



Chloride anion-induced dimer capsule based on a polyfluorinated macrocycle *meta*-WreathArene

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ABSTRACT

[1_n]metacyclophanes are a class of important building blocks for supramolecular assembly of artificial capsules. Herein we present the preparation and properties of a novel polyfluorinated macrocycle *meta*-WreathArene, a C₂-symmetrical [1₄]metacyclophane. Adopting a cone conformation in acetone solution, the macrocycle can form dimer capsules through hydrogen bonds induced by chloride anions. Each dimer capsule consists of two *meta*-WreathArene and two chloride anions, and has been unambiguously characterized both in solution and in solid state.

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The construction of artificial capsules is a rapidly advancing direction in the field of supramolecular self-assembly [1–5]. Among the widely-used building blocks for artificial capsules, macrocycles, especially [1_n]metacyclophanes ([1_n]MCPs) with cone-shaped conformations, have attracted much attention [6–8]. [1_n]MCPs feature neutral macrocyclic backbones composed of methylene-bridged *meta*-phenylenes, where *n* represents the number of arene moieties in the molecular skeleton [9,10]. In the [1_n]MCP family, [1₄]MCPs containing electron-rich arenes, such as calix[4]arene, resorcin[4]arene and pyrogallol[4]arene, are the most studied ones because of their facile synthesis (Fig. 1a) [11–13]. The upper rims of [1₄]MCPs are often functionalized for artificial capsule formation through various assembly mechanisms including hydrogen bonds [14–17], electrostatic interactions [18–21], and metal-ligand coordinations [22–29]. In parallel to these capsule-assembly approaches, although anions have been frequently present in the process of [1_n]MCP-based capsule formation [30–34], literature examples on anion-induced molecular capsules through the assembly of [1_n]MCPs remain limited [35–38].

In addition, Friedel–Crafts-type reactions are predominant methods for the preparations of conventional [1₄]MCPs which re-

quire electron-rich arene subunits on the macrocyclic skeletons [11–17]. We envisioned that the development of efficient synthesis of complementary [1₄]MCPs bearing electron-withdrawing groups would facilitate the discovery of new supramolecular properties. Instead of late-stage functionalizations on the macrocycle rims [39,40], we have recently developed a convergent access to WreathArene, a polyfluorinated [1₆]paracyclophane (Fig. 1b) [41], employing direct C–H activation/coupling reactions to construct its electron-deficient arene scaffold. As our continuing quest to utilize this synthetic approach, here we present the preparation and properties of a novel polyfluorinated [1₄]MCP, *meta*-WreathArene (*mWA*). Prepared through three steps from tetrafluorobenzene, *mWA* can bind chloride anions both in solution and in solid state, and form hydrogen-bonded molecular capsules, each of which contains two macrocycles and two chlorides (Fig. 1c).

The synthesis of *mWA* commenced with Pd-catalyzed C–H activation/coupling [42] between bis(benzyl bromide) **1** and excess 1,2,3,5-tetrafluorobenzene. The resulting polyfluorinated **2** further coupled with **1** to furnish two C(sp²)–C(sp³) bonds, and afforded the cyclized product **3**. Treatment of **3** with BBr₃ smoothly removed the methyl groups to provide *mWA* (Fig. 2a), which were characterized by ¹H, ¹³C and ¹⁹F NMR and high-resolution mass spectrometry (Figs. S7–S10 in Supporting information). In parallel to the hydroxyl-containing *mWA*, its *tert*-butyl and unsubstituted analogues were also obtained successfully following the same syn-

