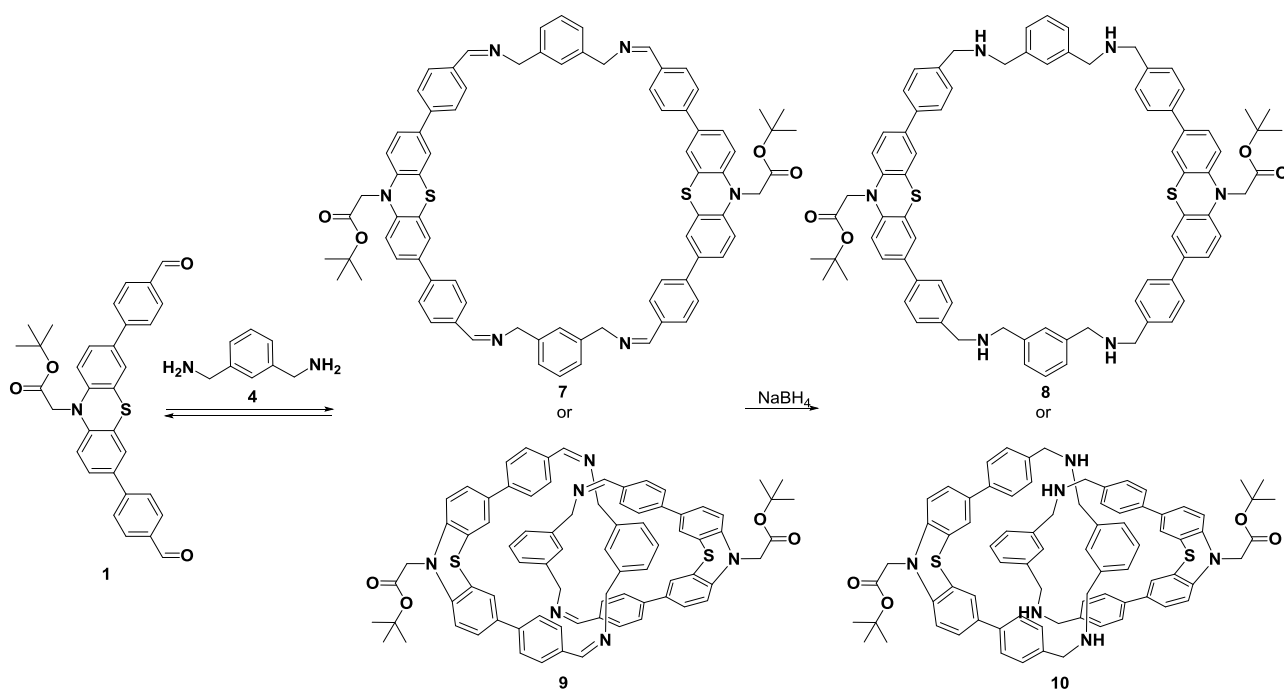
macrocycles (I) or the mechanically interlocked molecule, the [2]catenane (II).

RESULTS AND DISCUSSION

Dialdehyde **1** (Scheme 1)^{8c} and commercially available diamine **4** were submitted to macrocyclization reactions under classic conditions for the formation of imines (Scheme 2). The processes were monitored by HPLC-MS.



Scheme 1 – Synthesis of dialdehyde **1**.



Scheme 2 – Macrocyclization reaction of dialdehyde **1** with diamine **4**; the formation of imine dimer macrocycle **7** and imine [2]catenane **8** and of the corresponding secondary amines **9** and **10**.

