Synthesis of four new carboxylic derivatives based on the [1.1.1.1]metacyclophane backbone blocked in 1,3-Alternate conformation

Mir Wais Hosseini, Ekaterina F Chernova, Alexander S Ovsyannikov, Sylvie Ferlay, Svetlana E Solovieva, Igor S Antipin, Alexander I Konovalov, Nathalie Kyritsakas, Mir Wais Hosseini

► To cite this version:

Mir Wais Hosseini, Ekaterina F Chernova, Alexander S Ovsyannikov, Sylvie Ferlay, Svetlana E Solovieva, et al.. Synthesis of four new carboxylic derivatives based on the [1.1.1.1]metacyclophane backbone blocked in 1,3-Alternate conformation. *Tetrahedron Letters*, 2018, 59 (14), pp.1377-1381. 10.1016/j.tetlet.2018.02.060 . hal-02300922

HAL Id: hal-02300922

<https://hal.science/hal-02300922>

Submitted on 26 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis of four new carboxylic derivatives based on the [1.1.1.1]metacyclophane backbone blocked in 1,3-Alternate conformation

Ekaterina F. Chernova^{a,b}, Alexander S. Ovsyannikov^{b,c}, Sylvie Ferlay^{a,*}, Svetlana E. Solovieva^{b,c}, Igor S. Antipin^{b,c}, Alexander I. Konovalov^{b,c}, Nathalie Kyritsakas^a, Mir Wais Hosseini^{a,*}

^a Molecular Tectonics Laboratory, University of Strasbourg, UMR UDS-CNRS 7140, Institut le Bel, 4, rue Blaise Pascal, F-67000 Strasbourg, France

^b Kazan Federal University, Kremlevskaya str.18, 420008, Kazan, Russian Federation

^c A.E. Arbutov Institut of Organic and Physical Chemistry of Kazan Scientific Center of Russian Academy of Science, Arbuzov str. 8., 420008, Kazan, Russian Federation

ARTICLE INFO

ABSTRACT

Article history:

Received

Received in revised form

Accepted

Available online

Four new tetrasubstituted [1.1.1.1]metacyclophanes (**4-7**), that are inherently adopting a 1,3-Alternate conformation, bearing four or eight peripheral carboxylic binding sites, and appended with spacers group (alkyl or phenyl) differing by the flexibility, have been synthesised in high yields. The structures of the obtained compounds have been investigated in solution as well as in the solid state, for three of them, by using single-crystal X-ray analysis.

Keywords:

Carboxylate ligand

1,3-Alternate conformation

Metacyclophane backbone

Ester derivatives

Suzuki coupling

Calix[n]arenes¹ and especially calix[4]arenes and thiacalix[4]arenes,² are macrocyclic units presenting large cavities and flexible conformations. These compounds, as well as calix[4]resorcinarenes,³ composed of four phenolic or resorcinolic units and connected through bridging CH₂ or S groups, have been intensively exploited as molecular receptors in supramolecular chemistry⁴ for binding substrate, for the recognition of different substances and for the transport of neutral molecules or ions.⁵ This class of preorganized backbones offers unlimited possibilities for molecular design through functionalization of the lower and/or upper rims of the macrocyclic backbones. They seem also effective organic ligands for coordination of metallic cations, leading to the formation of clusters⁶ and also extended coordination networks⁷ or well-known MOFs, obtained by bridging inorganic and organic molecular building units through coordination bonds, where the organic units (linkers/bridging-ligands) are often rigid carboxylates, or other organic anions.⁸

In order to restrict the flexibility of calixarene based ligands and enhance their propensity to form extended supramolecular architectures via coordination bonds, one of a possible strategy is based on the appending of methyl groups to the macrocyclic backbone, thus blocking the spontaneous rotation of aryl units around the C-C single bonds in solution, as well as in the solid state. This can be observed while using the mesitylene based [1.1.1.1]metacyclophane (**1**, Figure 1), as a

conformationally preorganized macrocycle, that was synthesized decades ago by condensation of mesitylene in the presence of hard Lewis bases with CH₂Cl₂.⁹ When substituted or not, these compounds, presenting a rigid concave surface, are blocked in the 1,3-Alternate conformation over a wide range of temperature (60°C to 150°C).¹⁰ It is important to note that, for a macrocycle, this blocked conformation is especially well suited for the formation of extended coordination networks of high dimensionalities, through combination with metals, because of the tetrahedral orientation of the terminal binding sites.

