Optical readout of controlled monomer-dimer self-assembly

Journal Name

COMMUNICATION

Optical Readout of Controlled Monomer-Dimer Self-Assembly

Pavel A. Tarakanov,*[ab] Ekaterina N. Tarakanova,[a] Pavel V. Dorovatovskii,[c] Yan V. Zubavichus,[c] Victor N. Khrustalev,[d] Stanislav A. Trashin,[ae] Karolien De Wael,[e] Margarita E. Neganova,[a] Denis V. Mischenko,[b] Jonathan L. Sessler,[f] Pavel A. Stuzhin,[g] Victor E. Pushkarev*[ah] and Larisa G. Tomilova[ah]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

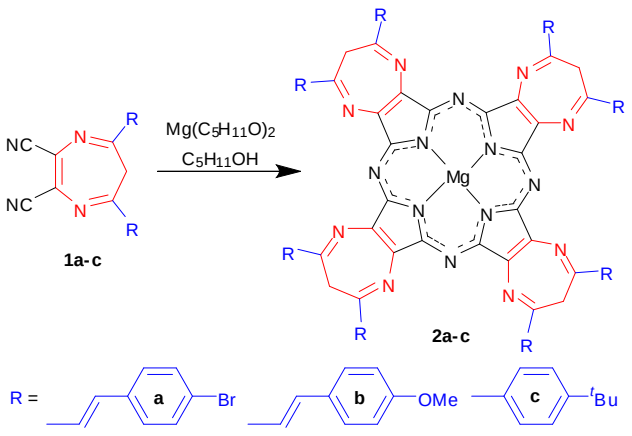
www.rsc.org/

5,7-Substituted 1,4-diazepinoporphyrazine magnesium(II) complexes were synthesized via Mg(II)-alkoxide templated macrocyclization. A single crystal growth synchrotron diffraction analysis permitted what is to our knowledge the first structural characterization of a 1,4-diazepinoporphyrazine. It exists as a dimer in the solid state. *In silico* calculations supported by solution phase spectral studies involving a series of representative derivatives, provided insights into the factors governing dimerization of 1,4-diazepinoporphyrazines. The present 1,4-diazepinoporphyrazines serve as useful probes for understanding the determinants that guide dimer-monomer equilibria and the self-assembly of phthalocyanine derivatives.

All biological systems are based on molecules demonstrating a propensity to undergo self-assembly. Control over the underlying processes through external stimuli is a hallmark of living systems and is one feature that differentiates them from inanimate objects that might self-assemble in complex, but ultimately static patterns. A challenge for the chemist is to create systems whose aggregation properties can be easily controlled through judicious application of inputs, such as solvent, heat, ion, and the like.[1] Even more difficult is the creation of simple artificial systems whose controlled self-assembly can be monitored in real time by optical means. Here we report a diazepine-containing macroheterocycle, namely the three 5,7-substituted 1,4-diazepinoporphyrazine magnesium(II) complexes **2a-c** (Scheme 1) for which the dimer-monomer equilibrium and associated spectral features depends on the substituent pattern and solution phase conditions. While the dimeric form dominates under most conditions, in the presence of DMSO, particularly DMSO containing a F^- anion source, the monomeric form is obtained. Tetrapyrrole macrocycles are useful building blocks for the construction of self-assembled supramolecular architectures.[2, 3] Considerable effort has been devoted to understanding the non-covalent interactions that drive the underlying self-assembly processes.[4] However, much less effort has been devoted to the search for new oligopyrrolic structures that support controlled self-assembly. 1,4-Diazepinoporphyrazines, first reported by Ercolani and co-workers in 1999,[5] could represent such a class of materials. Their spectral properties are atypical for phthalocyanine derivatives.[6-10] This led to suggestions that these systems exist in the form of stable, self-assembled dimers.[11-13] Based on a combination of quantum-chemical calculations and natural bond orbital (NBO) analyses we have proposed that intermolecular hydrogen bonding supports dimer formation in the case of the metal-free