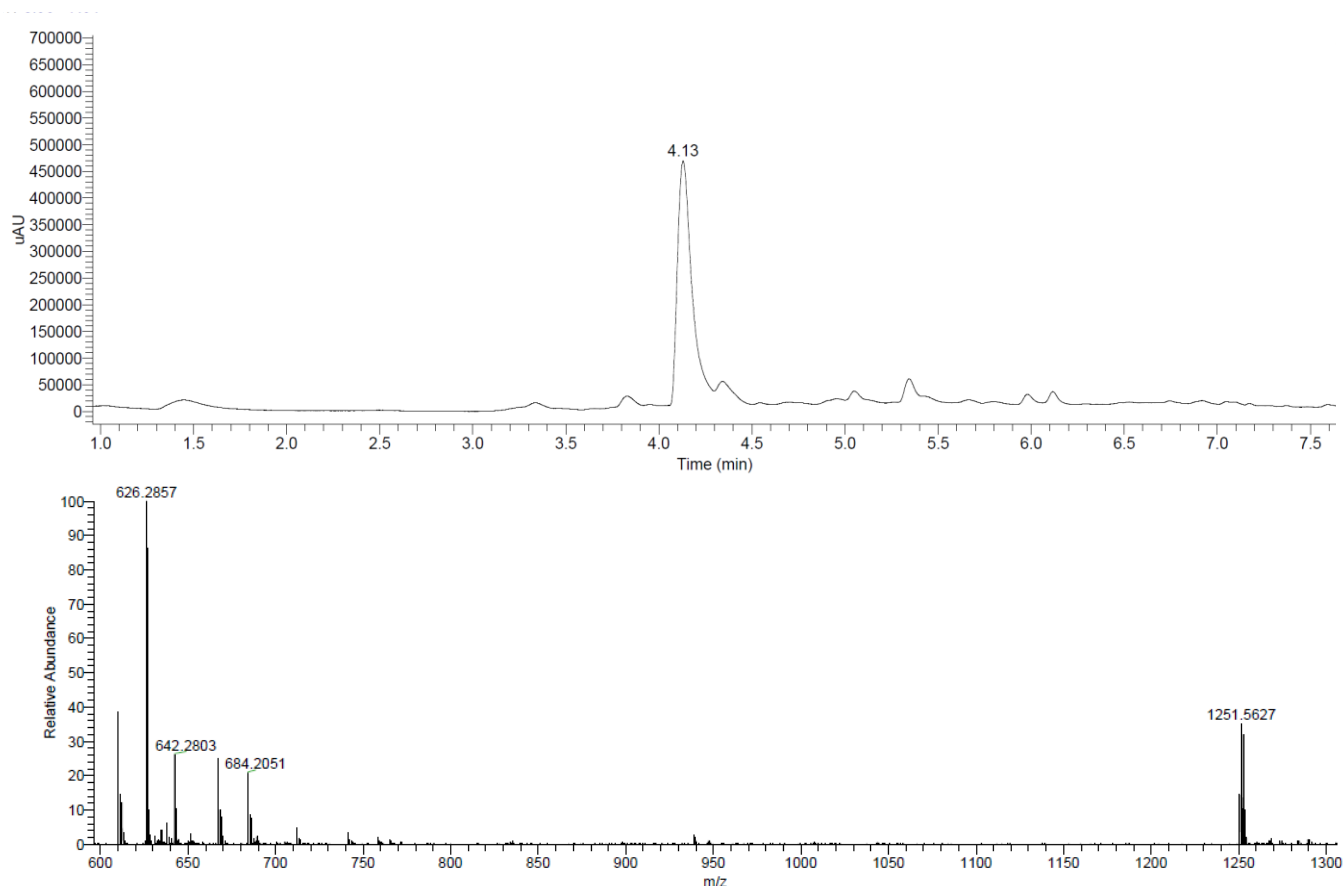


Fig. 1 – RP-HPLC chromatogram of the frozen equilibrium reaction products for the reaction of **1** with **4** after 6 days reaction time, UV detection at 280 nm (top); HRMS-spectrum of the major peak at RT=4.13 (bottom).

Samples of the reaction mixture were collected at different reaction times, the equilibria were frozen by the reduction with NaBH_4 ($-\text{CH}=\text{N}- \rightarrow \text{CH}_2\text{-NH}-$) and then the reduced samples were investigated by HPLC-MS. After six days the evolution of the equilibrium underwent towards the formation of a largely major product (see Figure 1).

At this stage the reaction was stopped by reduction with sodium borohydride and the major product (secondary amine) was separated and its structure was investigated by HRMS and ^1H NMR. The results of MS investigations [$m/z = 1251.5627$ ($\text{C}_{80}\text{H}_{79}\text{N}_6\text{O}_4\text{S}_2$) $^+$ and 626.2857 ($\text{C}_{80}\text{H}_{80}\text{N}_6\text{O}_4\text{S}_2$) $^{2+}$] of the product suggested as possible structures either the dimer macrocycle (**8**) or the corresponding [2]catenane (mechanically interlocked molecule **10**; Scheme 2). The possible intermediary imines (**7** or **9**) were not separated and experimentally investigated.

The ^1H NMR spectrum of the separated reduced product (Figure 2) fit to both proposed structures (**8** or **10**) and the assignment of the spectrum to the dimer macrocycle (**8**) or to the [2]catenane (**10**)

structures was not possible. The spectrum exhibits a singlet for the protons of the *t*-butyl groups ($\delta = 1.53$ ppm), three singlets ($\delta = 4.25, 4.28$ and 4.53 ppm; ratios of intensities = 2/2/1) corresponding to the methylene units connecting the aliphatic amino groups or belonging to the *N*-methylester groups, respectively.

In addition for the aromatic protons the specific pattern [$\delta = 6.74$ (doublet, 1-H, 9-H); 7.32 (doublet, 4-H, 6-H); 7.39 ppm (doublet of doublets, 2-H, 8-H)] for the protons attached to the phenothiazine units could be assigned, while the other aromatic protons give two groups of overlapped peaks at $\delta = 7.47\text{-}7.50$ (6H) and $7.60\text{-}7.63$ ppm (18H). Unfortunately, the ROESY spectra run with this compound could not bring supplementary clarifications (no clear correlations that could be assigned to a single structure were observed). Therefore, we decided to perform theoretical calculations as support for the selection of the preferred structure in this reaction.

