FULL PAPER

Molecular Modeling Study of the PtCl$_2$ Complexes of Unsaturated S$_2$O$_{n+1}$–Coronands: Dynamic Simulations and Investigation of the Ring Interconversion

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Abstract Maleonitrile-dithiacrown ethers mn-12S$_2$O$_2$ - mn-21S$_2$O$_5$ (mn = maleonitrile) are preorganized S$_2$O$_{n+1}$-coronands (n = 1 – 4) which force B, AB and A class metal ions into mixed S/O coordination spheres. Moreover, they form chelate complexes with MX$_2$ salts (M = Pd, Pt; X = Cl, Br), which were studied in this paper. The structures of mn-S$_2$O$_{n+1}$ and [PtCl$_2$(mn-S$_2$O$_{n+1}$)] (n = 2, 3) were investigated theoretically by empirical and semiempirical methods using SYBYL (TRIPOS force field) and MSI/DISCOVER97 (ESFF force field). mn-12S$_2$O$_2$ was investigated experimentally by X-ray analysis and 1D and 2D NMR spectroscopy in solution and the complex formation was studied by ^{1}H, ^{13}C and [195]Pt NMR titration experiments, respectively. S-inversion was also investigated in order to determine the ring corresponding interconversional barriers. Different orientations of the macrocyclic ring system mn-18S$_2$O$_4$ and of its transition states are shown.

Keywords Thiacrown ether, NMR, Pt(II) complexes, Molecular dynamic simulations, Ring interconversion

Introduction

Thiacrown ethers having a mixed donor set of sulphur and oxygen heteroatoms differ in their metal binding properties from their purely sulphur or oxygen relatives [1, 2]. Maleonitrile-dithiacrown ethers mn-12S$_2$O$_2$ – mn-21S$_2$O$_5$ (mn = maleonitrile) (*cf.* Figure 1) (e. g. mn-18S$_2$O$_4$ = 1,4,7,10-Tetraoxa-13,16-dithiacyclooctadec-14-ene-14,15-dicarbonitrile) are preorganized S$_2$O$_{n+1}$–coronands (n = 1 – 3) which force B, AB and A class metal ions into mixed S/O coordination spheres [3, 4]. Moreover, they form chelate complexes with MX$_2$ salts (M = Pd, Pt; X = Cl, Br), which were studied in this paper.

It is the major objective of this paper to examine the molecular dynamics of both the ligands mn-S$_2$O$_{n+1}$ (n = 2, 3) and its Pt^{II} complexes. S-inversion has also been investigated in order to determine the corresponding ring interconversional barriers.

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Table 1 *Coalescence temperatures (K) / free energy of activation (kJ/mol) of mn-S_2O_{n+1}*

	S**C**H$_2$CH$_2$O	SCH$_2$**C**H$_2$O	OCH$_2$CH$_2$O	solvent
mn-12S$_2$O$_2$	263 / 51.5	263 / 51.7	253 / 51.4	CD$_2$Cl$_2$ (F.p. -95°C)
mn-15S$_2$O$_3$	173 / 32.7	173 / 33.6	–	CD$_2$Cl$_2$/CCl$_2$FH (10 : 90) (F.p. -135°C)
mn-18S$_2$O$_4$	–	–	–	CD$_2$Cl$_2$ (F.p. -95°C)

Methods

Molecular modeling studies

Molecular mechanics The structures of mn-S_2O_{n+1} and [PtCl$_2$(mn-S_2O_{n+1})] (n = 2, 3) were investigated theoretically. The molecular dynamic simulations (NVT statistical ensemble) of the ligands and its Pt^{II} complexes were performed using the program MSI/DISCOVER97 [5] (ESFF force field [6]). The ESFF has been proved to reproduce structures of metal complexes with good accuracy. It is able to deal with a broad variety of metal centres without any extensive parameterisation [7].