[a] Institute of Physiologically Active Compounds, Russian Academy of Sciences, 1 Severny Proezd, 142432 Chernogolovka, Moscow Region, Russian Federation. E-mails: tarakanov_pa@ipac.ac.ru; pushkarev@ipac.ac.ru
[b] Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 Academician Semenov Avenue, 142432 Chernogolovka, Moscow Region, Russian Federation
[c] National Research Centre "Kurchatov Institute", 1 Akad. Kurchatov Sq., Moscow 123182, Russia.
[d] Inorganic Chemistry Department, Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklay St., Moscow 117198, Russian Federation.
[e] AXES Research Group, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerpen, Belgium.
[f] Department of Chemistry, Shanghai University, Shanghai 200444, China
[g] Research Institute of Macroheterocycles, Ivanovo State University of Chemistry and Technology, 153000 Ivanovo, Russia
[h] Department of Chemistry, M.V. Lomonosov Moscow State University, 1 Leninskie Gory, 119991 Moscow, Russian Federation

† Electronic Supplementary Information (ESI) available: X-ray crystallographic data (CIF); experimental details, 1D and 2D NMR spectra, and additional crystallographic, spectral, electrochemical, and biological data (PDF). CCDC 1489687. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthesis of magnesium complexes **2a-c**.

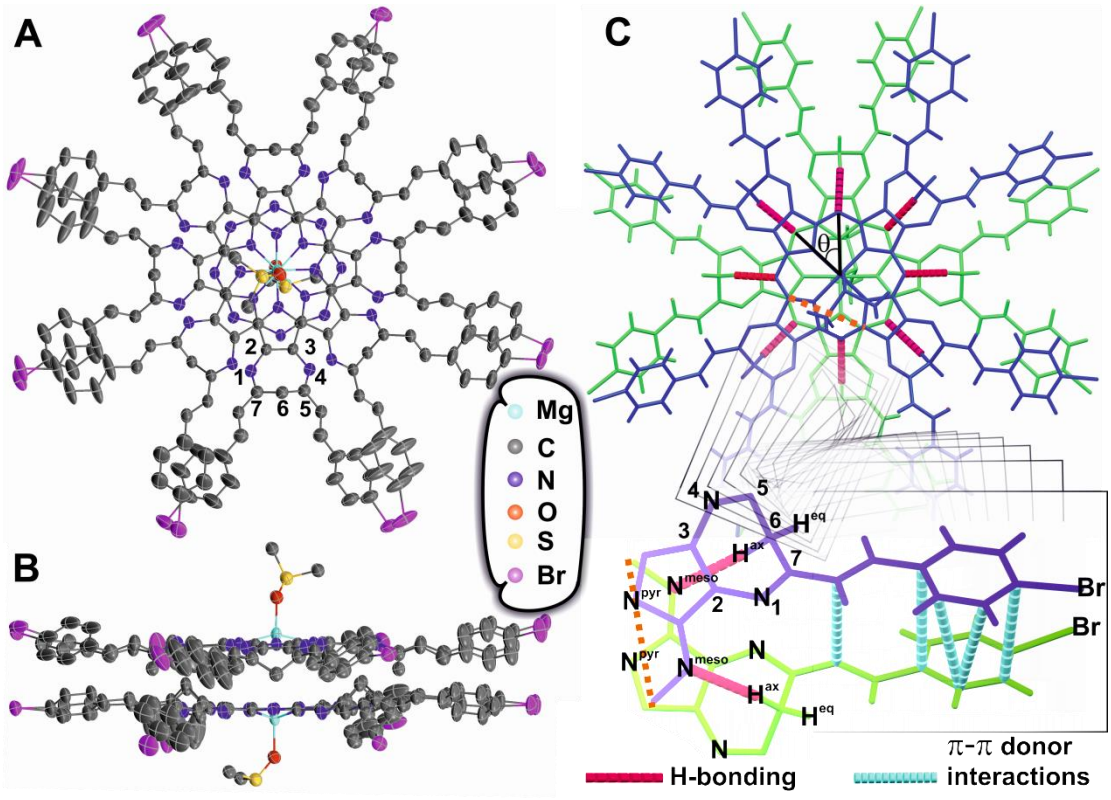


Figure 1. Molecular structure of **2a**. Ellipsoid style presentation: A, B – top and front view, respectively (hydrogen atoms are omitted for clarity). Capped sticks style presentation with color by symmetry equivalence, hydrogen bonding and short contacts options were applied: C – top view.

tetrakis(5,7-bis(4-*tert*-butylphenyl)-6*H*-1,4-diazepino)[2,3-*b,g,l,q*]porphyrazine and the corresponding lanthanide complexes.[14] However, no X-ray diffraction structural data was put forward in support of these suggestions. Thus, the exact nature of the intermolecular interactions in diazepinoporphyrazines remains unclear. Also recondite is how various environmental inputs might serve to influence the monomer-dimer self-assembly process and how, if at all, the inter-macrocycle interactions might be monitored in solution.