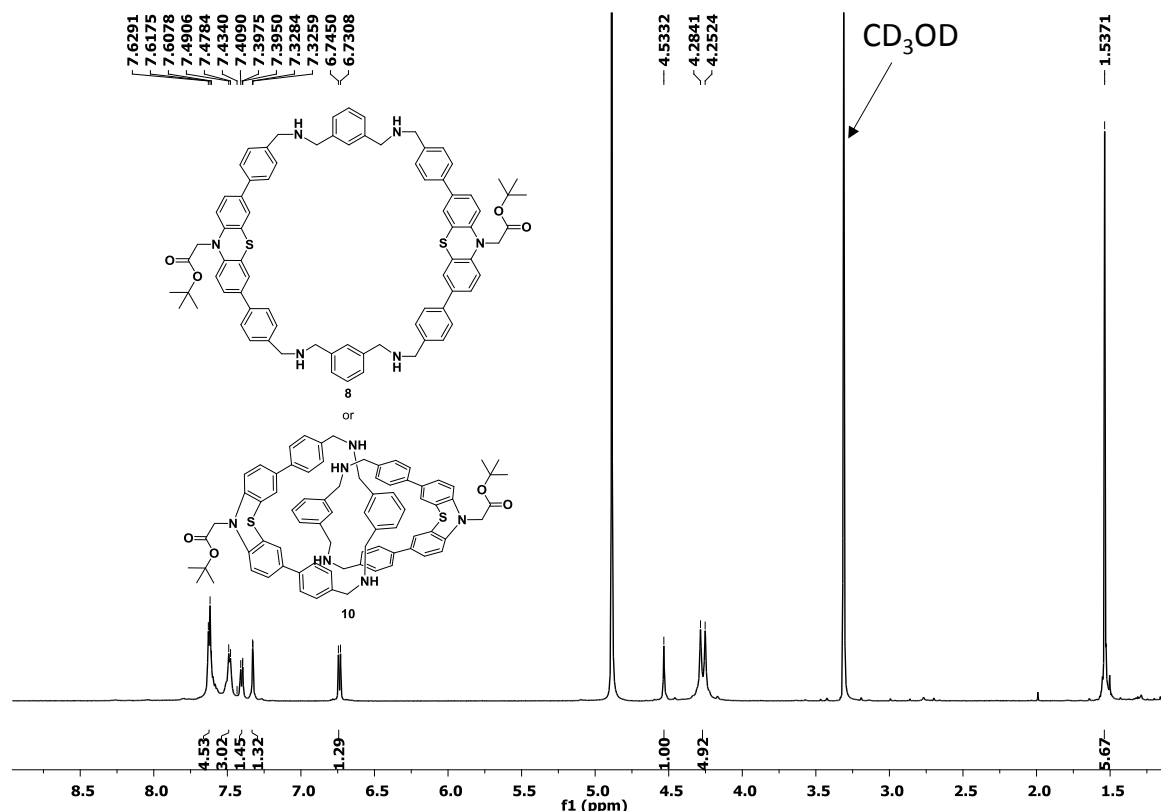


Fig. 2 – ¹H NMR spectrum (400 MHz, CD₃OD) of the main product (after reduction with NaBH₄) in the reaction of **1** and **4**.

Test experiments run with the other two dialdehydes (**2** and **3**) revealed the evolution of the reactions toward a major product which were identified either as the corresponding dimer macrocycles (reduction products of **11** or **13**) or as [2]catenanes (reduction products of **12** and **14**, Chart 2), as inferred by RP-HPLC experiment, RT = 4.03 and 4.67, respectively. There are many examples in the literature (see references¹⁶⁻¹⁹) where the formation of catenanes is preferred versus the formation of the isomeric dimer macrocycles ([2+2] products). The higher stability of [2]catenanes {consisting of interlocked monomer macrocycles ([1+1] products)} occurs as a result of the supramolecular contacts between different groups belonging to the different macrocycles, that are in proximity in the interlocked structure due to the interpenetration of the cycles. These supramolecular contacts are missing in dimer macrocycles ([2+2] products). In order to elucidate the nature of macrocyclization products possible in the reaction of *para* (**1**), *meta* (**2**) and *ortho* (**3**) isomers of the phenothiazine dialdehydes with diamine **4** we considered of interest to carry out theoretical calculations and establish the energy levels for dimer macrocycles **7**, **11** and **13** and for the [2]catenanes **8**, **12** and **14**

(Chart 2). In addition the calculations were extended to the investigation of the monomeric macrocycles **8a**, **12a** and **14a** which are the constituent building blocks of the corresponding [2]catenanes **8**, **12** and **14** (Chart 2).

The theoretical investigations were performed at density functional theory (DFT) level using Gaussian 09 package.²⁰ The geometries of all macrocycles and [2]catenanes were optimized without any symmetry constrains, considering the dispersion corrected form of B3LYP exchange-correlation functional (B3LYP-D3, with D3 standing for Grimme's dispersion corrections)²¹ and the valence double-zeta Def2-SVP basis set.²² 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 also performed on the optimized structures. The strain of monomeric macrocycles was calculated by considering (theoretically) hyperhomodesmotic reactions²³ in which macrocyclic compounds (with steric strain) are open to acyclic products (without steric strain) and computing the enthalpies of reagents (*i.e.* the macrocycles) and products (*i.e.* acyclic compounds, Scheme 3) the strain energy can be calculated as $-\Delta_r H^\circ_{\text{Hyperhomodesmotic}}$.

