

Synthesis and Conformational Studies on [3.3.3]Metacyclophane Oligo-ketone Derivatives, and Their Metal Ion Recognition

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Abstract

Chemical reactions were used to synthesize 2,11,20-tris(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **2** and 2,11-bis(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **4** from 6,15,24-tri-tert-butyl-9,18,27-trimethoxy[3.3.3]metacyclophane-2,11,20-trione **1** and -2,11-dione **3**. The yields of **2** and **4** were 70% and 81% respectively. The conformations of the synthesized compounds **2** and **4** were studied using mainly solution Proton Nuclear Magnetic Resonance (¹H NMR) spectroscopic methods. Compounds **2** and **4** were found to have a partial-cone conformation. Detailed variable temperature Proton Nuclear Magnetic Resonance studies further confirmed the partial-cone conformation for the two products, **2**, **4**. During the variable temperature nuclear magnetic resonance spectroscopic studies, compound **2** was found to have a coalescence temperature of about 0°C. Extraction of silver ions with compound **2** gave an extractability of 82% while the parent compound **1** showed zero (0) silver affinity. A 1:1 mol/mol mixture of compound **2** and silver ions studied by solution ¹H NMR revealed a novel "Molecular Roulette" type of motion.

Keywords

Metacyclophanes, Macrocyclic Compounds, Cone, Partial-Cone, Conformation, Variable Temperature Proton Nuclear Magnetic Resonance Spectroscopy, Coalescence Temperature

1. Introduction

For several decades various research groups have been attracted to the chemistry and spectral properties of the

metacyclophanes [1] [2]. Some of the studies both on synthesis and conformational studies of the macrocyclic compounds in which researchers try to convert the flexible conformations of the synthesized macrocyclic compounds into rigid structures to serve as suitable platforms for various complexation experiments. Notable among the methods employed in constructing the rigid structures are those that deal with the introduction of various functional groups into the upper and lower rims, **Figure 1**, of the cyclic structures [3]. This method of preparing very stable units for host-guest studies places the functional groups on the aromatic units within the cyclic structure [4]-[7]. Other ways of freezing the various conformers include the introduction of the functional groups into the aliphatic units linking the various aromatic groups. This approach has been employed in studies involving cyclophanes with aromatic rings linked through $-\text{CH}_2\text{COCH}_2-$ bridges [8] [9]. These bridges are of special interest because of the ease with which carbonyl groups can be converted into other functional groups. For example, the conversion of the carbonyl groups into dithio groups yields hosts with sulfur atoms which can serve as further binding units for molecular recognition studies. The sulfur atoms together with the benzene rings tend to serve as sources of electrons needed to bind guests in the form of metal ions.

Cyclophane compounds bearing sulfur atoms [8] [9] have been known as intermediates in the preparation of various cyclophanes, particularly the paracyclophanes [10]. However, the use of sulfur atoms as binding units within cyclophane units is limited. The few examples include those compounds known to bind strongly to gold surfaces thus making it possible for several self-assembled monolayers of adsorbates with a surface-active sulfur group, an alkyl chain and a terminal functional group [11] [12]. Reinhoudt and his coworkers also reported the synthesis of various resorcin [4] arene adsorbates with four dialkyl sulfide chains underneath, a receptor, which they used in detecting a specific gas [13]-[17]. In this study sulfur units were employed to freeze the conformation of some cyclophanes in order to use them for metal ion recognition studies.

2. Experimental

All melting points are uncorrected. IR (KBr or NaCl): Nippon Denshi JIR-AQ20M. ^1H NMR: Nippon Denshi JEOL FT-270 in CDCl_3 , TMS as reference. UV: Hitachi 220A spectrophotometer. MS: Nippon Denshi JMS-01SA-2. Elemental analysis: Yanaco MT-5.

2.1. Direct Cyclization of 2,6-Bis(bromomethyl)-4-tert-butylanisole with TosMIC [3] [18]

To a suspension of NaH (2.1 g, 51 mmol) in DMF (35 ml) a solution of 2,6-bis(bromomethyl)-4-tert-butylanisole (6 g, 17.1 mmol) and TosMIC (3.3 g, 22.0 mmol) in DMF (35 ml) was added dropwise over a period of 6 h. After the suspension was stirred for additional 5 h at room temperature, it was gently poured into ice-water (300 ml) and extracted with CH_2Cl_2 (3×100 ml) and washed with water (200 ml), dried with Na_2SO_4 , and concentrated in vacuo to 15 ml after which conc HCl (15 ml) was added. The solution was stirred for 15 min. The or-

