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Conformational preferences of thiacrown ethers containing a 5,5′-bi-1,2,4-triazine subunit: X-ray analysis and DFT calculations

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Abstract

The crystal structure determinations and theoretical calculations at DFT/B3LYP/6-311++G(d,p) level of 5,5′-bi-1,2,4-triazine thiacrown ethers containing 16-, 19- and 22-membered macrocyclic ring were used to analyze their conformational preferences in the crysalline state and gaseous phase.

Keywords: 5,5′-bi-1,2,4-triazine; conformational analysis; crown ethers; theoretical calculations at DFT/B3LYP/6-311++G(d,p) level; X-ray analysis.

Introduction

2,2′-Bipyridine (bpy) based macrocycles have a wide range of applications in a number of fields such as catalysis, metal extraction and molecular recognition (Kaes et al., 2000). In contrast, the properties of their analogs containing sulfur atoms directly attached to the 2,2′-bipyridine rings were unknown until recently, owing to lack of the efficient methods for their synthesis (Buhleier and Vögtle, 1977). Such ligands should be able to coordinate to softer metal ions than those containing oxygens as donor atoms, and may constitute a valuable starting material for the synthesis of enantiomerically enriched mono and bis(sulfoxide)s (Ławecka et al., 2008). We have previously shown that 6,6′-bis(alkylsulfanyl)-5,5′-bi-1,2,4-triazines easily undergo Diels-Alder/retro Diels-Alder (DA-rDA) reactions with electron-rich dienophiles to give bpy alkyl sulfides in good yield (Rykowski et al., 2000). The method appeared to be ideally suited for the synthesis of bpy thiacrown ethers in which the key steps would involve homocoupling reaction of 1,2,4-triazine bis-sulfides tethered to poly(ethylene glycol) derivatives **1a–c** and DA-rDA reaction of such obtained 5,5′-bi-triazine intermediates **2a–c** with 2,5-norbornadiene or cyclic enamine (Scheme 1) (Ławecka et al., 2010).

The efficiency of this strategy may be attributed to the favorable conformation of the linear precursors **1a–c** resulting in low activation energy for cyclization, and geometrical parameters of the intermediates **2a–c**. In order to establish the geometry of bi-1,2,4-triazine thiamacrocycles **2a–c**, ^{1}H NMR, X-ray analysis, and the theoretical calculations at DFT level were undertaken.

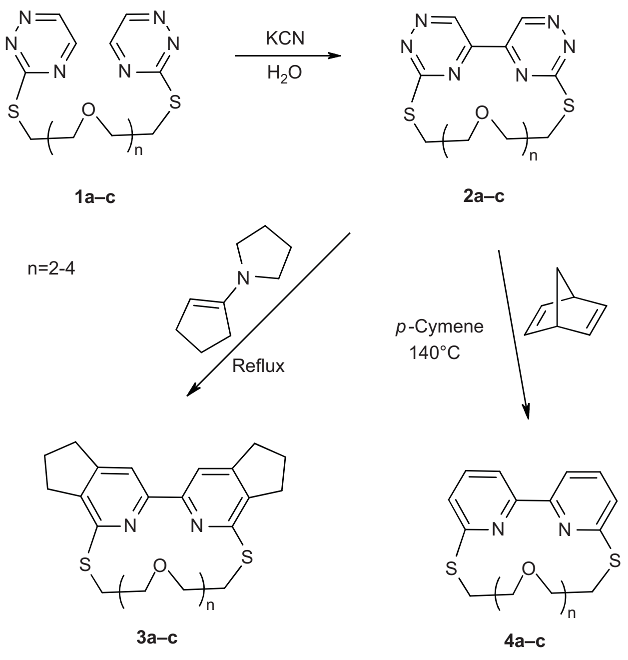
Results and discussion

The ^{1}H NMR data of the molecules **1a–c** and **2a–c** are presented in Table 1.