An improved synthetic procedure of metacyclophane backbone based on the condensation of mesitylene or its functional derivatives (bromomesitylene or hydroxymesitylene¹¹), in the presence of SnCl₄, with an electrophilic agent like chloromethyl methyl ether, allowed to obtain compound **1** without any functional groups on the macrocyclic backbone (R₁=R₂=R₃=R₄=H, Figure 1 A), tetrachloromethylated compound **2**¹¹ (R₁=R₂=R₃=R₄=CH₂Cl, Figure 1 A) and tetrabromo derivative **3**¹² (R₁=R₂=R₃=R₄=Br, Figure 1 A). The synthesis of all these reported metacyclophanes prompted us to study further modifications of this appealing rigid macrocyclic platform in order to obtain new coordination compounds based on the metacyclophane platform.

Figure 1: **A:** Macrocyclic compounds derived from [1.1.1.1]metacyclophane blocked in 1,3-Alternate conformation; the mesitylene [1.1.1.1]metacyclophane **1**, the tetrachloromethylene **2** and the tetrabromo **3** precursors, together with targeted ligands **4-7** based on [1.1.1.1]metacyclophane and their corresponding ester intermediates **4'**, **6'** and **7'**. **B:** The synthetic strategy used for preparation of targeted ligands **4-7**.

The formation of new coordinating ligands towards transition metals based on [1.1.1.1]metacyclophane derivatives possessing two or four coordinating sites located in an alternate fashion above and below the mean plane of the cyclophane ring, was undertaken essentially by *Hosseini et al.* Disubstituted compounds, with coordinating sites located in *syn* fashion ($R_1=R_2$, $R_3=R_4$, Figure 1 A) containing phenol, thiophenol, methylthio, *p*-methylthiophenyl, *p*-methoxyphenyl groups have been synthesised and characterised in solution as well as in the solid state by X-ray diffraction.¹³ Other disubstituted compounds with N donor coordinating groups like cyano¹³ or pyridyl,^{13,14} imidazolyl or pyrazolyl¹⁵ have also been obtained leading to V-shaped preorganized ligands which have been involved in 1D or 2D coordination networks or metallomacrocycles in the crystalline phase.¹⁶ Furthermore, the synthesis of tetrasubstituted [1.1.1.1]metacyclophane bearing mercapto,¹⁷ thiomethyl,¹⁸ aldehyde,¹⁸ acid,¹⁴ nitro,¹⁴ amino,¹⁴ diphenylphosphanyl¹⁸ or diphenylphosphoryl,¹⁸ bipyridyl and bisquinolinyl¹⁹ groups has also been achieved but no related coordination compounds have been reported. In contrast, the tetrasubstituted [1.1.1.1]metacyclophane appended with N donor coordinating groups such as cyano,²⁰ pyridyl^{18,21} imidazolyl²² and pyrazolyl²³ have been prepared and different coordination compounds (0D-3D) have been generated when the ligands were combined with different metal salts.¹⁶ A less symmetrical tetrasubstituted ligand bearing two sets of coordinating sites, *i.e.* pyridyl and imidazolyl, has also been synthesised together with its corresponding 2D coordination networks.¹⁵

Among the O donor coordinating groups, carboxylate moieties attract lots of interest, because of their high ability to form stable coordination compounds with d and f metal cations. For example, lots of MOFs derivatives are built using carboxylate-based ligands. To the best of our knowledge, only one tetrasubstituted carboxylic acid derivative of [1.1.1.1]metacyclophane has been reported, bearing four carboxylic groups directly attached to the macrocyclic backbone ($R_1=R_2=R_3=R_4=CO_2H$, figure 1A).¹⁸ But

no related coordination compounds have been reported yet, this can be probably due to the inaccessibility of the carboxylate coordinating sites caused by steric hindrances imposed by the vicinal methyl groups.