The nonbonded interactions (long-range Coulomb and van der Waals forces) were pairwise calculated without any cut-off. Energy minimisations were performed until the absolute value of the largest partial derivatives of the energy with respect to the coordinates was below 0.001 kcal/mol/Å. Steepest descent and conjugated gradient (Polak-Ribiere scheme) methods, quasi-Newton-Raphson algorithm in combination with the BFGS update scheme were used [8]. The MD runs were executed with time steps of 1 fs. Each MD run was carried out up to 510 ps at different temperatures (T = 300, 373, 500 K) in order to explore the conformational space efficiently. During the first 10 ps the system was equilibrated. For data sampling the coordinates were saved every ps. After the MD simulation each of the saved structures was used as starting geometry for a subsequent ESFF energy minimisation.

Further, the flexibility of the ligands (energy hypersurface) was studied by the Grid search algorithm of SYBYL [9] (TRIPOS force field [10]). The step width of 10° about all

rotatory bonds (OCCO, SCCO) was used. For nonbonded interactions, described by van der Waals forces and long range Coulomb interactions, an atom-based cut-off at 8 Å was imposed. Atomic charges were evaluated by the Gasteiger Marsili scheme [11].

Grid search is useful for a systematic search of the whole conformational space.

Semiempirical calculations The heats of formation and the transition states were calculated semiempirically using the program MOPAC [12] (PM3 [13]).

The calculations were performed on a Silicon Graphics IRIS-INDIGO XS24 and IBM RS6000.

NMR spectroscopy mn-12S$_2$O$_2$ was investigated experimentally by X-ray analysis and 1D, 2D NMR spectroscopy in solution; furthermore, the complex formation was studied by ^{1}H, ^{13}C and ^{195}Pt NMR titration experiments. For running the NMR spectra an ARX 300 (Bruker) was used. All samples were dissolved in CD$_3$NO$_2$ or, in the case of low-temperature measurements, in CD$_2$Cl$_2$ or CD$_2$Cl$_2$/CCl$_2$FH (10 : 90). The ^{1}H, ^{13}C and ^{195}Pt NMR spectra were recorded at 300.13, 74.47 and 64.52 MHz in 5 mm probe tube. ^{1}H and ^{13}C: 30° pulse, 2 s repetition time, 32 K data points; ^{195}Pt: 0.5 s repetition time. For the H,H-COSY, HMQC and the HMBC 2D experiments, the standard Bruker software was employed.

Results and discussion

Dynamic NMR spectroscopy

The ^{1}H NMR spectra of the uncomplexed macrocycles indicate that these compounds are still flexible (broad signals) at room temperature. The corresponding Pt complexes show rather complex ^{1}H NMR spectra - coalescence phenomena could not be observed.

At lower temperatures coalescence phenomena of mn-S_2O_{n+1} were observed in the ^{1}H NMR spectra. The coalescence temperatures of mn-15S$_2$O$_3$ (Table 1) (*cf.* mn-12S$_2$O$_2$ [3]) could be measured by temperature-dependent ^{1}H NMR spectra and therefrom the interconversional barriers calculated. The determination of the free energy of activation of mn-18S$_2$O$_4$ was not possible, because the experimental accessible temperature limit (150 K) of the NMR spectrometer
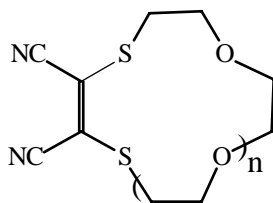

Figure 1 *Scheme of the Maleonitrile-dithiacrown ethers mn-S_2O_{n+1} (n = 1 - 3)*

Table 2 *Comparison of some selected bond angles and bond distances of [PtCl₂(mn-15S₂O₃)] as studied by X-ray analysis and ESFF calculations (cf. Fig. 2a)*

	bond distance (Å)			bond angle (°)	
	X-ray	ESFF		X-ray	ESFF
PtS3	2.26	2.36	C1C2S3	120.0	121.1
PtCl14	2.31	2.30	S3PtCl14	89.3	92.8
C1C2	1.34	1.34	C2S3C3	101.0	99.8
S3C3	1.85	1.83	S3C3C4	110.5	115.5
C3C4	1.51	1.54	C3C4O4	110.9	110.5
C4O4	1.40	1.42	C4O4C5	116.6	115.3
O4C5	1.46	1.43	O4C5C6	116.0	115.5
C5C6	1.44	1.54	C5C6O6	112.6	112.2
C6O6	1.39	1.43	C6O6C7	114.7	114.9

was reached without freezing out the preferred conformations.