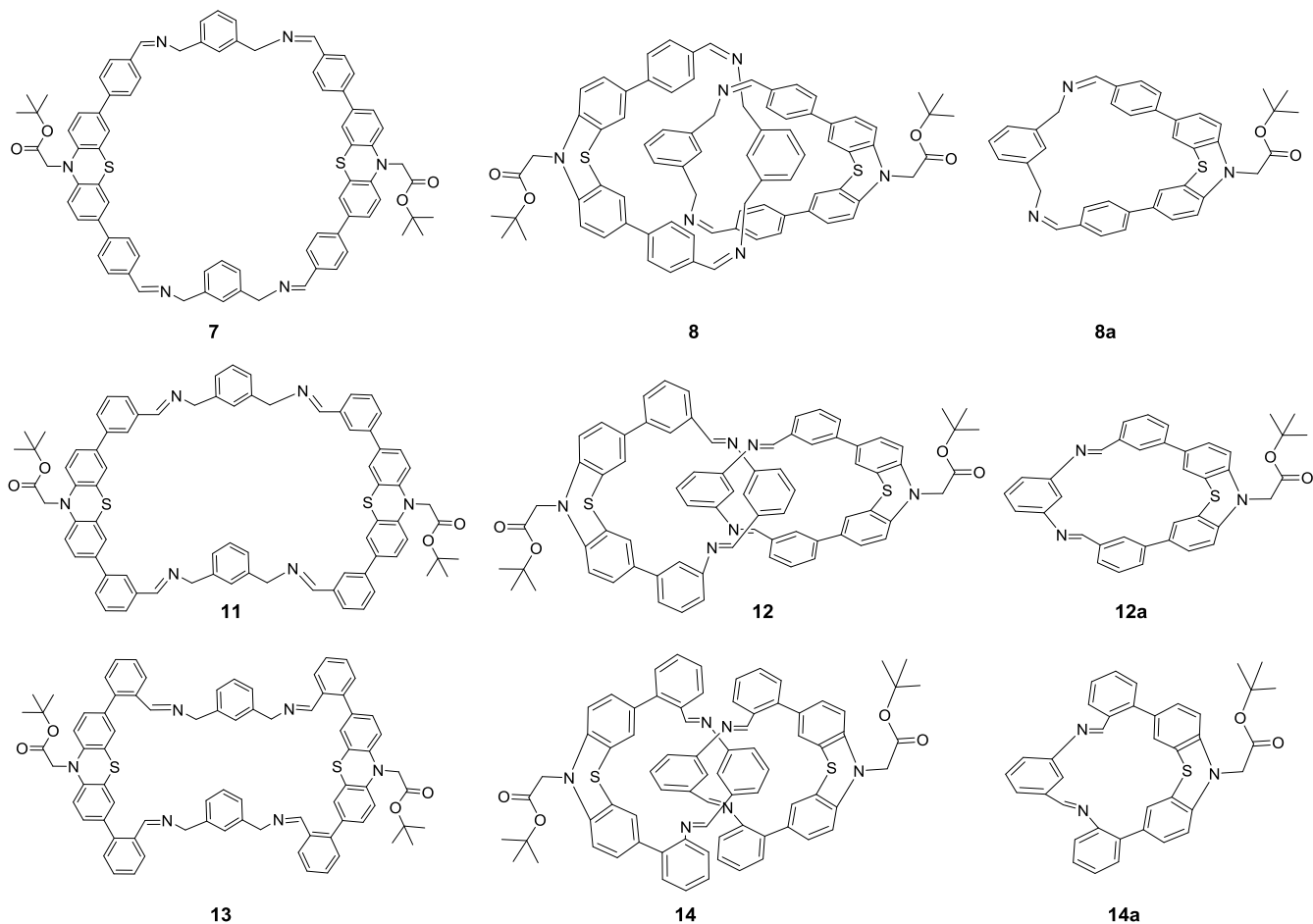
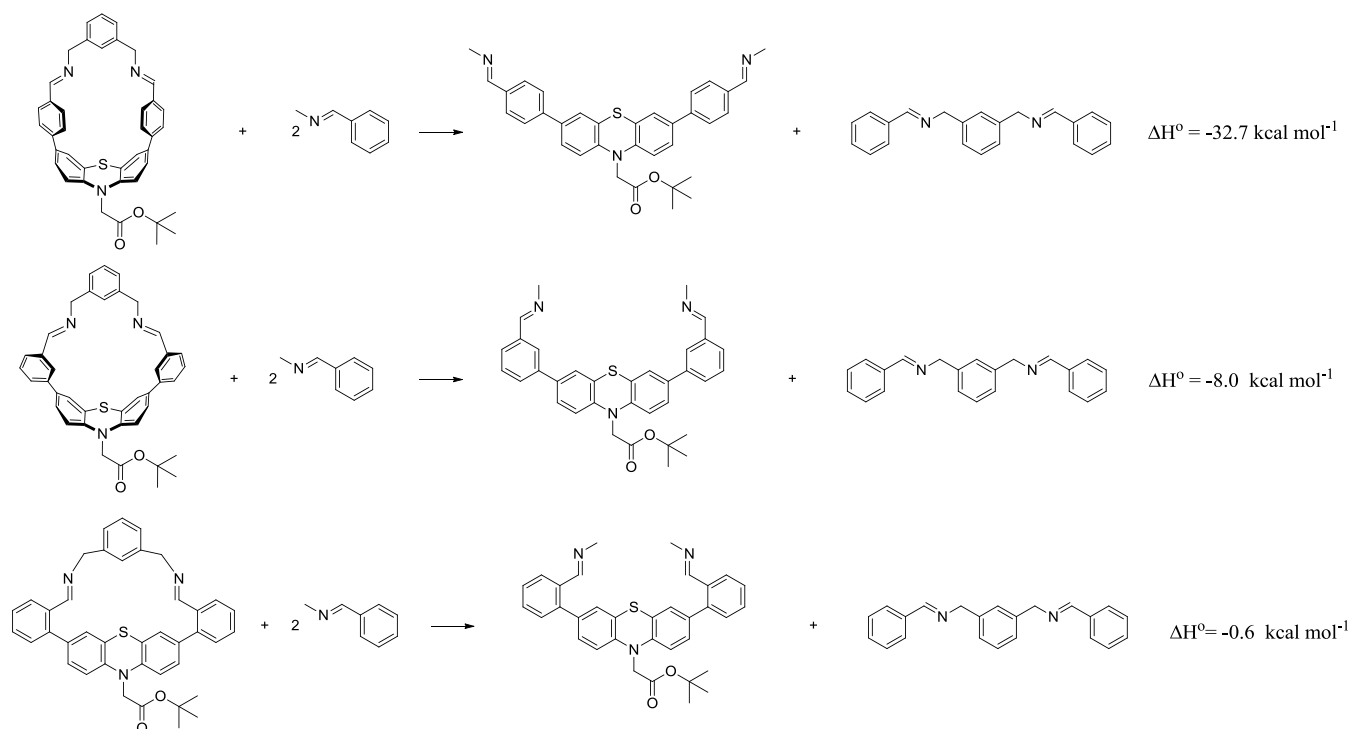


Chart 2 – Structures of the compounds investigated by theoretical methods.



Scheme 3 – Hyperhomodesmotic reactions of monomeric macrocycles.

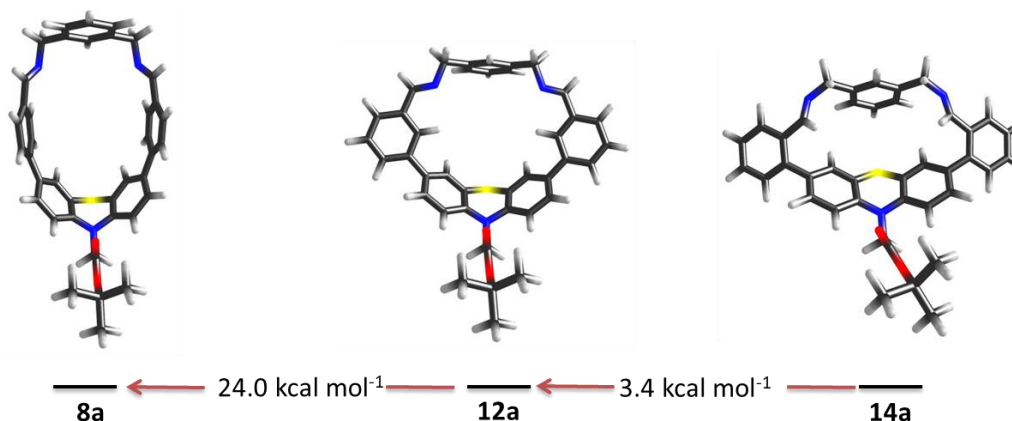


Fig. 3 – Optimized geometries and relative enthalpies of **8a**, **12a** and **14a**. Each arrow indicates the sense of the enthalpy increase.