In order to overcome this, we designed new series of macrocyclic ligands bearing carboxylic groups, and here we report the synthesis and characterization of four new carboxylic ligands based on the [1.1.1.1]metacyclophane platform (compounds **4-7**, Figure 1), inherently blocked in 1,3-Alternate conformation, and differing by the nature of the spacers connecting the carboxylic groups with the macrocyclic backbone (ethyl or phenyl), and also by the number of anchored carboxylic groups. Two different spacers between the [1.1.1.1]metacyclophane backbone and the carboxylic moieties were used: a flexible one (alkyl chain, compounds **4** and **5**) and a rigid one (phenyl unit, compounds **6** and **7**). In addition, **4** was decorated with eight carboxylic groups, derived from the malonic acid, whereas **5-7** bear 4 carboxylic groups.

As already mentioned, the tetrasubstituted compound¹⁸ bearing the carboxylic groups grafted directly on the macrocycle backbone ($R_1=R_2=R_3=R_4=CO_2H$, figure 1) has been synthesized through CO_2 gaseous bubbling in a THF solution containing tetralithiated intermediate ($R_1=R_2=R_3=R_4=Li$, figure 1), that was obtained from bromine/lithium exchange of **3** ($R_1=R_2=R_3=R_4=Br$, figure 1) by reaction with 8 equiv. of *t*BuLi in THF at $-78^\circ C$.¹⁸ In contrast to this method, for the preparation of **4-7** (Figure 1), another synthetic pathway (figure 1 B), based on the coupling of spacers involving an ester group (malonic ester for **4** and **5**, and **6'** and **7'** (figure 1) for **6** and **7**) on the macrocyclic backbone, followed by an hydrolysis in strong basic media of either LiOH or NaOH solutions, was adopted. This method appears very efficient for the high yield formation of macrocyclic new ligands.

As shown in figure 1B, **4** was obtained in two steps starting from condensation between tetrasubstituted chloromethylene based [1.1.1.1]metacyclophane **2** with sodium diethyl malonate affording the tetrasubstituted malonic ester intermediate **4'** (Figure 1) in 48% yield (see experimental section in Supplementary Materials). An hydrolysis of **4'** was achieved with a high yield (85%) using LiOH in a EtOH:H₂O:THF mixture (2:1:2) (see experimental part in Supplementary Materials) leading to **4**. Compound **5** was successfully obtained in a high yield (78%) using a simple acidic decarboxylation of a DMF solution containing **4**.

For preparation of compounds **6** and **7**, a synthetic pathway similar to the one previously described for tetrapyridyl [1.1.1.1]metacyclophane derivative,²¹ was applied, as shown in figure 1 B. The tetraester derivatives **6'** or **7'** (figure 1) were obtained in 60% and 75% yields, respectively, by Suzuki coupling of the *para* or *meta* substituted boronic acid pinacol ester with the tetrabromo derivative **3** using the microwave heating conditions.²⁴ Treatment of **6'** or **7'** with LiOH or NaOH in a EtOH:H₂O:THF mixture led to **6** and **7** with 60 and 75% yields, respectively (see experimental section in Supplementary Materials).

All intermediates **4'**, **6'** and **7'** as well as the targeted compounds **4-7**, were studied and characterized in solution by ¹H/¹³C-NMR spectroscopies, mass spectrometry (ESI or MALDI) and by elemental analysis in the solid state. For targeted compounds **4-7**, additional characterization techniques like ¹³C-NMR spectroscopy and melting point were also performed. As expected, in the case of the tetraester derivative **4'** and tetraacids **4-5**, the proton signals of macrocycle backbone as well as of appended substituents were found to be highly resolved in ¹H NMR spectra, because of fast rotation around the C-C single

bond of alkyl spacers. The number and splitting of proton signals revealed the high symmetrical molecular structure of the obtained compounds, that adopted in *1,3-Alternate* conformation (see experimental section in Supplementary Materials). In contrast, for compounds **6'-7'** and **6-7** bearing phenyl spacers, the closely located *ortho* methyl groups of the metacyclophane backbone constrain the spontaneous rotation of the aromatic substituent around the C-C single bonds, which destroys the molecular symmetry and sophisticates the splitting of the aryl groups, (see ESI).