To explore the above issues, we have prepared three related diazepinoporphyrazine magnesium(II) complexes, namely **2a**-**c** that differ in the nature of the substituents. These complexes were obtained via the Linstead macrocyclization of the corresponding 1,4-diazepinodicarbonitriles **1** (Scheme 1), which were prepared according to previously described procedures.[11, 12, 15] A lower yield was seen in the case of **2a** as compared to **2b**. This reduction in yield is ascribed to the fact that the alkenyl substituents present in **1a** are relatively weak electron donors.[15] As a result, side reactions, such as nucleophilic substitution of the cyano group, are favored under the Linstead macrocyclization conditions.

Recent studies involving a series of 5,7-bis(2'-arylethenyl)-6*H*-1,4-diazepine-2,3-dicarbonitriles revealed that these compounds can exist in different conformational states as the result of rotation of the arylalkenyl substituents on the 1,4-diazepine moieties.[15] However, by means of gel permeation chromatography we were able to separate and characterize both **2a** and **2b** in conformationally and configurationally pure form as inferred from NMR and UV-vis spectral studies (cf. Supporting Information). Complex **2a** yielded single crystals suitable for synchrotron radiation-based single-crystal X-ray diffraction (SR-XRD) analysis, thus allowing the structure to be confirmed unambiguously. To our knowledge, the resulting structure (Figure 1) is the first to be reported for a diazepine-containing phthalocyanine analogue.

The SR-XRD data for **2a** revealed that the unit cell contains four symmetry-related molecules, which exist in the form of a pair of dimers (Figure S11). These dimers are characterized by a stacked coaxial (C_4) disposition of the two constituent macrocycles, which are rotated by θ = 45° with respect to one another (Figure 1C). The self-assembly and molecular ordering seen in the solid state is ascribed to the presence of a number of intermolecular interactions between the individual molecules of **2a**. This ordering is manifest in the conformational state of the 1,4-diazepine heterocycles, which adopt boat conformations that are flattened at the "stern" but tucked into an adjacent macrocycle at the "prow" (Figures 1B and S12). The orientation of the 1,4-diazepine heterocycles within the dimer is ascribed to the presence of intermolecular hydrogen bonding interactions, denoted as C-H^{ax}…N^{meso}, that involve axial diastereotopic protons at the C6 position of the diazepine rings (H^{ax}) and *meso*-nitrogen atoms (N^{meso}) of the adjacent macrocycle (Figure 1A, C). These hydrogen bonds are characterized by an average distance (DH...A) of 2.759 Å and an average angle (D-H...A) of 169°. Based on these metric parameters, the interactions are considered to be strong.

The porphyrazine macrocycles (as defined by the pyrrole nitrogen atoms) are nearly planar. They deviate from a strict