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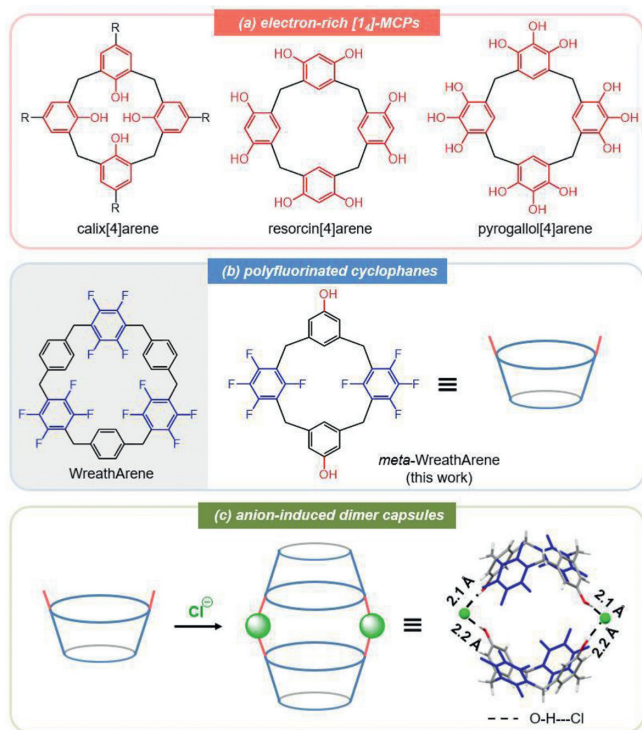


Fig. 1. (a) [14]MCP macrocycles containing electron-rich arenes. (b) Polyfluorinated cyclophanes. (c) Chloride anion-induced capsule formation of *meta*-WreathArene (*mWA*).

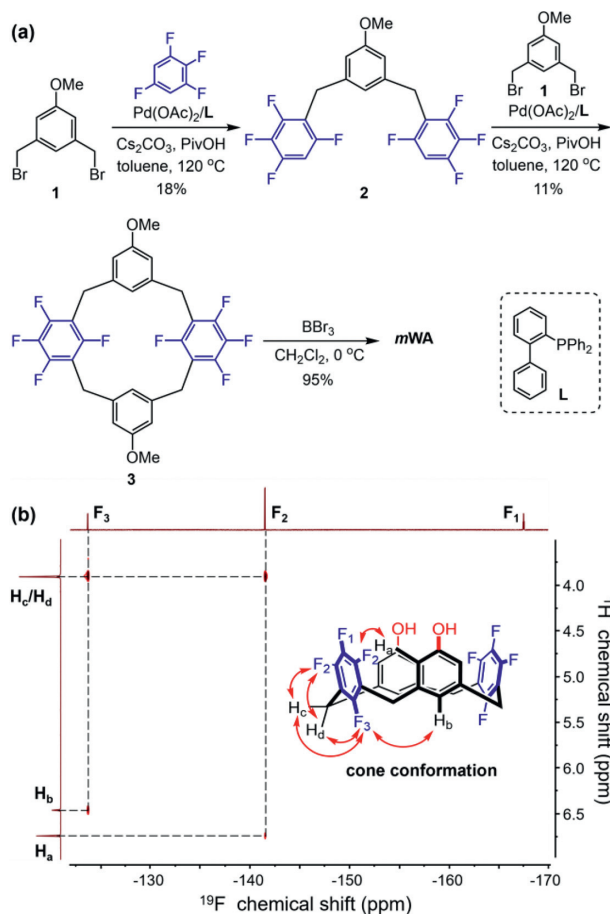


Fig. 2. (a) The synthesis of *mWA*. (b) ^{19}F - ^1H HOESY spectra of *mWA* (4 mmol/L) in acetone- d_6 (600 MHz, 298 K).