Molecular modeling studies

Molecular mechanics In order to investigate theoretically the dynamic process, especially the S inversion of the Pt^{II} complexed mn-S₂O$_{n+1}$ (n = 2, 3) was firstly studied, rather than the whole ring interconversion.

Therefore, molecular dynamic simulations at 300 (~ room temperature), 373 (high temperature limit of the NMR spectrometer) and 500 K were carried out but also Grid search calculations of the ligands mn-S₂O$_{n+1}$ and its Pt^{II} complexes

were performed. The coordinates of the X-ray analysis were used as starting conformations [14, 15]. As a result different ground state conformations both for mn-S₂O$_{n+1}$ (n = 2, 3) and its Pt^{II} complexes were obtained.

The five membered ring connectivity (PtS10C1C2S3, *cf.* Fig. 2a) does not change during the dynamic simulations. Nevertheless, the sulphur inversion still readily can take place, warranting the high flexibility of the macrocyclic ring system. The sulphur inversion were observed at 500 K for [PtCl₂(mn-15S₂O₃)] and at 373 K for [PtCl₂(mn-18S₂O₄)].

The lowest energy conformations of the complexes [PtCl₂(mn-15S₂O₃)] and [PtCl₂(mn-18S₂O₄)] found by MD simulations (ESFF) and subsequent energy minimisation are

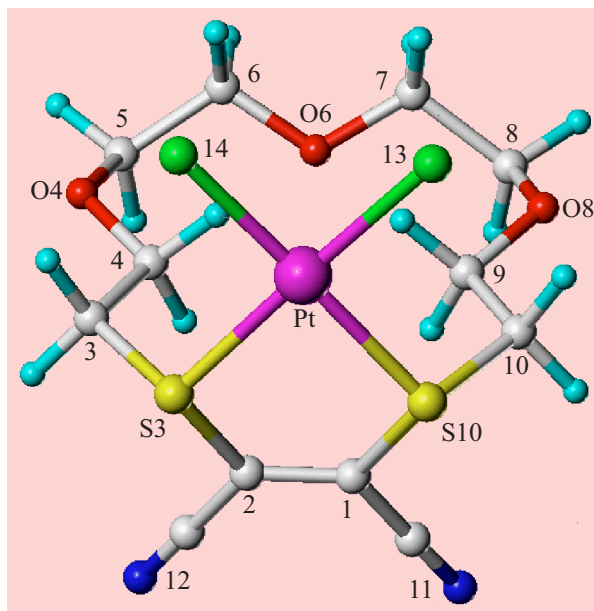**Figure 2a** *The lowest energy conformation of [PtCl₂(mn-15S₂O₃)] found by MD simulation and subsequent ESFF energy minimisation (For a better illustration the structure is available as PDB file)*
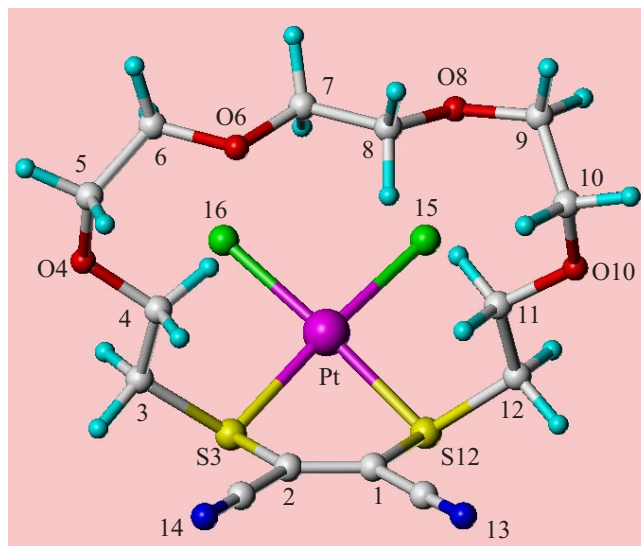
Figure 2b *The lowest energy conformation of [PtCl₂(mn-18S₂O₄)] found by MD simulation and subsequent ESFF energy minimisation (For a better illustration the structure is available as PDB file)*