These results reveal a high strain in macrocycle **8a** (32.7 kcal/mol) a moderate one in **12a** (8.0 kcal/mol) and quite no strain in **14a** (0.6 kcal/mol). The energy differences between macrocycles **12a** and **8a** calculated using either the relative strain energies or the relative enthalpies (Figure 3) are insignificant ($\Delta\Delta H^\circ$ in both cases are around 24 kcal/mol), while in the calculation of the energy differences between compounds **14a** and **12a** the two methods show slight differences (≈ 4.0 kcal mol⁻¹), which arise from the small enthalpies differences between of *ortho*- and *meta*-phenothiazine products of hyperhomodesmotic reactions.

The converged geometries of macrocycle **7** and its [2]catenane analog **8** are depicted in Figure 4a. The values of relative enthalpies indicate a 28.1 kcal/mol destabilization of **8** relative to **7**. The components of the interlocked system tend to adopt a proper geometry for the minimization of steric repulsions and the maximization of supramolecular contacts. However, the strain energy stored in each macrocycle (32.7 kcal/mol) has a more significantly opposite effect, resulting in an increasing of enthalpy value. This higher energy in monomeric macrocycles is due to a severe deformation of the phenothiazine unit (a requirement for the macrocyclization) which can be observed by the dramatic increase of the bend angle (α) of the phenothiazine moiety (37.5°) as compared to the values found in **14a** (18.4°) and *tert*-butyl 2-(10H-phenothiazin-10-yl)acetate (18.2°) (Table 1). The α angles in the macrocycles belonging to [2]catenane **8** are 37.7° and 36.5°, while in the dimeric macrocycle **7** the similar angles exhibit considerably smaller values (16.3°

and 12°, respectively). The destabilization of [2]catenane **8** versus macrocycle **7** is mainly due to the steric constraints required to form the monomeric macrocycles.

The higher energy of [2]catenane **12** as compared to macrocycle **11** is not so dramatic ($\Delta\Delta H^\circ = 6.4$ kcal/mol; however enough high to completely shift a reaction towards the formation of **11**). Dimer macrocycle **11** is very stable (more stable than **7** and **13**), while the monomeric macrocycle **12a** (compared to **14a**) and [2]catenane **12** (compared to **11**) are of higher energy due to the deformation of the phenothiazine units [values of α angles are 26.9° (**12a**) and 29.5°, 24.6° (**12**), Table 1]. These results are in agreement with the lower steric strain ($\Delta\Delta H^\circ = 8.0$ kcal/mol) measured for macrocycle **12a** (component of **12**).

The monomer macrocycle **14a** is the most stable (compared to **8a** and **12a**) because phenothiazine structure is not bent upon macrocyclization (α value is kept around 18°). In the dimer macrocycle **13** the tension in the phenothiazine units is quite low (α angles = 19° and 21.8°), while in the corresponding [2]catenane a high increase of the deformation (α angles = 26.1° and 27°) of the heterocycles is observed (Table 1).

These modifications are required to interlock the macrocycles into the catenane **14** less stable than macrocycle **13** with about 12 kcal/mol. In all cases the stability of the monomer is lower than the stability of the dimer (*e.g.* for monomer macrocycle **14a** and dimer macrocycle **13** the calculations [$2 \times \Delta H^\circ(\mathbf{14a}) - \Delta H^\circ(\mathbf{13}) = 28.8$ kcal/mol indicate a consistent destabilization of the monomer).