As expected, the chemical shifts for the aliphatic protons in **2a–c** are nearly identical to those observed for their linear precursors **1a–c**. The aromatic signals are different in that they appear at 8.35–8.92 ppm for 1,2,4-triazine bis-sulfides **1a–c** and 9.48–9.88 ppm for bi-1,2,4-triazine macrocycles **2a–c**, respectively. The preferential conformations of the latter are ascertained by the size of the polythioetheral bridge in **2a–c** and can be determined by analyzing the chemical shifts of the bi-triazine protons (Ławecka et al., 2010). The resonances of bi-1,2,4-triazine hydrogens in compounds **2a–b** (9.48–9.67 ppm) indicate *cis* arrangement for these macrocycles in solution. They show the same conformation in the solid state. These compounds, **2a** and **2b**, containing respectively 16- and 19-membered macrocyclic ring, gave crystals suitable for X-ray analysis. The structures of their molecules in the crystalline state are shown in Figure 1.

The geometry (bond lengths and angles) and conformation (torsion angles) of the thiaether system in **2a** and **2b** are very similar to those found in related structures of annulated 2,2′-bipyridine thiamacrocycles (Ławecka et al., 2010). Both molecules exist in the *cis* (*syn*) conformation with the torsion angle φ=N4A–C5A–C5B–N4B about the central bond of the bitriazinyl system of 38.7(3)° for **2a** and 3.12(18)° for **2b**. The conformations of molecules **2a** and **2b** obtained after their geometry optimization and energy minimization using DFT method are very similar to those observed in the crystals; calculated torsion angles φ are 41.6° and 28.2° for **2a** and **2b**, respectively.

In contrast to **2a** and **2b**, the chemical shift of bi-1,2,4-triazine protons in **2c** (δ=9.88 ppm) and their downfield shift, delta (Δδ=0.21–0.40) show a *trans* conformation for this pentaethylene chain ligand. These values are consistent with the chemical shift of 1,2,4-triazine protons (δ=10.08 ppm) in the parent 3,3′-dimethyl-5,5′-bi-1,2,4-triazine which has *trans* conformation exclusively with torsion angle ψ=N–C–C′–N′



Scheme 1 Synthesis of macrocycles **2a**–**c** and their Diels-Alder reaction.

about the central bond of the bitriazinyl system of 174.41° (Courcot et al., 2007).

Due to the lack of the suitable crystal to X-ray analysis of thiamacrocycle **2c** with 22-membered macrocyclic ring, the molecular modeling studies were undertaken to investigate its conformational preferences in the gaseous phase. The molecule **2c** was modeled in two starting conformations with respective *trans* and *cis* mutual position of triazine rings in the biheterocyclic system. Theoretical calculations at the DFT/B3LYP/6-311++G(d,p) level showed that isomer *trans* (φ=152.4°) obtained after energy minimization and geometry optimization is more energetically stable than isomer *cis* (φ=-24.2°), with a difference in the energy between the *cis* and *trans* forms of 2.925 kcal/mol. This result is in good agreement with our theoretical studies on energy effects of the free rotation between the pyridine rings in structurally related 2,2′-bipyridine thiamacrocycles, which showed that the elongation of the thiaether chain to form 22-membered macrocyclic system gives possibility to change the mutual orientation of heterocyclic rings in biheterocyclic system with distinct energetical dominance of the isomer *trans* above isomer *cis* (Ławecka et al., 2011). The structures of modeled **2c** macrocycle in *trans* and *cis* conformation of the bitriazinyl system obtained after geometrical parameters optimization and energy minimization are shown in Figure 2.

The natural bond order (NBO) charges on the atoms in molecules **2a**–**c** calculated at DFT/B3LYP/6-311++G(d,p) level are listed in Table 2. As can be seen, these NBO values do not depend on the length of the thiaether chain and conformation of the biheterocyclic ring. In triazine rings the large negative and positive charges at N and C atoms, respectively, cause the strong polarization of the bonds and give tendency to antiparallel orientation of the partial dipoles of N4–C5 bonds characteristic for *trans* conformation of the biheterocyclic system. Therefore, it can be concluded, that the *cis* or *trans* conformation of 5,5′-bitriazinyl system is the effect of electrostatic dipole-dipole interaction and steric interaction of the methine H atoms forced into the *trans* conformation in **2c** and strong strain effect in 16- and 19-membered macrocyclic ring giving *cis* conformation in **2a** and **2b**.