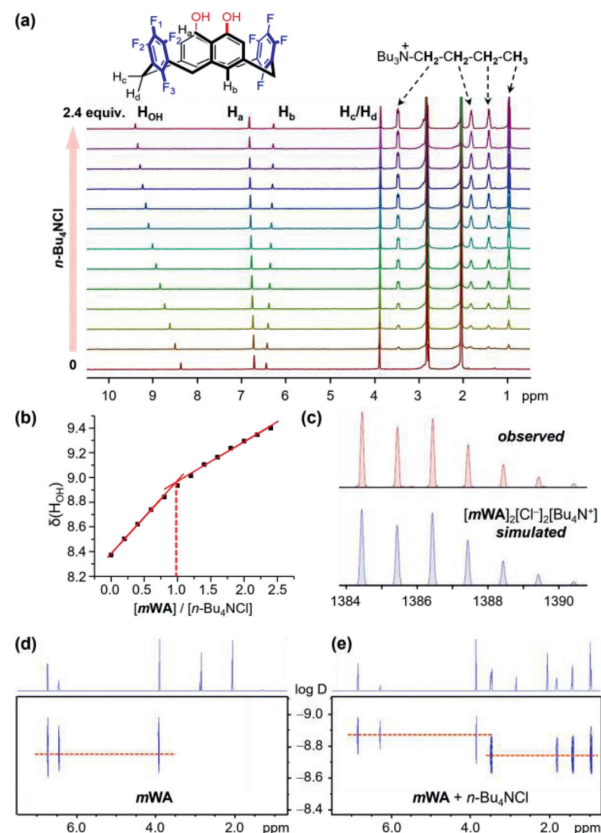


Fig. 3. (a) NMR titration of *mWA* (1 mmol/L) by $n\text{-Bu}_4\text{NCl}$ in acetone- d_6 (400 MHz, 298 K). (b) Mole ratio plot indicating a stoichiometric ratio of 1 for *mWA* and $n\text{-Bu}_4\text{NCl}$. (c) High-resolution mass spectrometry of an acetone solution of equimolar *mWA* and $n\text{-Bu}_4\text{NCl}$. (d) DOSY spectrum of *mWA* (10 mmol/L) in acetone- d_6 (600 MHz, 298 K). (e) DOSY spectrum of *mWA* (10 mmol/L) in the presence of equimolar $n\text{-Bu}_4\text{NCl}$ in acetone- d_6 (600 MHz, 298 K).

thetic strategy, showing the utility of this method for versatile polyfluorinated [14]metacyclophanes (Fig. S11 in Supporting information).

In analogy to calix[4]arene [43,44], *mWA* may have multiple conformations caused by possible rotations of the arene moieties. Accordingly, conformational analyses of *mWA* in solution was conducted using the ^{19}F - ^1H heteronuclear overhauser enhancement spectroscopy (HOESY) which reflects important intramolecular spatial information between the hydrogen and fluorine atoms (Fig. 2b) [45,46]. The HOESY spectra of *mWA* in acetone- d_6 showed evident spatial correlations between the following heteronuclear pairs: F_2 - H_a , F_2 - H_c/H_d (overlapped), F_3 - H_b and F_3 - H_c/H_d (overlapped); whereas correlations for other possible combinations, particularly F_2 - H_b and F_3 - H_a , were absent. These observations suggest that *mWA* should prefer to adopt the cone conformation in acetone solution (Fig. S21 in Supporting information).

Next, the anion binding properties of *mWA* were explored through NMR titration experiments. Upon mixing *mWA* with increasing amount of $n\text{-Bu}_4\text{NCl}$ in acetone- d_6 , the proton NMR signals of *mWA* evidently shifted, suggesting the existence of non-covalent interactions. Further examination revealed that the most significant changes were the downfield-shifted H_{OH} signals. The H_a and H_b signals, which correspond to the *ortho*- and *para*-protons to the hydroxyl group of the same *meta*-phenylene moiety, moderately shifted toward downfield and upfield, respectively (Fig. 3a). In contrast, minimal changes were observed for the H_c and H_d of *mWA* and the butyl protons of the tetraalkylammonium cation. These results indicate that the non-covalent interactions of *mWA*