A similar steric effect caused by two methyl groups located in *ortho*-position was also reported earlier with the tetra 4-pyridyl and *p*-methoxyphenyl derivatives of [1.1.1.1]metacyclophane.¹⁸

In order to investigate the structure of synthesized tetraacids in the solid state, X-ray analysis on single crystals has been performed for **4-6**. Unfortunately, to date all attempts to obtain the single crystals of **7** suitable for X-ray analysis failed. Crystals of compound **4** were obtained upon ether diffusion into DMF solution containing **4** at room temperature, while crystals of **5** were also obtained by ether diffusion into DMF solution, that was preliminarily heated with pyridine. Crystals of compound **6** were obtained upon slow evaporation of a concentrated DMF solution containing **6**. (see experimental section and Crystallographic table S1 in Supplementary Materials).

In agreement with NMR studies in solution, **4-6** display, as expected, the *1,3-Alternate* conformation in the crystalline phase, with the carboxylic groups located in an alternate fashion above and below the main plane of the cyclophane backbone, composed of four bridged mesitylene units (see figure 2).

4 and **5** ligands crystallise in the *C2/c* and *P2₁/c* space groups respectively (monoclinic system) whereas **6** crystallises in a more symmetrical tetragonal system (*P4₂/n* space group) (see Crystallographic table 1). Whereas in the solid state **5** forms solvate with four pyridine molecules, crystals of **4** and **6** contain hydrogen bonded DMF molecules (see figure 2).

For **4-6**, the metrics for the macrocyclic part are close to those observed for the parent [1.1.1.1]metacyclophane^{14a} and will not be detailed here. Relevant bond distances and angles are gathered in table 2, illustrating the formation of the carboxylic moieties on each ligand. For **4-6**, the C-O distance corresponding to the carboxylic acid is varying between 1.180(9) Å for the shortest distance and 1.319(9)Å (see table 2) for the protonated oxygen atoms, in accordance with the presence of carboxylic moieties. As expected, **4-6** present a double settle-like shape which is evidenced by the angle between two opposite mesitylene moieties, varying between 28.4 and 43.8° see table 2). For **6**, presenting an aromatic spacer between the carboxylic ligands and the macrocyclic ring, this angle is less pronounced and is equal to 28.4°.

There is a hydrogen bond between DMF molecules located in the lattice and the carboxylic groups of the macrocyclic ligands for **4** and **6** ($d_{OO} = 2.492(14)$ and $2.605(2)$ respectively). In the case of crystal of **5**, a H-bonding between the pyridine molecule and carboxylic acid moieties with N-O distances varying between $2.623(4)$ and $2.684(4)$ Å, is observed (figure 2).

In addition, for **4** presenting eight carboxylic group, four of these recognise themselves through the well-known 6-members H bonded ring (COO)₂, as shown in figure 2, with O-O distance of $2.636(8)$ and $2.669(7)$ Å. It is interesting to note that in this case the H-bonding between two carboxylic groups belonging to opposite substituents does not influence the value of dihedral

angle between opposite mesitylene moieties of macrocycle backbone.

Figure 2: Solid-state structures of **4-6** showing the *1,3-Alternate* conformation of [1.1.1.1]metacyclophane backbones. Solvents and H atoms, except for the one involved in hydrogen bonds are not presented for clarity. For bond and distances, see text.

Table 2: Relevant bonds and angles for **4-6**.

	4	5	6
d _{CO} (Å)	1.180(9)	1.275(3)	
	1.251(6)	1.295(3)	1.240(4)
	1.279(7)	1.301(4)	1.301(4)
	1.319(9)	1.314(3)	
Dihedral angle between opposite mesitylene moieties (°)	43.2	43.8	28.4

As already stated, although all three ligands possess outside orientated carboxylic moieties and unlike the calix[4]arene or thiocalix[4]arene based carboxylic compounds, no intermolecular H-bonding has been found in the crystalline state. Other crystallization conditions (solvents, in particular) should be investigated in order to obtain stable H-bonded networks based on the tetraacid derivatives of compounds **4-7** in the crystalline phase.