Conclusion

It appears that conformation of the bitriazinyl system in 5,5′-bi-1,2,4-triazine based macrocycles **2a**–**c** (*cis* or *trans*) is influenced by the length of the thiaether chain, steric interaction of its methine groups and electrostatic interactions of polarized N–C bonds in triazine rings.

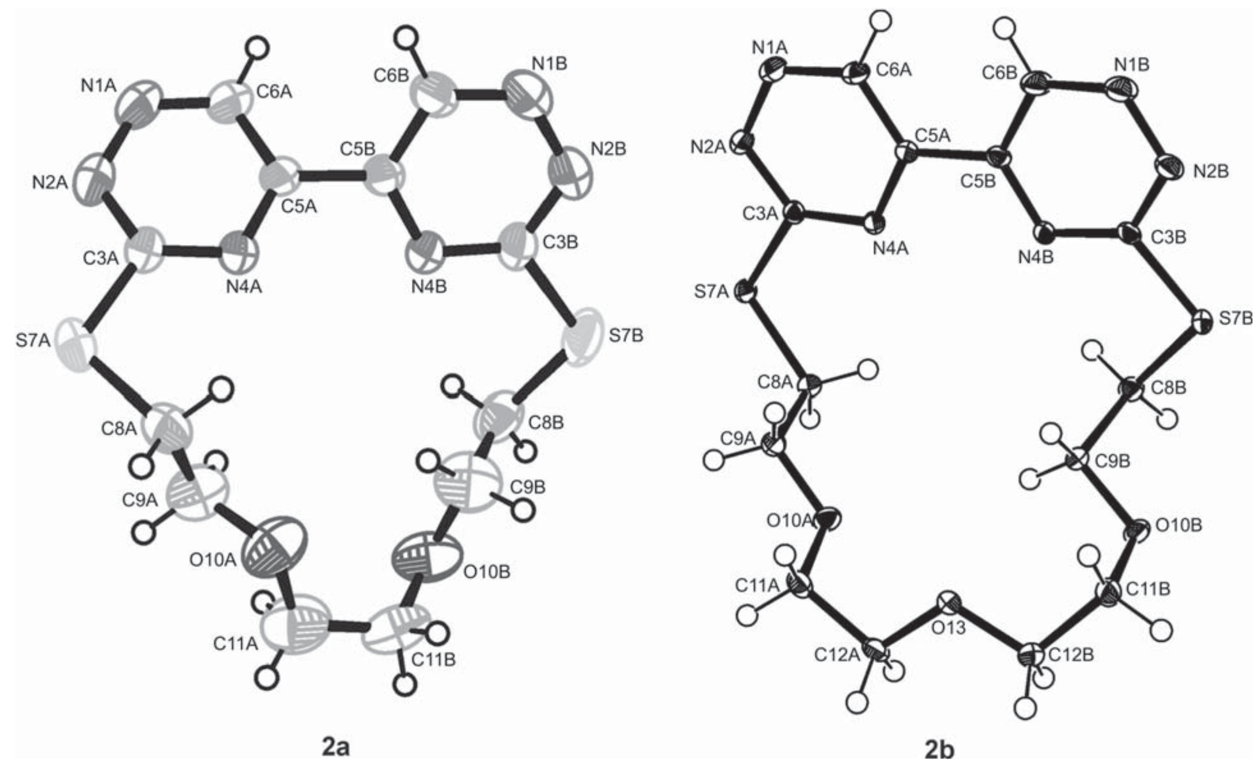
Experimental section

X-ray structure determinations of 2a and 2b

X-ray data of **2a** and **2b** were collected on the Bruker SMART APEX II CCD diffractometer; crystal sizes 0.50×0.42×0.03 mm (**2a**) and 0.49×0.06×0.03 mm (**2b**), MoKα (λ=0.71073 Å) radiation, ω scans. Both structures were solved by direct methods using SHELXS97 (Sheldrick, 2008) and refined by full-matrix least-squares with SHELXL97 (Sheldrick, 2008). The H atoms were positioned geometrically and treated as riding on their parent C atoms with C-H distances of 0.93 Å (aromatic) and 0.97 Å (CH_2). All H atoms were refined with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. All calculations were performed using WINGX version 1.64.05 package (Farrugia, 1999). CCDC-807787 (**2a**), CCDC-807788 (**2b**) contain the supplementary