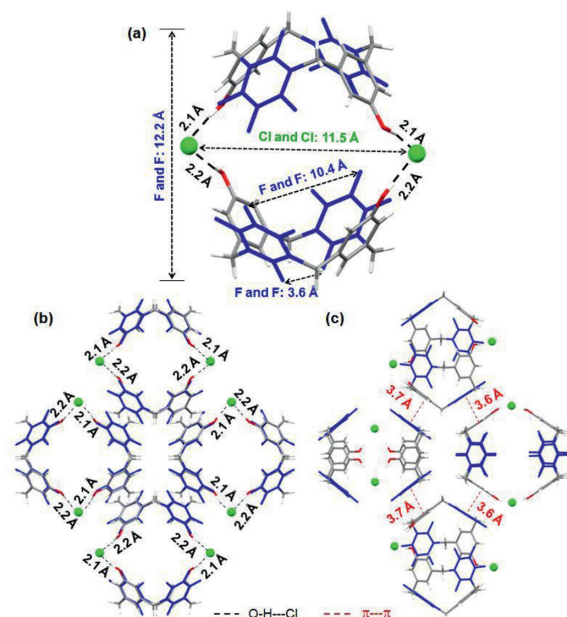


Fig. 4. (a) Crystal structure of chloride-induced dimer capsule of *mWA*. (b, c) Solid-state molecular packing viewed along *c*-axis and $(\bar{1}11)$ -plane, respectively. Solvents and cations were omitted for clarity.

and *n*-Bu₄NCl most likely occur between the hydroxyl groups and chloride anions. Indeed, when the *mWA*'s hydroxyl groups are protected or replaced, the corresponding *mWA* analogues display negligible changes of their proton NMR spectra in the presence of *n*-Bu₄NCl (Fig. S29 in Supporting information). In addition, larger halides (Br⁻ and I⁻) exhibit significantly weakened interactions with *mWA*, and non-halide anions including SCN⁻, NO₃⁻, ClO₄⁻, BF₄⁻ and PF₆⁻ were found inactive under otherwise identical conditions (Figs. S31 and S32 in Supporting information). The interactions between chloride anions and *mWA* remain evident by NMR when the tetrabutylammonium cation was replaced by Et₄N⁺ and BnEt₃N⁺ (Fig. S33 in Supporting information). The results of these control experiments again support the correlations between the supramolecular changes of *mWA* and the effect of chloride anion.

Having identified the chloride binding property of *mWA*, we recorded the molar ratio plot and Job's plots, both of which showed a stoichiometric ratio of 1 for the supramolecular complex consisting of *mWA* and chloride (Fig. 3b and Fig. S27 in Supporting information). Based on the observation of [mWA]₂[Cl⁻]₂[*n*-Bu₄N⁺] anionic species by high-resolution mass spectrometry analysis of an equimolar solution of *mWA* and *n*-Bu₄NCl, the exact stoichiometry was suggested as 2:2 (Fig. 3c and Fig. S28 in Supporting information).

Furthermore, diffusion-ordered NMR spectroscopy (DOSY) analysis was employed to investigate the supramolecular complex formation in solution (Figs. 3d and e) [47]. The DOSY spectrum of *mWA* in acetone-*d*₆ at 298 K displayed a single band of signals with a diffusion coefficient (*D*) of 1.77×10^{-9} m²/s. According to the spherical model of Stokes–Einstein equation, the hydrodynamic diameter of *mWA* was calculated as 0.81 nm (Table S1 in Supporting information), matching the size of a single macrocycle observed in the crystal structure (Fig. 4a). In comparison, DOSY signals of *mWA* in the presence of equimolar *n*-Bu₄NCl exhibited two distinct sets of bands corresponding to the protons of *mWA* and *n*-Bu₄N⁺, respectively. In addition, the *n*-Bu₄N⁺ signals also changed upon mixing with *mWA*, suggesting that the tetraalkylammonium cations are not fully encapsulated in, but may form tight ion pairs with the supramolecular complexes in solution [35–38].