Table 3 *^{13}C chemical shifts of mn-12S_2O_2 and [PtCl$_2$(mn-12$\tilde{S}_2O_2$)] in CD$_3$NO$_2$*

	C=C	SCH_2	SCH$_2$$CH_2$O	OCH$_2$CH$_2$O	C≡N
ligand	127.19	**_37.16_**	71.46	69.67	115.43
complex	131.34	**_43.60_**	68.35	68.87	111.28

shown in Fig. 2. The S atoms point out of the ring, the exodentate orientation of the S atoms proved to be preferred.

For [PtCl$_2$(mn-15S$_2$O$_3$)] a rmsd value of 0.34 Å between crystal structure and ESFF result (energy minima) was achieved. Some characteristic X-ray values of selected bond angles and bond distances are compared with theoretically obtained values (*cf.* Tab. 2). In contrast to the X-ray analysis where the cycle PtS10C1C2S3 (Figure 2a) is nearly planar, the ESFF calculation yielded a folded cycle (torsional angle of C2S3PtS10 -1.5° (X-ray) and 22.4° (ESFF)).

Semiempirical calculations The conformations of the ligands obtained by molecular dynamic simulations and Grid

search calculations were optimised by PM3 energy minimisation and used as starting conformations for the semiempirical investigations of the transition states.

The transition state algorithm was employed as followed: first a SADDLE [16] calculation was carried out. Then, the conformation obtained was optimised by the TS search (Eigenvector Following, recalc = 5, dmax = 0.05) [17]. Finally, the force constants were calculated in order to characterise the transition state. The saddle points of first order are characterised by only one negative force constant.

The localization of the TS was very difficult because simultaneous changes of more than one dihedral angle were necessary.
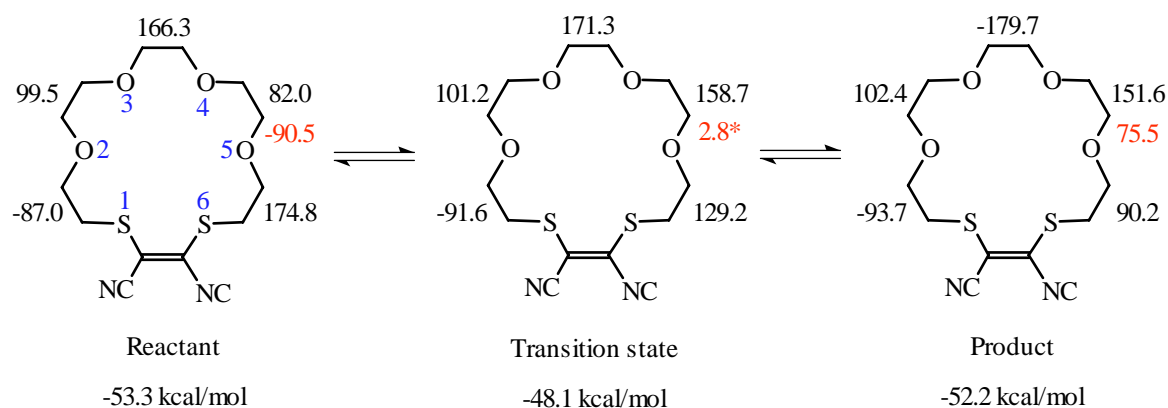