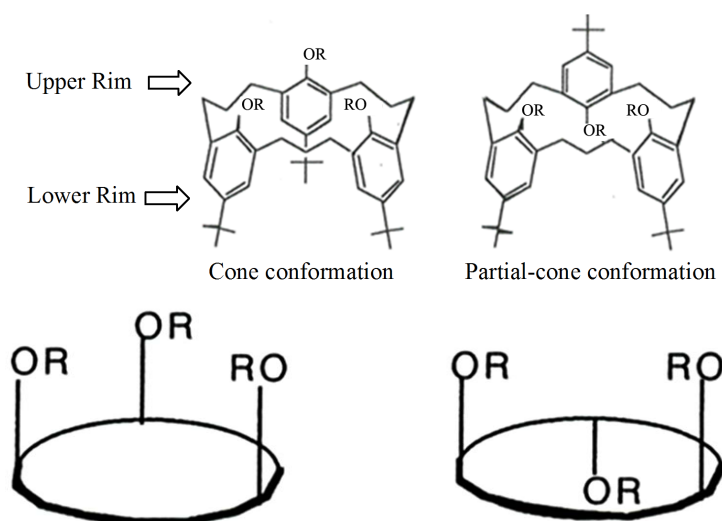


Figure 1. Possible conformers for [3.3.3]metacyclophanes [3]-[5].

ganic layer was again extracted with CH_2Cl_2 (3×100 ml), washed with water (2×100 ml) dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was chromatographed on silica gel using benzene/ CHCl_3 (1:1 v/v) as eluting solvents to give 821.2 mg (1.25 mmol, 22%) of 6,15,24-tri-tert-butyl-9,18,27-trimethoxy [3.3.3]metacyclophane-2,11,20-trione (**1**); colorless prisms (benzene), m.p. $228^\circ\text{C} - 229^\circ\text{C}$. IR (KBr): ν [cm^{-1}] = 1720 (C=O). ^1H NMR (CDCl_3): δ = 1.20 (27H, s), 3.34(9H, s), 3.62(12H, s), 6.92(6H, s). MS (75 eV): m/z = 654 [M^+]. $\text{C}_{42}\text{H}_{54}\text{O}_6$ (654.9); calcd. C 77.03, H 8.31; found, C 76.97, H 8.19.

2.2. Preparation of 6,15,24-Tri-tert-butyl-9,18,27-trimethoxy[3.3.3]metacyclophane-2,11-dione **3**

To a suspension of NaH (2.1 g, 51 mmol) in DMF (150 ml) a solution of 1,3-bis [5-tert-butyl-3-(bromomethyl)-2-methoxyphenyl]propane (4.7 g, 8.5 mmol) and a TosMIC adduct (5.0 g, 8.5 mmol) in DMF (35 ml) was added dropwise over a period of 6 h after which the suspension was stirred for an additional 5 h at room temperature. It was gently poured into ice-water (300 ml) and extracted with CH_2Cl_2 (3×100 ml), washed with water (2×200 ml), dried with Na_2SO_4 , and concentrated in vacuo to 15 ml. Conc. HCl (15 ml) was added, and the solution was stirred for 15 min. The organic layer was again extracted with CH_2Cl_2 (3×100 ml), washed with water (2×100 ml), dried with Na_2SO_4 , and concentrated and condensed under reduced pressure. The residue was chromatographed on silica gel using CHCl_3 as solvent to give crude **3** as a pale yellow solid. Recrystallization from benzene yielded 3.70 g (5.78 mol, 68%) of 6,15,24-tri-tert-butyl-9,18,27-trimethoxy [3.3.3]metacyclophane-2,11-dione **3** as pale yellow prisms, m. p. $188^\circ\text{C} - 189^\circ\text{C}$. IR (KBr): ν [cm^{-1}] = 1716 (C=O). ^1H NMR (CDCl_3): δ = 1.19 (9 H, s), 1.27 (18 H, s), 1.79 - 1.85 (2 H, m), 2.51 - 2.60 (4 H, m), 3.07 (3 H, s), 3.38 (6 H, s), 3.58 (4 H, s), 3.60 (4 H, s), 6.95 (2 H, s), 7.06 (4 H, s). MS (75 eV): m/z = 640 [M^+]. $\text{C}_{42}\text{H}_{56}\text{O}_5$ (640.9); calcd. C 78.71, H 8.81; found C 78.95, H 8.77.