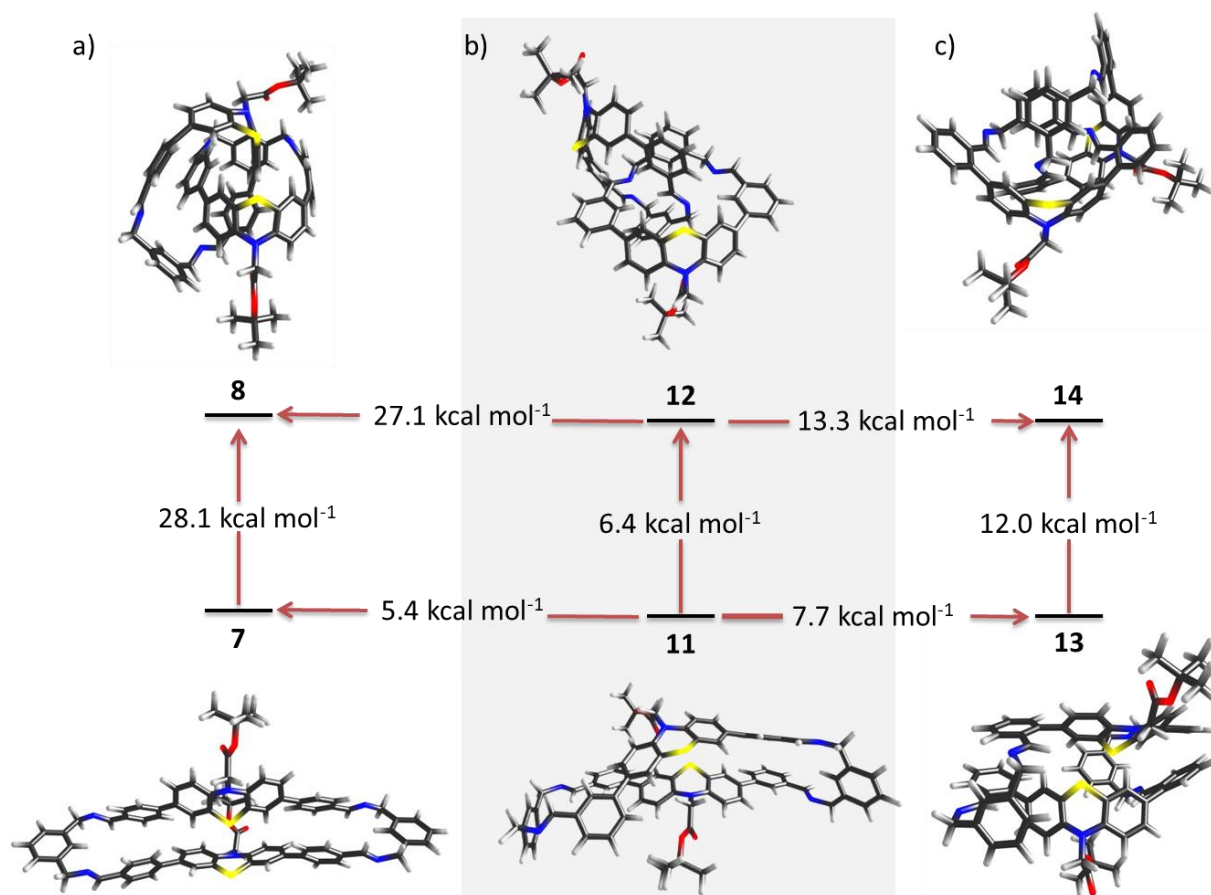
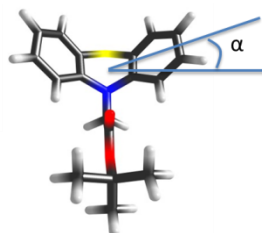


Fig. 4 – Macrocycle and catenane's equilibrium geometries and their relative enthalpies in the case of *para*- (a), *meta*- (b) and *ortho*- (c) formylphenyl substituted phenothiazine moiety. Each arrow indicates the sense of the enthalpy increase.

Table 1

Bend angles (α) in phenothiazine moieties in dimer macrocycles (7, 11, 13), their analog [2]catenanes (8, 12, 14) and in monomeric macrocycles (8a, 12a, 14a)

Name	α (°)	
tert-butyl 2-(10H-phenothiazin-10-yl)acetate	18.2	
7	16.3	12.0
8	37.7	36.5
8a	37.5	
11	18.0	17.0
12	29.5	24.6
12a	26.9	
13	21.8	19.0
14	27.1	26.0
14a	18.4	



EXPERIMENTAL PART

General experimental data. ^1H and ^{13}C NMR spectra were recorded at room temperature (*rt*) on a Bruker Avance 400 spectrometer. 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. Reverse-phase (RP)-HPLC analyses were carried out on a Thermo Scientific Accela 1250 HPLC system, equipped with UV detection and coupled to MS, using an analytical Hypersil Gold Thermo Scientific (50 x 2.1 mm, 1.9 μm) column and a linear gradient of 35-70% acetonitrile/water (0.1% TFA) for 6 min. The retention time (RT) is given in

minutes. 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. Theoretical calculations were performed using the high-performance computational facility at Babeş-Bolyai University.

Procedure for the synthesis of **6**

To a solution of 3,7-dibromo-10*H*-phenothiazine **5**²⁴ (4 mmol) in dry THF (100 mL) sodium hydride (10 mmol) was added under argon at 0°C and then the reaction mixture was stirred for two more hours in these conditions. Then, a solution containing *tert*-butylbromoacetate (5 mmol) in dry THF (15 mL) was added drop wise and the reaction mixture was stirred at *r.t.* for 48 h. The reaction mixture was filtered through a thin pad of celite and the celite was washed with 30 mL diethylether. The solvents of the combined organic phases were removed *in vacuo* and the residue was chromatographed on silicagel.

Tert-butyl-2'-(3,7-dibromo-10*H*-phenothiazin-10-yl)acetate **6**

White solid, yields: 60% (1.12g), m.p. = 103-104°C, R_f = 0.48 (pentane:ethylacetate = 70:1). ¹H NMR (400 MHz, DMSO-*d*₆), δ (ppm): 1.44 [s, 9H, C(CH₃)₃], 4.55 (s, 2H, 2'-H), 6.60 (d, 2H, *J* = 9.3 Hz, 1-H, 9-H), 7.34 (dd, 2H, *J* = 9.3 Hz, 2.2 Hz, 2-H, 8-H), 7.35 (d, 2H, *J* = 2.2 Hz, 4-H, 6-H); ¹³C NMR (75 MHz, DMSO-*d*₆), δ (ppm): 27.64, 50.38, 81.85, 114.41, 116.73, 123.59, 128.56, 130.24, 142.93, 167.98. HRMS (APCI+): calcd. for C₁₈H₁₇Br₂NO₂S [M]⁺: 470.9310; found: 470.9321.