Figure 3a *Calculated dihedral angles (SCCO, OCCO) of mn-18S$_2$O$_4$ of the reactant, transition state and product (for the starred (*) dihedral angle CCO5C a negative force constant was obtained) (PM3)*
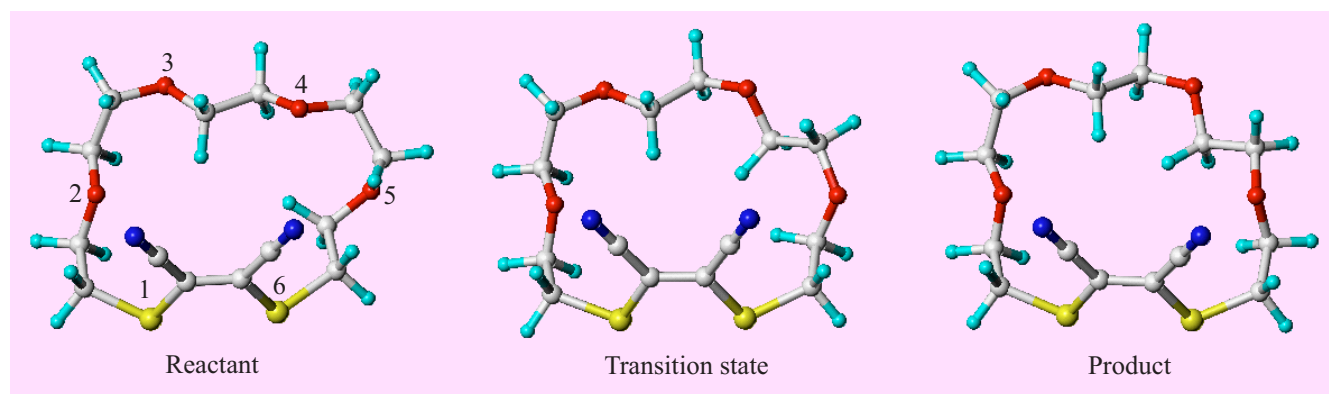

Figure 3b *Structures of reactant, transition state and product of mn-18S$_2$O$_4$ according to Figure 3a*

Transition states for the larger ring mn-$18S_2O_4$ could be obtained. The interconversion between different orientations of this macrocyclic ring system with respect to the torsional angles CCO5C (Fig. 3) and S1CCO2 (Fig. 4) are shown schematically. The energy barriers were found to be about 5 kcal/mol (21 kJ/mol). These low barriers correspond with the high flexibility of the whole ring system.

For the smaller rings (n = 1, 2) it was not yet possible to identify a TS.

NMR spectroscopy The NMR technique is a powerful tool for studying the complexation of thiacrown ethers and transition metal ions in solution. The X-ray analysis [15] of the mn-S_2O_{n+1} complexes showed the Pt^{II} ion to be coordinated to the sulphur atoms. ^{13}C NMR studies yielded the same results for the mn-S_2O_{n+1} complexes of $PtCl_2$ in nitromethane solution. The ligands are bound to platinum(II) *via* the thiaether S donor atoms (Table 3). Accordingly, in the ^{13}C NMR spectrum of [$PtCl_2$(mn-$12S_2O_2$)] the methylene

resonances next to sulphur are shifted downfield upon complexation.

The number of ^{13}C signals proved C_s symmetry to be preferred which is in agreement with the conformations found by the MD simulations (*cf.* Fig. 2).