Four new ligands based on the rigid [1.1.1.1]metacyclophane backbone, blocked in *1,3-Alternate* conformation and appended with carboxylic groups were designed. These ligands differ either by 1) the nature of the spacer (alkyl or phenyl) connecting the binding units to the macrocyclic backbone and 2) the number of anchored carboxylic groups alternately located on each side of the macrocyclic unit. Following a very simple but efficient synthetic pathway including the formation of intermediate ester derivatives, all targeted compounds were prepared in high yields and characterized. All obtained tetraacids **4-7** are very attractive to form extended molecular networks in the crystalline phase, using coordination or hydrogen bonds. The ability of these ligands to bind transition or rare-earth metal cations, either in solution or in the solid state are currently under investigations.

Acknowledgments

This work has been financially supported by Russian Foundation for Basic Research project № 16-03-00920 and by subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities (4.1493.2017/4.6 и 4.5151.2017/6.7). We thank French government for Vernadsky

Ph.D. fellowship (E. Chernova). University of Strasbourg, the International Centre for Frontier Research in Chemistry (icFRC), the Labex CSC (ANR-10-LABX- 0026 CSC) within the Investissement d'Avenir program ANR-10-IDEX-0002-02, the CNRS, the Institut Universitaire de France (IUF) are also gratefully acknowledged.

Supplementary Material

Table for X-ray diffraction studies of **4-6** and complete experimental part.