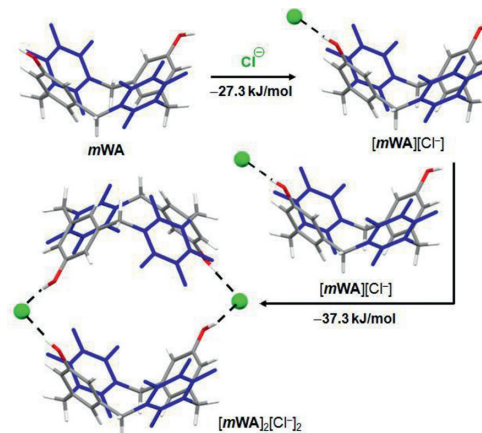


Fig. 5. Theoretical calculation of chloride-induced dimer capsule formation of *mWA*.

In particular, the diffusion coefficient of *mWA* in the presence of equimolar *n*-Bu₄NCl decreased to 1.32×10^{-9} m²/s, which is convertible to an estimated hydrodynamic diameter of 1.1 nm (Fig. 4a). The enhanced diameter value suggests the chloride-induced formation of supramolecular aggregates, consistent with the aforementioned 2:2 stoichiometry for *mWA* and chloride anion.

Further evidence for the 2:2 *mWA*–chloride supramolecular aggregate was obtained through solid-state crystal structure. After extensive attempts, suitable single crystals containing tetragonal unit cells were grown by slow diffusion of diethyl ether into a solution of *mWA* and excess Et₄NCl in mixed solvents of acetone and acetonitrile (Fig. 4). Consistent with the solution-based characterizations (NMR titration, mass spectrometry, and DOSY), the crystal structure unambiguously displays a molecular capsule of two cone-shaped *mWA* macrocycles connected by two chloride anions (Fig. 4a). The upper-rims of the two *mWA* macrocycles face each other, and each chloride interacts with two hydroxyl groups through hydrogen-bonds with an average O–H...Cl distance of 2.1 Å [48–52]. Matching the calculated diameter value based on DOSY data of Fig. 3e, the dimensions of the capsule in the solid state are measured as 11.5 Å in width (distance between the chlorides), 10.4 Å in depth (distance between the fluorine atoms at the upper-rim of the same macrocycle), and 12.2 Å in height (distance between the top and bottom fluorine atoms). Inspection of the molecular packing revealed that the capsules adopt two orthogonal orientations in the crystal structure. Through inter-capsule π...π interactions [53,54], each fluorinated arene is always facing an unfluorinated arene of another macrocycle to stabilize dense packing (Figs. 4b and c). In addition, the disordered Et₄N⁺ cations are located at the capsule cavities as well as the vacancies surrounded by capsules in the crystal structure (Figs. S39 and S40 in Supporting information).

To further assess the chloride anion-induced dimer capsule formation of *mWA*, the geometries of *mWA* and its dimer capsule were optimized by DFT calculations (Fig. 5). The calculated energies indicate that the strength of a single O–H...Cl hydrogen-bond is 27.3 kJ/mol [55], based on the formation of a 1:1 *mWA*–chloride intermediate. In addition, the capsule assembly from two 1:1 *mWA*–chloride intermediates ([mWA][Cl⁻]) leads to an estimated 37.3 kJ/mol energy downhill. Thus, the overall capsule formation is thermodynamically favoured with -91.9 kJ/mol [equals to $(-27.3) \times 2 + (-37.3)$] relative to two molecules of *mWA* and two chloride anions, which matches with the experimental observations in solution and in crystalline state.

In conclusion, we have synthesized a polyfluorinated cyclophane *mWA* via direct C–H activation/coupling reactions. The notable feature of this C₂-symmetrical macrocycle is the chloride

anion-induced formation of a 2:2 dimer capsule which were characterized both in solution and in solid state. Further investigation on the development of anion-binding arene-based macrocycles is ongoing in our laboratory, and will be reported in due course.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2022.108042.