Qualitative and quantitative information about the complexation of thiacrown ethers is readily available from the detailed study of chemical shift variations of the metal cations as a function of its concentration in the crown ether solution. In order to study the corresponding complex formation, the coronand was added to K_2PtCl_4 solutions (D_2O/ DMF-d_6). The dependence of the ^{195}Pt chemical shifts ($\Delta\delta=\delta$[coronand]/[K_2PtCl_4] – δ [K_2PtCl_4]) on the [K_2PtCl_4]/ [coronand] molar ratio was investigated (*cf.* Fig. 5). The exchange between the free and the complexed mn-$12S_2O_2$ is generally fast on the NMR time scale; averaged shifts were obtained. The $\Delta\delta$ *vs.* molar ratio [salt]/[coronand] curves show a single sharp bend when the molar ratio is approximately 1:1. Accordingly, the formation of a 1:1 complex was concluded.
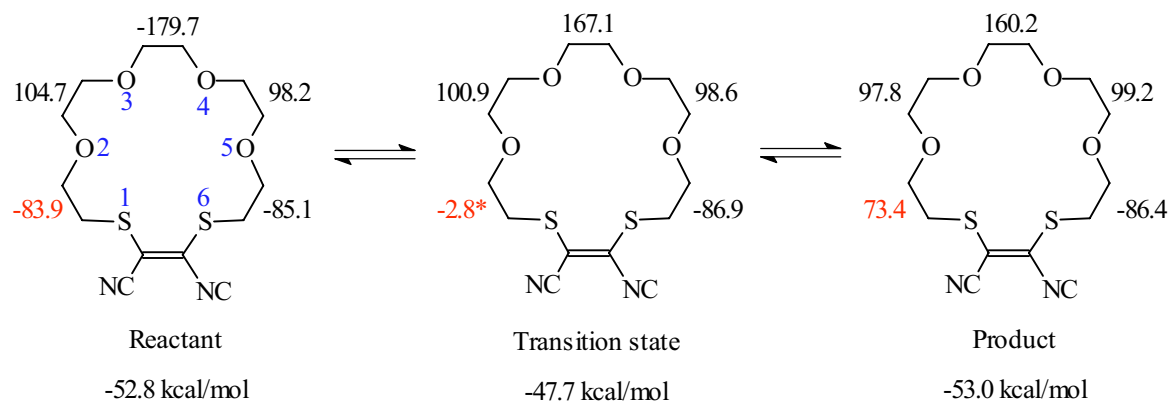

Figure 4a *Calculated dihedral angles (SCCO, OCCO) of mn-$18S_2O_4$ of the reactant, transition state and product (for the starred (*) dihedral angle S1CCO2 a negative force constant was obtained) (PM3)*
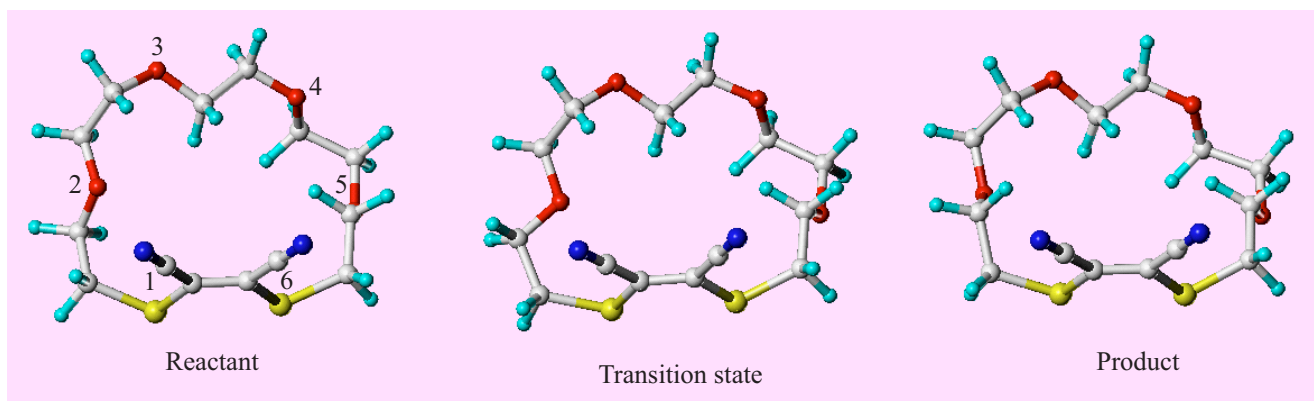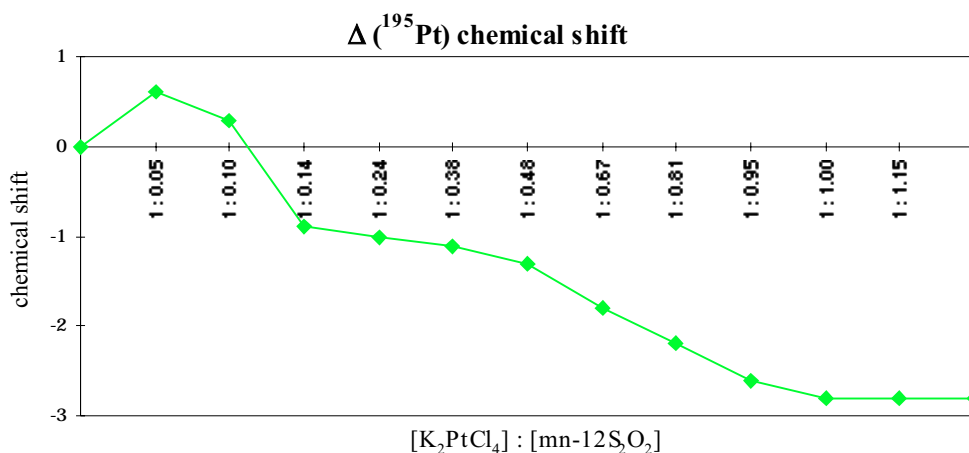