Procedure for the synthesis of **1**

A mixture of **6** (1 mmol) and (4-formylphenyl)boronic acid and cesium carbonate (6 mmol) in 20 mL of methanol/toluene/water 10/5/5 solution was degassed and maintained under a flow of argon for one hour. Then Pd(PPh₃)₄ (0.1 mmol) was added and the reaction mixture was stirred under argon overnight at 80°C. After cooling at *rt*, toluene (20 mL) was added and the reaction mixture was filtered through a thin pad of celite. The organic phase of the filtrate was separated and the aqueous layer was washed several times with small portions of toluene (3x10 mL). The combined organic phases were washed with aqueous NaOH 5% (3x10 mL) and then with water (3x10 mL). The combined organic layers were dried over anhydrous MgSO₄, the solvent was removed under vacuum and the crude product was chromatographed on silica gel. Dialdehydes **2** and **3** were obtained following similar experimental procedures by Suzuki cross-coupling of **8** and (3-formylphenyl)boronic acid or (2-formylphenyl)boronic acid, respectively.^{8c}

Tert-butyl-2'-[(3,7-bis(4''-formylphenyl)-10*H*-phenothiazin-10-yl)]acetate **1**

Yellow-orange solid, yields: 66% (0.344g), m.p. = 205-206°C, R_f = 0.25 (dichloromethane:pentane = 10:1), ¹H NMR (400 MHz, acetone-*d*₆), δ (ppm): 1.55 [s, 9H, -C(CH₃)₃], 4.67 (s, 2H, 2'-H), 6.92 (d, 2H, *J* = 8.5 Hz, 1-H, 9-H), 7.55 (d, 2H, *J* = 2.2 Hz, 4-H, 6-H), 7.61 (dd, 2H, *J* = 8.5 Hz, 2.2 Hz, 2-H, 8-H), 7.89 (d, 4H, *J* = 8.3 Hz, 2''-H, 6''-H), 7.99 (d, 4H, *J* = 8.3 Hz, 3''-H, 5''-H), 10.07 (s, 2H, -CHO); ¹³C NMR (100 MHz, acetone-*d*₆); δ (ppm): 28.39, 51.91, 83.04, 116.42, 124.05, 126.08, 127.37, 127.64, 130.94, 135.10,

136.35, 145.11, 145.97, 169.01, 192.45. HRMS (APCI+): calcd. for C₃₂H₂₈NO₄S [M+H]⁺: 522.1720; found: 522.1734.

General procedure for the formation of imine macrocycles

Dialdehydes **1**, **2** or **3** (1 mmol) and diamine **4** (1mmol) were dissolved in a mixture of anhydrous THF/methanol = 5/12 (20 mL) and the reaction mixture was heated at 60°C. The reaction was monitored by HPLC-MS (*i.e.* small portion from the reaction mixture were taken at various reaction times and reduced with sodium borohydride prior to HPLC-MS analysis) and stopped when the reaction equilibrium was reached (*i.e.* no changes in products distributions was observed).

General procedure for the imine→amine reduction

NaBH₄ (5eq) was added to a solution of of imine (1 eq.) in a mixture of THF/methanol = 5/12. The reaction mixture was stirred on a cooling bath for two hours at 0°C, and then was allowed to warm to *r.t.* The solvent was removed under *vacuum* and the residue was dissolved in CH₂Cl₂. The organic layer was separated and the aqueous phase was washed with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄, the solvent was removed *in vacuo* and the crude products were investigated and/or separated on HPLC (C₁₈, 30%-70% water (containing 0.1% TFA) / acetonitrile as gradient, with a flow rate of 5mL min⁻¹, and UV detection at 230, 254 and 280 nm).

CONCLUSIONS

In summary, the experimental investigation of the imine formation macrocyclization reactions of phenothiazine dialdehydes **1-3** with diamine **4** revealed the obtaining under thermodynamic control of a unique product. However, 1D and 2D-NMR could not differentiate between [2]catenane and its isomer dimer macrocycle ([2+2] product). The theoretical investigations concerning the competition between the formation of dimer macrocycles and [2]catenanes in the investigated macrocyclization reactions revealed the higher stability of [2+2] macrocycles compared to the possible isomeric [2]catenanes (formed by the interlocking of two [1+1] macrocycles). The higher energy differences between the dimer macrocycle and the corresponding [2]catenane was observed for the products of dialdehyde **1** (*p*-formyl derivative; $\Delta\Delta H^\circ = 28.1$ kcal/mol), while in the other two cases these differences were considerably smaller [products of dialdehyde **3** (*o*-formyl derivative); $\Delta\Delta H^\circ = 12.0$ kcal/mol; products of dialdehyde **2** (*m*-formyl derivative); $\Delta\Delta H^\circ = 6.4$ kcal/mol] but high enough to shift the macrocyclization reactions towards the major formation of the dimer macrocycles.