References

- [1] J. Rebek Jr., *Angew. Chem. Int. Ed.* 44 (2005) 2068–2078.
- [2] S. Zarra, D.M. Wood, D.A. Roberts, J.R. Nitschke, *Chem. Soc. Rev.* 44 (2015) 419–432.
- [3] J. Gaitzsch, X. Huang, B. Voit, *Chem. Rev.* 116 (2016) 1053–1093.
- [4] Y. Ferrand, I. Huc, *Acc. Chem. Res.* 51 (2018) 970–977.
- [5] M. Yokoya, S. Kimura, M. Yamanaka, *Chem. Eur. J.* 27 (2021) 5601–5614.
- [6] J. Rebek Jr., *Chem. Commun.* 8 (2000) 637–643.
- [7] F. Hof, S.L. Craig, C. Nuckolls, J. Rebek Jr., *Angew. Chem. Int. Ed.* 41 (2002) 1488–1508.
- [8] K. Wang, E.C. Yang, X.J. Zhao, H.X. Dou, Y. Liu, *Cryst. Growth Des.* 14 (2014) 4631–4639.
- [9] V. Böhmer, *Angew. Chem. Int. Ed.* 34 (1995) 713–745.
- [10] Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens, *Calixarenes*, Kluwer Academic Publishers, Dordrecht, 2001.
- [11] A. Ikeda, S. Shinkai, *Chem. Rev.* 97 (1997) 1713–1734.
- [12] Z. Liu, S.K.M. Nalluri, J.F. Stoddart, *Chem. Soc. Rev.* 46 (2017) 2459–2478.
- [13] J.L. Liu, M. Sun, Y.H. Shi, et al., *J. Incl. Phenom. Macro. Chem.* 102 (2022) 201–233.
- [14] R.E. Brewster, S.B. Shuker, *J. Am. Chem. Soc.* 124 (2002) 7902–7903.
- [15] L. Adriaenssens, P. Ballester, *Chem. Soc. Rev.* 42 (2013) 3261–3277.
- [16] G. Aragay, P. Ballester, *H-Bonding Assembly of Macrocycles*, Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2016.
- [17] S. Merget, L. Catti, S. Zev, D.T. Major, N. Trapp, *Chem. Eur. J.* 27 (2021) 4447–4453.
- [18] F. Corbellini, R. Fiammengo, P. Timmerman, et al., *J. Am. Chem. Soc.* 124 (2002) 6569–6575.
- [19] R. Zadmand, T. Schrader, T. Grawe, A. Kraft, *Org. Lett.* 4 (2002) 1687–1690.
- [20] S.M. Birosa, J. Rebek Jr., *Chem. Soc. Rev.* 36 (2007) 93–104.
- [21] M.A. Beatty, F. Hof, *Chem. Soc. Rev.* 50 (2021) 4812–4832.
- [22] M. Johnston, M.J. Larter, *Supramol. Chem.* 17 (2005) 595–607.
- [23] S.J. Dalgarno, N.P. Power, J.L. Atwood, *Coord. Chem. Rev.* 252 (2008) 825–841.
- [24] P.P. Cholewa, S.J. Dalgarno, *CrystEngComm* 16 (2014) 3655–3666.
- [25] Y. Voloshin, I. Belaya, R. Krämer, *The Encapsulation Phenomenon: Synthesis, Reactivity and Applications of Caged Ions and Molecules*, Springer International Publishing, Switzerland, 2016.
- [26] M. Morie, R. Sekiya, T. Haino, *Chem. Asian J.* 16 (2021) 49–55.
- [27] K. Sikligar, S.P. Kelley, L. Shao, G.A. Baker, J.L. Atwood, *Cryst. Growth Des.* 21 (2021) 1891–1897.