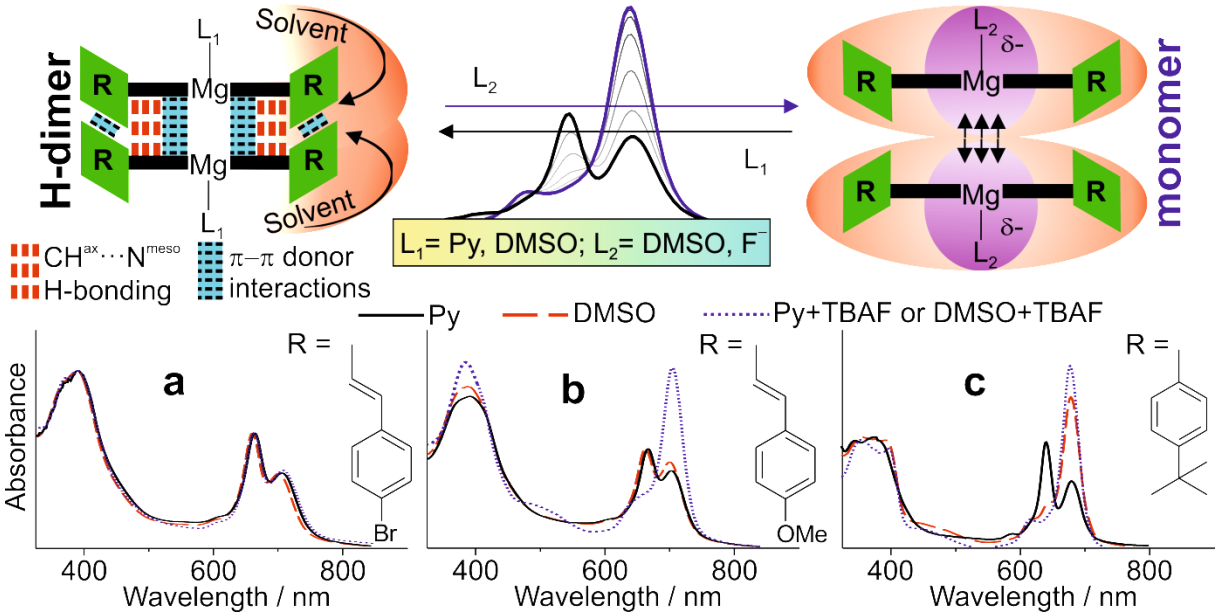


Figure 2. Schematic view of the factors governing the self-assembly of tetrakis-1,4-diazepinoporphyrazinato magnesium complexes **2a-c** in solution. The effect of substituents (a–c) and axial ligands on the dimer–monomer equilibrium is specifically highlighted. Also shown (panels a-c) are the spectral changes resulting from changes in the peripheral substituents and solvent conditions. Py = pyridine. C_M(**2a-c**) = 2–5 μM. C_M(TBAF) = 500 μM.

parallel orientation by only 1.1°, and are separated by a distance of 3.47 Å. The short distance is expected to support strong exciton coupling as the result of efficient π-π donor-acceptor interactions between the porphyrazine cores of the adjacent macrocycles (Figure 1C). In the case of **2a** the peripheral ethylene subunits and aryl moieties were found to be separated by distances in the range of 3.53–3.77 Å and 3.53–3.79 Å, respectively. Although consistent with π-π donor-acceptor interactions, the associated planes (as defined by the relevant sp^2 hybridized atoms) deviate from planarity by 1.2–16.6° and 4.6–19.3° in the case of the ethylene and aryl moieties, respectively. These latter deviations could reflect the presence of destabilizing steric interactions. We thus consider it likely that the dimerization seen in the solid state is primarily driven by hydrogen bonding interactions but that the nature and extent of dimerization could be modulated by the specific choice of peripheral diazepine substituents.

Typically, 1,4-diazepinoporphyrazines dimerize so efficiently, that they are isolated in dimeric form during synthesis. Moreover, the resulting dimers generally remain stable when subject to both dilution and heating. The stability of the dimeric form has prevented identification of the form of the product in early studies.[5] In the case of the present tetrakis-1,4-diazepinoporphyrazinato magnesium complexes it was anticipated that the dimer-monomer equilibrium could be perturbed and the optical spectrum would vary as a consequence. The UV-Vis spectra recorded for pyridine solutions of complexes **2a–c** are characterized by a split Q-band that is ascribed to exciton interactions between the chromophores that make up the dimers (Figure **2a-c**, solid line). A putative monomer form would be expected to lack this feature. Thus, changes in the Q-band could serve as a useful gauge of whether or not the extent of dimerization was being modified through changes in substituent features.

Initial support for the proposition the nature of the peripheral substituents, particularly their steric effect, could influence the stability of the dimer came from quantum-chemical studies carried out in the gas phase.[14] The inferences drawn from the SR-XRD analysis discussed above led us to consider it likely that increases in the size of the 1,4-diazepine heterocycle units could enhance steric strain and reduce the inherent complementarity between the central porphyrazine macrocycles, as well as the ring-to-ring proximity essential for effective hydrogen bonding. Thus, three related Mg(II) complexes, bearing different substituents at the 1,4-diazepine moiety (i.e., the 4-bromophenylethenyl, 4-methoxyphenylethenyl, and 4-*tert*-butylphenyl derivatives **2a–c**, respectively) were studied. The effect of solvent was also analyzed. In DMSO, which can effectively solvate the hydrogen bonding centers (Figure **2a–c**, dashed line), extensive dissociation occurs in the case of the 4-*tert*-butylphenyl substituted derivative (**2c**). Based on a spectral analysis, the extent of dissociation reaches 98% when the concentration of **2c** is 3 μM. Under the same conditions, dimer **2b** is roughly 14% dissociated, whereas there is no evidence of appreciable dissociation in the case of **2a** (Figures S13-14).