Table 1 ^{1}H NMR data of compounds **1a**–**c** and **2a**–**c** (Ławecka et al., 2010).

Compound	H^5 ($H^{5'}$) (δ, ppm)	H^6 ($H^{6'}$) (δ, ppm)	Poly(ethylene glycol) chain protons (δ, ppm)
1a	8.36 (s, 2H)	8.92 (s, 2H)	3.48 (t, *J*=6.5 Hz, 4H, CH_2); 3.68 (s, 4H, CH_2), 3.82 (t, *J*=6.5 Hz, 4H, CH_2)
1b	8.36 (s, 2H)	8.92 (s, 2H)	3.48 (t, *J*=6.4 Hz, 4H, CH_2), 3.67 (s, 8H, CH_2), 3.82 (t, *J*=6.4 Hz, 4H, CH_2)
1c	8.35 (s, 2H)	8.91 (s, 2H)	3.43 (t, *J*=6.6 Hz, 4H, CH_2), 3.62 (s, 12H, CH_2), 3.77 (t, *J*=6.6 Hz, 4H, CH_2)
2a	–	9.48 (s, 2H)	3.43-3.51 (m, 4H, CH_2), 3.69 (s, 4H, CH_2), 3.81-3.89 (m, 4H, CH_2)
2b	–	9.67 (s, 2H)	3.25-3.27 (m, 4H, CH_2), 3.44-3.46 (m, 4H, CH_2), 3.54 (t, *J*=5.8 Hz, 4H, CH_2), 3.81 (t, *J*=5.8 Hz, 4H, CH_2)
2c	–	9.88 (s, 2H)	3.11 (s, 4H, CH_2), 3.36-3.40 (m, 4H, CH_2), 3.54-3.62 (m, 8H, CH_2), 3.85 (t, *J*=6.0 Hz, 4H, CH_2)



2a **2b**

Figure 1 A view of the X-ray molecular structures of **2a–b** with the atomic labeling. Non-H atoms are represented by displacement ellipsoids of 50% probability.

crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

Crystal data of 2a $C_{12}H_{14}N_6O_2S_2$, M=338.41, orthorhombic, space group $Pbca$, a=10.1788(3), b=8.0434(3), c=37.3239(12) Å, V=3055.79(18) Å^3, Z=8, d_{calc}=1.471 Mg/m^3, F(000)=1408, μ(Mo Kα)=0.365/mm, T=293K, 32 294 measured reflections (θ range 1.09–25.11°), 2729 unique reflections (R_{int}=0.025), final R=0.038, wR=0.115, S=1.108 for 2369 reflections with I>2σ(I).

Crystal data of 2b $C_{14}H_{18}N_6O_3S_2$, M=382.46, monoclinic, space group $P2_1/c$, a=18.8850(9), b=10.6367(5), c=8.7267(5) Å, β=102.121(1)°, V=1713.89(15) Å^3, Z=4, d_{calc}=1.482 Mg/m^3, F(000)=800, μ(Mo Kα)=0.339/mm, T=100K, 31 885 measured reflections (θ range 1.10–32.38°), 6128 unique reflections