References and notes

- (a) C.D. Gutsche, *Calixarenes Revisited: Monographs in Supramolecular Chemistry, The Royal Society of Chemistry*, **1998**, 6; (b) Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens, *Calixarenes: Kluwer Academic Dordrecht*, **2001**; (c) P. Neri, J. Sessler, M.-X. Wang, *Calixarenes and Beyond, Springer International Publishing*, **2016**.
- (a) H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama, S. Miyano *Tetrahedron Lett.*, **1997**, 38, 3971-3974; (b) H. Akdas, L. Bringel, E. Graf, M. W. Hosseini, G. Mislin, J. Pansanel, A. De Cian, J. Fischer *Tetrahedron Lett.*, **1998**, 39, 2311-2314. Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, 106, 5291-5316.
- (a) A. Bayer *Ber. Dtsch. Chem. Ges.*, **1872**, 5, 25-26; (b) P. Timmerman, W. Verboom, D. N. Reinhoudt, *Tetrahedron*, **1996**, 52, 2663-2704. (c) V. K. Jain and P. H. Kanaiya *Russ. Chem. Rev.*, **2011**, 80, 75-102.
- Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*, 1995, VCH, Weinheim.
- (a) Shinkai, S.; Koreishi, H.; Veda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.*, **1987**, 109, 6371-6376; (b) Arnaud-Neu, F.; Schwing-Weill, M. J.; Ziat, K.; Cremin, S.; Harris, S. J.; McKerver, M. A. *New J. Chem.*, **1991**, 15, 33-37; (c) Stoikov, I. I.; Omran, O. A.; Solovieva, S. E.; Latypov, S. K.; Nikeev, K. M.; Gubaidullin, A. T.; Antipin, I. S.; Konovalov A. I. *Tetrahedron*, **2003**, 59, 1469-1476.
- (a) T. Kajiwara, N. Iki, M. Yamashita *Coord. Chem. Rev.* **2007**, 251, 1734-1746; (b) G. Karotsis, S. J. Teat, W. Wernsdorfer, S. Piligkos, S. J. Dalgarno, E. K. Brechin *Angew. Chem. Int. Ed.* **2009**, 48, 8285-8288; (c) B. S. Creavena, D. F. Donlona, J. McGinley *Coord. Chem. Rev.* **2009**, 253, 893-962; (d) Y. Bi, S. Du, W. Liao *Coord. Chem. Rev.*, **2014**, 276, 61-72.
- A. Ovsyannikov, S. Solovieva, I. Antipin and S. Ferlay *Coord. Chem. Rev.*, **2017**, 352, 151-186.
- (a) G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé and I. Margiolaki, *Science*, 2005, **309**, 2040-2042; (b) J. R. Long and O. M. Yaghi, *Chem. Soc. Rev.*, **2009**, 38, 1213-1214; (c) N. R. C. S. R. Batten, X.-M. Chen, J. Garcia-Martinez, S. Kitagawa, L. Öhrström, M. O'Keeffe, M. P. Suh and J. Reedijk, *Pure Appl. Chem.*, **2013**, 85, 1715-1924; (d) M. Bosch, S. Yuan, W. Rutledge, H.-C. Zhou, *Acc. Chem. Res.*, **2017**, 50, 857-865; (e) L. Li, S. Xiang, S. Cao, J. Zhang, G. Ouyang, L. Chen, C.-Y. Su, *Nature Comm.*, **2013**, 4, 1774-1783.
- (a) J. L. Ballard, W. B. Kay, E.L. Kropa *J. Paint Technol.*, **1966**, 38, 251-277; (b) F. Bottino, G. Montaudo, P. Maravigna, *Ann. Chim.* **1967**, 57, 972-991. (c) T.-T Wu, J. R. Speas, *J. Org. Chem.* **1987**, 52, 2330-2332.
- S. Pappalardo, F. Bottino, G. Ronsisvalle *Phosphorus Sulfur* **1984**, 19, 327-333.
- S. Pappalardo, G. Ferguson, J. F. Gallagher, *J. Org. Chem.* **1992**, 57, 7102-7109.
- C. Klein, E. Graf, M. W. Hosseini, A. De Cian and J. Fischer *Chem. Commun.*, **2000**, 239-240.
- C. Klein, E. Graf, M. W. Hosseini, A. De Cian, N. Kyritsakas-Gruber, *Eur. J. Org. Chem.*, **2003**, 395-399.
- (a) C. Klein, E. Graf, M. W. Hosseini, A. De Cian and N. Kyritsakas-Gruber, *Eur. J. Inorg. Chem.*, **2003**, 1299-1302; (b) C. Klein, E. Graf, M. W. Hosseini and N. Kyritsakas-Gruber, *Transactions ACA*, **2004**, 39, 103-109.
- J. Ehrhart, J.-M. Planeix, N. Kyritsakas-Gruber and M. W. Hosseini *Dalton Trans.*, **2010**, 2137-2146.
- A.S. Ovsyannikov, S. Ferlay, E.F. Chernova, S.E. Solovieva, I.S. Antipin and M.W. Hosseini *Macroheterocycle*, **2017**, 10, 410-420.
- X. Delaigue and M. W. Hosseini, *Tetrahedron Lett.*, **1993**, 34, 8111-8112.
- C. Klein, E. Graf, M. W. Hosseini, A. De Cian and N. Kyritsakas, *Eur. J. Org. Chem.*, **2002**, 802-809.
- C. Klein, E. Graf, M. W. Hosseini and A. De Cian, *Tetrahedron Lett.*, **2000**, 41, 9043-9046.
- a) E. F. Chernova, A. S. Ovsyannikov, S. Ferlay, S. E. Solovieva, I. S. Antipin, A. I. Konovalov, N. Kyritsakas and M. W. Hosseini *Mendeleev Commun.*, **2017**, 27, 260-262.
- a) C. Klein, E. Graf, M. W. Hosseini and A. De Cian *New J. Chem.*, **2001**, 25, 207-209; b) G. Laugel, E. Graf, M. W. Hosseini, J.-M. Planeix and N. Kyritsakas *New J. Chem.*, **2006**, 30, 1340-1346.
- J. Ehrhart, J.-M. Planeix, N. Kyritsakas-Gruber and M. W. Hosseini *Dalton Trans.*, **2009**, 2552-557.
- J. Ehrhart, J.-M. Planeix, N. Kyritsakas-Gruber and M. W. Hosseini *Dalton Trans.*, **2009**, 6309-6314.
- J. Ehrhart, Ph. D., Université Louis Pasteur, **2009**.