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REFERENCES

1. a) F. Mietzsch, *Angew. Chem.*, **1954**, *66*, 363–371; b) M. Ionescu and H. Mantsch, *Adv. Heterocycl. Chem.*, **1967**, *8*, 83–113; c) C. Bodea and I. Silberg, *Adv. Heterocycl. Chem.*, **1968**, *9*, 321–460; d) I. A. Silberg, G. Cormos and D. C. Oniciu, *Adv. Heterocycl. Chem.*, **2006**, *90*, 205–237.
2. a) C. Wagner and H.-A. Wagenknecht, *Chem. Eur. J.*, **2005**, *11*, 1871–1876; b) N. Motohashi, M. Kawase, J. Molnár, L. Ferenczy, O. Wesolowska, A. B. Hendrich, M. Bobrowska-Hägerstrand, H. Hägerstrand and K. Michalak, *Drug Res.*, **2003**, *53*, 590–599; c) M. T. Tierney, M. Sykora, S. I. Khan and M. W. Grinstaff, *J. Phys. Chem. B*, **2000**, *104*, 7574–7576; d) M. T. Tierney and M. W. Grinstaff, *J. Org. Chem.*, **2000**, *65*, 5355–5359.
3. a) J. D. Bell, J. F. Blount, O. V. Briscoe and H. C. Freeman, *Chem. Commun. (London)*, **1968**, *24*, 1656–1657; b) D. Pan and D. L. Philips, *J. Phys. Chem. A*, **1999**, *103*, 4737–4743. c) A. Bende, I. Grosu and I. Turcu, *J. Phys. Chem. A*, **2010**, *114*, 12479–12489.
4. a) Y. Liu, J. Li, H. Cao, H. Qu, Z. Chen, Q. Gong, S. Xu and S. Cao, *Polym. Adv. Technol.*, **2006**, *17*, 468–473; b) S.-K. Kim, J.-H. Lee and D.-H. Hwang, *Synth. Met.*, **2005**, *152*, 201–204; c) M. Lapkowski, S. Plewa, A. Stolarczyk, J. Doskocz, J. Soloduchko, J. Cabaj, M. Bartoszek and W. W. Sulkowski, *Electrochim. Acta*, **2008**, *53*, 2545–2552.
5. a) N. Bucci and T. J. J. Müller, *Tetrahedron Lett.*, **2006**, *47*, 8323–8327; b) N. Bucci and T. J. J. Müller, *Tetrahedron Lett.*, **2006**, *47*, 8329–8332; c) T. Klumpp, M. Linsenmann, S. L. Larson, B. R. Limoges, D. Bürssner, E. B. Krissinel, M. Elliott and U. E. Steiner, *J. Am. Chem. Soc.*, **1999**, *121*, 1076–1087; d) P. K. Poddutoori, A. S. D. Sadanayaka, N. Zarrabi, T. Hasobe, O. Ito and A. van der Est, *J. Phys. Chem. A*, **2011**, *115*, 709–717.
6. M. Hauck, J. Schönhaber, A. J. Zuccherro, K. I. Hardcastle, T. J. J. Müller and U. H. F. Bunz, *J. Org. Chem.*, **2007**, *72*, 6714–6725.
7. M. Sailer, A. W. Franz and T. J. J. Müller, *Chem. Eur. J.*, **2008**, *14*, 2602–2614.
8. a) A. W. Franz, Z. Zhou, R. Turdean, A. Wagener, B. Sarkar, M. Hartmann, S. Ernst, W. R. Thiel and T. J. J. Müller, *Eur. J. Org. Chem.*, **2009**, 3895–3905; b) R. Turdean, E. Bogdan, A. Terec, A. Petran, L. Vlase, I. Turcu and I. Grosu, *Centr. Eur. J. Chem.*, **2009**, *7*, 111–117; c) M. I. Rednic, S. Szima, E. Bogdan, N. D. Hädade, A. Terec and I. Grosu, *Rev. Roum. Chim.* **2015**, *60*, 637–642
9. a) L. F. Lindoy, “The Chemistry of Macrocyclic Ligand Complexes”, Cambridge University Press: UK, 1989; b) W.-B. Hu, W.-J. Hu, Y. A. Liu, J.-S. Li, B. Jiang and K. Wen, *Chem. Commun.*, **2016**, *52*, 12130–12142; c) M. Iyoda and H. Shimizu, *Chem. Soc. Rev.*, **2015**, *44*, 6411–6424; d) V. E. Semenov, *J. Incl. Phenom. Macrocycl. Chem.*, **2013**, *77*, 1–22; e) J. J. Christensen, D. J. Eatoughand, R. M. Izatt, *Chem. Rev.*, **2002**, *74*, 351–384.
10. a) J. W. Steed and J. L. Atwood, “Supramolecular Chemistry”, Wiley & Sons: New York, 2009; b) F. Davis and S. Higson, “Macrocycles: Construction, Chemistry and Nanotechnology Applications”, Wiley & Sons: New York, 2011; c) D. Parker, “Macrocyclic Synthesis a Practical Approach”, Oxford University Press, 1996; d) M. I. Rednic, N. D. Hädade, E. Bogdan and I. Grosu, *J. Incl. Phenom. Macrocycl. Chem.*, **2015**, *81*, 263–293.
11. M. C. Florian, I. Grosu, E. Condamine, L. Toupet, Y. Ramondenc, G. Plé and P. Cardinael, *Supramol. Chem.*, **2007**, *19*, 383–392.
12. a) M. Balog, I. Grosu, G. Plé, Y. Ramondenc, E. Condamine and R. Varga, *J. Org. Chem.*, **2004**, *69*, 1337–1345; b) N. Bogdan, I. Grosu, G. Benoît, L. Toupet, Y. Ramondenc, E. Condamine, I. Silaghi Dumitrescu and G. Plé, *Org. Lett.*, **2006**, *8*, 2619–2622.
13. A. Petran, A. Terec, E. Bogdan, A. Soran, E. Lakatos and I. Grosu, *Tetrahedron*, **2014**, *70*, 6803–6809.
14. a) D. Demeter, C. Lar, J. Roncali and I. Grosu, *Tetrahedron Lett.*, **2013**, *54*, 1460–1462; b) D. Demeter, P. Blanchard, I. Grosu and J. Roncali, *J. Incl. Phenom. Macrocycl. Chem.*, **2008**, *61*, 227–239.
15. C. Lar, M. E. Moisă, E. Bogdan, A. Terec, N. D. Hädade, I. Grosu, L. David, C. Paizs, I. G. Grosu, *Tetrahedron Lett.*, **2019**, *60*, 335–340.
16. M. Matache, E. Bogdan and N. D. Hädade, *Chem. Eur. J.*, **2014**, *20*, 2106–2131.
17. A. Diac, M. Matache, I. Grosu and N. D. Hädade, *Adv. Synth. Catal.*, **2018**, *360*, 817–845.
18. K. Caprice, M. Pupier, A. Krueve, C. A. Schalley and F. B. L. Cougnon, *Chem. Sci.*, **2018**, *9*, 1317–1322.
19. A. Pun, D. A. Hanifi, G. Kiel, E. O’Brien and Y. Liu, *Angew. Chem. Int. Ed.*, **2012**, *51*, 13119–13122.
20. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson *et al.*, Gaussian 09, revision E.01, Gaussian, Inc., Wallingford, CT, 2009.
21. S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, **2010**, *132*, no. 154104.
22. A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.*, **1992**, *97*, 2571–2577.
23. S. E. Wheeler, K. N. Houk, P. v. R. Schleyer, W. D. Allen, *J. Am. Chem. Soc.*, **2009**, *131*, 2547–2560.
24. N. Leventis, C. Muguo and C. Sotiriou-Leventis, *Tetrahedron*, **1997**, *53*, 10083–10092.