Figure 4b *Structures of reactant, transition state and product of mn-$18S_2O_4$ according to Figure 4a*

Figure 5 *The titration results of K_2PtCl_4 with mn-12S$_2$O$_2$ in DMF-d$_6$/D$_2$O solution*

The ^{195}Pt resonance of [PtCl$_2$(mn-12S$_2$O$_2$)] appears as a single line at -3779 ppm (*vs.* 0.1 M Na$_2$PtCl$_6$ (D$_2$O)). This is an upfield shift to related *cis*-PtCl$_2$S$_2$ complexes (δ(^{195}Pt): [PtCl$_2$(1,4,7-trithiocyclononane)] -3605 ppm; [PtCl$_2$(SMe$_2$)$_2$] -3551 ppm) [18]. The different donor atoms of the complexes ([PtCl$_2$(mn-12S$_2$O$_2$)]: oxygen and sulphur atoms; [PtCl$_2$(SMe$_2$)$_2$]: only sulphur atoms) are responsible for the chemical shift variation obtained.

Conclusions

The ^{1}H-NMR-spectra prove the ligands mn-S$_2$O$_{n+1}$ (n = 1 - 3) to be very flexible compounds. The flexibility was verfied by MD simulations and Grid search calculations.

NMR spectroscopic investigations as well as molecular mechanical calculations identify the lowest energy conformations of mn-S$_2$O$_{n+1}$ and [PtCl$_2$(mn-S$_2$O$_{n+1}$)] (n = 2, 3) to be symmetrical structures. In the Pt^{II} complexes the ligands are bound to platinum(II) *via* the thiaether S donor atoms.

Transition states for the interconversion of the dihedral angles CCO5C and S1CCO2 in mn-18S$_2$O$_4$ could be obtained. The ^{13}C and ^{195}Pt NMR spectra are impressive indicators of the variations in the conformations of thiacrown ether during the complexation of transition metal ions.

The thiacrown ether mn-S$_2$O$_2$ studied forms a stable 1:1 complex with platinum cations.

Supplementary material For a better illustration the structures of the found global minima conformation of [PtCl$_2$(mn-15S$_2$O$_3$)] and [PtCl$_2$(mn-18S$_2$O$_4$)] are available as PDB files as listed below.

[PtCl$_2$(mn-15S$_2$O$_3$)]   0072s01.pdb
[PtCl$_2$(mn-18S$_2$O$_4$)]   0072s02.pdb

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