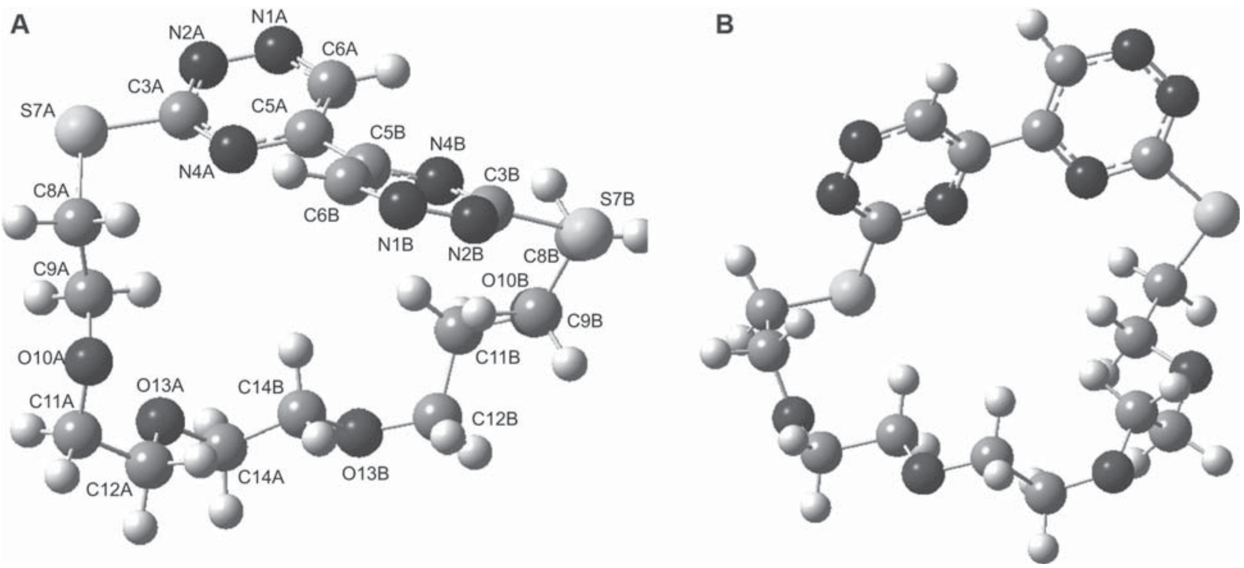


Figure 2 B3LYP/6-311G** DFT calculations molecular structures of **2c** in the *trans* (A) and *cis* (B) conformation.

Table 2 The NBO charges (×1000 *e*) on the atoms in A/B parts of molecules calculated at DFT/B3LYP/6-311++G(d,p) level for **2a**–**c**.

Atom	**2a**	**2b**	**2c** (*trans*)	**2c** (*cis*)
N1	-169/-169	-170/-172	-171/-170	-173/-171
N2	-259/-258	-259/-256	-257/-259	-300/-252
C3	+244/+243	+245/+239	+244/+243	+239/+239
N4	-470/-466	-467/-470	-483/-491	-441/-471
C5	+193/+189	+190/+185	+185/+188	+188/+182
C6	-27/-29	-24/-29	-11/-7	-20/-27
S7	+320/+326	+320/+329	+315/+315	+323/+340
C8	-519/-517	-519/-520	-514/-516	-517/-516
C9	-25/-32	-25/-36	-33/-37	-29/-33
O10	-615/-613	-607/-608	-605/-602	-610/-604
C11	-42/-34	-32/-30	-33/-38	-25/-38
C12		-30/-45	-47/-39	-40/-43
O13		-513	-611/-600	-604/-601
C14			-26/-41	-37/-43

(R_{int}=0.053), final R=0.039, wR=0.098, S=1.026 for 4739 reflections with $I>2\sigma(I)$.

Theoretical calculations

The theoretical calculations at the DFT/B3LYP level with 6-311++G(d,p) basis set implemented in GAUSSIAN 03 (Frisch et al., 2004) were carried out via Natural Bond Order (NBO) analysis to investigate the conformational preferences and electronic parameters of **2a**–**c**. The structures were fully optimized without any symmetry constraint. The initial geometries of **2a** and **2b** were built from their crystallographic data. The initial geometries of **2c** in started *cis* and *trans* conformation were built *de novo* using the AM1 semiempirical SCF-MO method implemented in the program package HYPERCHEM rel. 4.5.

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