- [28] L. Shao, X. Hu, K. Sikligar, G.A. Baker, J.L. Atwood, *Acc. Chem. Res.* 54 (2021) 3191–3203.
- [29] X. Fan, L. Yuan, J. Zhang, L. Zhang, *Chin. Chem. Lett.* 32 (2021) 2415–2418.
- [30] H. Mansikkamäki, M. Nissinen, K. Rissanen, *Chem. Commun.* 17 (2002) 1902–1903.
- [31] J.L. Atwood, A. Szumna, J. Supramol. Chem. 2 (2002) 479–482.
- [32] H. Mansikkamäki, M. Nissinen, C.A. Schalley, K. Rissanen, *New J. Chem.* 27 (2003) 88–97.
- [33] H. Mansikkamäki, M. Nissinen, K. Rissanen, *CrystEngComm* 7 (2005) 519–526.
- [34] A. Aman, M. Luostarinen, K. Rissanen, M. Nissinen, *New J. Chem.* 31 (2007) 169–177.
- [35] C. Gaeta, C. Talotta, P.D. Sala, et al., *J. Org. Chem.* 79 (2014) 3704–3708.
- [36] M. Chwastek, P. Cmoch, A. Szumna, *Angew. Chem. Int. Ed.* 60 (2021) 4540–4544.
- [37] M. Chwastek, P. Cmoch, A. Szumna, *J. Am. Chem. Soc.* 144 (2022) 5350–5358.
- [38] E.R. Abdurakhmanova, P. Cmoch, A. Szumna, *Org. Biomol. Chem.* 20 (2022) 5095–5103.
- [39] S.K. Menon, M. Sewani, *Rev. Anal. Chem.* 25 (2006) 49–82.
- [40] P. Hu, H. Cui, W. Huang, W. Guo, *Chem. Asian J.* 15 (2020) 2952–2959.
- [41] S. Niu, L.L. Mao, H. Xiao, et al., *Chin. Chem. Lett.* 33 (2022) 1970–1974.
- [42] S. Fan, C.Y. He, X. Zhang, *Chem. Commun.* 46 (2010) 4926–4928.
- [43] C.D. Gutsche, L.J. Bauer, *J. Am. Chem. Soc.* 107 (1985) 6052–6059.
- [44] R. Rathore, S.V. Lindeman, K.S. Rao, D. Sun, J.K. Kochi, *Angew. Chem. Int. Ed.* 39 (2000) 2123–2127.
- [45] D. Neuhaus, M.P. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis* 2nd ed., Wiley-VCH, New York, 2000.
- [46] P.S. Pregosin, P.G.A. Kumar, I. Fernández, *Chem. Rev.* 105 (2005) 2977–2998.
- [47] A. Macchioni, G. Ciancaleoni, C. Zuccaccia, D. Zuccaccia, *Chem. Soc. Rev.* 37 (2008) 479–489.
- [48] V. Balamurugan, J. Mukherjee, M.S. Hundal, R. Mukherjee, *Struct. Chem.* 18 (2007) 133–144.
- [49] Y.R. Zhong, M.L. Cao, H.J. Mo, B.H. Ye, *Cryst. Growth Des.* 8 (2008) 2282–2290.
- [50] J. Zhao, D. Yang, X.J. Yang, B. Wu, *Coord. Chem. Rev.* 378 (2019) 415–444.
- [51] S.A. Boer, E.M. Foyle, C.M. Thomas, N.G. White, *Chem. Soc. Rev.* 48 (2019) 2596–2614.
- [52] U. Manna, G. Das, *Coord. Chem. Rev.* 427 (2021) 213547.
- [53] L.M. Salonen, M. Ellermann, F. Diederich, *Angew. Chem. Int. Ed.* 50 (2011) 4808–4842.
- [54] C.R. Martinez, B.L. Iverson, *Chem. Sci.* 3 (2012) 2191–2201.
- [55] W. Caminati, S. Melandri, A. Maris, P. Ottaviani, *Angew. Chem. Int. Ed.* 45 (2006) 2438–2442.