Axial coordination of agents bearing a negative charge and capable of donating electron density to the complex according to the scheme shown in Figure 2 represents another means of potentially promoting the break up of the dimers. In the case of the 4-methoxyphenylethenyl substituted complex (**2b**) essentially complete dissociation is seen in DMSO when 500 μM of F^- is added (as the tetrabutylammonium salt). In pyridine, 100 μM of F^- is required for the full dissociation of **2b**. The following addition of $FeBr_3$ to both solutions leads to reverse binding of F^- resulting in a complete recovery of the initial dimeric structure. This is also true for the 4-*tert*-butylphenyl substituted complex **2c** (Figures S15-35). However,

in the case of the 4-bromophenylethenyl substituted derivative **2a**, the dimer structure remains stable even in the presence of added fluoride anion (Figure **2a**–**c**, dotted line). The stability of the dimeric form of **2a** under these conditions is rationalized in terms of a complementarity between pairs of peripheral substituents and strong intermolecular π-π donor-acceptor interactions.

The electrochemical properties of **2a** and **2b** were investigated in pyridine containing 0.1 M [TBA][BF_4] as the supporting electrolyte. Under these conditions the complexes exist in their dimeric forms as illustrated in Figures 2 and S36. One broad irreversible oxidation peak was observed at a potential of 0.804 and 0.777 V (*vs.* SCE) for **2a** and **2b**, respectively. Reductive scans revealed more complex electrochemistry; up to five reversible redox processes were observed (Table S1, Figure S37). Such behavior is consistent with the proposed dimeric nature of the complexes, which can lead to a splitting of redox transitions similar to what is seen in the case of double-decker sandwich complexes stabilized by a central lanthanide cation.[14, 16, 17]

In order to assess prospects for applying 1,4-diazepinoporphyrazines as environmental probes in biology and medicine, their *in vitro* toxicity was studied in rat cerebellar granule cells and neuroblastoma SH-SY5Y cells. As can be seen from Figure 3, good cell survival was seen in both cell lines over the 1 nM to 1 μM concentration range expected to be employed for potential probe studies. *In vivo* experiments in male hybrid BDF1 mice at intraperitoneal administration showed that **2a** and **2b** have no toxicity at doses up to 150 mg/kg body weight (all animals remained alive without any visible changes in the appearance and behavior). Furthermore, neither external nor internal damage of any major organs was revealed by autopsy.

In summary, we have shown that 1,4-diazepinoporphyrazines provide useful optical signaling agents that allow the dimer-monomer equilibrium to be probed in detail. We have shown that it is possible to control the self-assembly but also the structure of the resulting supramolecular dimers as inferred from spectral studies by changing the nature of 1,4-diazepine heterocycle substituents, as well as via the addition of a competitive solvent (DMSO) or anion (fluoride). Optical studies provide a convenient means of reading out the associated structural changes. We thus believe that systems such as **2** will aid in the analysis of self-associated aggregation effects. They may also emerge as useful probes of the solution phase conditions in both chemical and biological environments.

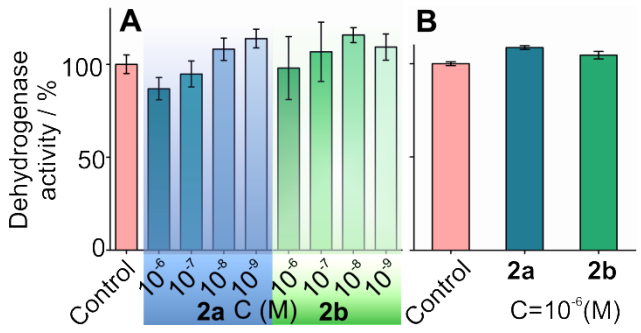


Figure 3. Influence of **2a** and **2b** on the viability of rat cerebellar granule cells (A) and neuroblastoma SH-SY5Y (B). Control samples contain DMSO (≤1%) instead of the tested compounds. Incubation times of 24 hours were used. The dehydrogenase activity was determined using a standard MTT assay.

Notes and references

We thank Dr. Alexander V. Chernyak for recording the NMR spectra. Synthetic and optical spectroscopic studies in this work were supported by the RSF (Grant 17-73-10413). NMR studies were supported by the Council under the President of the Russian Federation for State Support of Young Scientists and Leading Scientific Schools (Grant MD-2991.2017.3). SR-XRD studies were supported by the RUDN University Program "5-100". We also acknowledge support of electrochemical, *in vitro* and *in vivo* studies by the State Assignment (Theme 45.5 Creation of compounds with given physicochemical properties) and the facilities provided by the Center of Collective Use of IPAC RAS (Chernogolovka, Russia). Single-crystal X-ray measurements have been performed at the unique scientific facility Kurchatov Synchrotron Radiation Source supported by the Ministry of Education and Science of the Russian Federation (project code RFMEFI61917X0007).

1 D. Philp and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1154-1196.
2 J. A. A. W. Elemans, R. van Hameren, R. J. M. Nolte and A. E. Rowan, *Adv. Mater.*, 2006, **18**, 1251-1266.
3 N. A. Bragina, K. A. Zhdanova and A. F. Mironov, *Russ. Chem. Rev.*, 2016, **85**, 477-512.
4 M. D. Ward, *Chem. Soc. Rev.*, 1997, **26**, 365-375.
5 M. P. Donzello, C. Ercolani, P. A. Stuzhin, A. Chiesi-Villa and C. Rizzoli, *Eur. J. Inorg. Chem.*, 1999, 2075-2084.
6 S. Angeloni and C. Ercolani, *J. Porphyrins Phthalocyanines*, 2000, **04**, 474-483.
7 M. P. Donzello, D. Dini, G. D'Arcangelo, C. Ercolani, R. Zhan, Z. Ou, P. A. Stuzhin and K. M. Kadish, *J. Am. Chem. Soc.*, 2003, **125**, 14190-14204.
8 M. P. Donzello, C. Ercolani, L. Mannina, E. Viola, A. Bubnova, O. G. Khelevina and P. A. Stuzhin, *Aust. J. Chem.*, 2008, **61**, 262-272.
9 T. Goslinski, J. Piskorz, D. Brudnicki, A. J. P. White, M. Gdaniec, W. Szczolko and E. Tykarska, *Polyhedron*, 2011, **30**, 1004-1011.
10 J. Piskorz, E. Tykarska, M. Gdaniec, T. Goslinski and J. Mielcarek, *Inorg. Chem. Commun.*, 2012, **20**, 13-17.
11 P. A. Tarakanov, M. P. Donzello, O. I. Koifman and P. A. Stuzhin, *Macroheterocycles*, 2011, **4(3)**, 177-183
12 P. A. Stuzhin, P. Tarakanov, S. Shiryaeva, A. Zimenkova, O. I. Koifman, E. Viola, M. P. Donzello and C. Ercolani, *J. Porphyrins Phthalocyanines*, 2012, **16**, 968-976.
13 P. A. Tarakanov, A. O. Simakov, A. Y. Tolbin, I. O. Balashova, V. I. Shestov and L. G. Tomilova, *Spectrochim. Acta, Part A*, 2015, **139**, 464-470.
14 E. N. Tarakanova, S. A. Trashin, A. O. Simakov, T. Furuyama, A. V. Dzuban, L. N. Inasaridze, P. A. Tarakanov, P. A. Troshin, V. E. Pushkarev, N. Kobayashi and L. G. Tomilova, *Dalton Trans.*, 2016, **45**, 12041-12052.
15 P. A. Tarakanov, A. O. Simakov, A. V. Dzuban, V. I. Shestov, E. N. Tarakanova, V. E. Pushkarev and L. G. Tomilova, *Org. Biomol. Chem.*, 2016, **14**, 1138-1146.
16 V. E. Pushkarev, A. Y. Tolbin, N. E. Borisova, S. A. Trashin and L. G. Tomilova, *Eur. J. Inorg. Chem.*, 2010, 5254-5262.
17 P. Zhu, F. Lu, N. Pan, D. P. Arnold, S. Zhang and J. Jiang, *Eur. J. Inorg. Chem.*, 2004, 510-517.