2.3. Synthesis of 2,11-Bis(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **2**

To a mixture of compound **3** (200 mg, 0.312 mmol) and acetic acid (10 ml) was added 1,2-ethanedithiol (0.5 ml, 5.96 mmol) and boron trifluoride etherate [$\text{BF}_3 \cdot \text{OEt}_2$] (0.1 ml, 0.392 mmol), and the resulting reaction mixture stirred at room temperature for 24 h. The reaction mixture was gently poured into ice-water (50 ml) and extracted with CHCl_3 (4×50 ml). The CHCl_3 layer was washed with 10% NaHCO_3 (2×50 ml), and water (2×50 ml), dried with Na_2SO_4 and then evaporated under reduced pressure leaving a residue which was chromatographed over silica gel (C-300 Wako gel, 100 g) with CHCl_3 as solvent. This gave a solid crude which was recrystallized from methanol to obtain 200 mg (81%) of the cyclic thioketal as white crystals with melting point as $168^\circ\text{C} - 169^\circ\text{C}$. IR (KBr): ν [cm^{-1}] = 2955, 2925, 2866, 2824, 1503, 1500, 1481, 1453, 1392, 1352, 1331, 1295, 1276, 1244, 1202, 1174, 1115, 1016, 968, 825, 809. ^1H NMR: δ = 1.30 (18H, s), 1.34 (9H, s), 1.27 - 1.34 (4H, m), 1.86 - 2.00 (2H, m), 2.64 (6H, s, broad), 3.14 (3H, s, broad), 3.30-3.37 (16H, m), 7.06 (2H, d, J = 2.44 Hz), 7.56 (2H, d, J = 2.44 Hz), 7.76 (2H, s). MS (75 eV): m/z = 793 [M^+]. $\text{C}_{46}\text{H}_{64}\text{O}_3\text{S}_4$ (793.28); calcd. C 69.25, H 8.13; found C 69.81, H 8.11.

2.4. Synthesis of 2,11,20-Tris(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl [3.3.3]metacyclophane **2**

The synthesis and purification is the same as indicated above, yielding 191 mg (70%) of this cyclic thioketal, a white crystal after recrystallization from hexane, m. p. $254^\circ\text{C} - 255^\circ\text{C}$. IR (KBr): ν [cm^{-1}] = 2960, 2923, 2867, 2822, 1684, 1652, 1634, 1603, 1540, 1481, 1463, 1429, 1392, 1361, 1333, 1296, 1276, 1246, 1203, 1174, 1118, 1016, 956, 883. ^1H NMR (CDCl_3): δ = 1.29 (18H, s), 1.34 (9H, s), 2.72 (3H, s, broad), 2.98 (6H, s, broad), 3.21 (8H, d, J = 14.16 Hz), 3.19 - 3.24 (4H, m), 3.38 (8H, s, broad), 3.50 (4H, d, J = 14.16 Hz), 7.59 (2H, d, J = 1.95 Hz), 7.70 (2H, d, J = 1.95 Hz), 7.74 (2H, s, broad). MS (75 eV): m/z = 883 [M^+]. $\text{C}_{46}\text{H}_{64}\text{O}_3\text{S}_6$ (883.44); calcd. C 65.26, H 7.53; found C 64.87, H 7.17.

2.5. Determination of the Number of Silver Ions Complexed to 2,11,20-Tris(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **2** Using the Mole Ratio Method [19]

A freshly prepared stock solution of the host, cyclic thioketal **2** [40×10^{-5} M] using THF (UV grade) was se-

rially diluted to obtain 10 ml each of various concentrations. 5 ml of each of these solutions was mixed with 5 ml of 5.0×10^{-5} M solution of silver picrate (also in THF). These mixtures were shaken at 26°C for 3 h after which the absorbance of each was measured on a UV spectrophotometer in the wavelength range 500 - 200 nm. Absorbances at 220 nm were plotted against the mole ratio of host to guest which were whole numbers of 1, 2, 3, 4, 5, and 6. The point of inflexion on the mole ratio axis (x-axis) gave the number of silver ions complexed as 3.

3. Results and Discussion

The starting materials 6,15,24-tri-*tert*-butyl-9,18,27-trimethoxy [3.3.3]metacyclophane-2,11,20-trione (**1**) and 6,15,24-tri-*tert*-butyl-9,18,27-trimethoxy[3.3.3]metacyclophane-2,11-dione (**3**) were readily available via well-established procedures [3] [17] [18] [20] [21] in 22% and 68% yields respectively. Their spectral properties [22]-[27] also compared very well with those of literature [4] [5] [28]-[34].

In attempt to convert the flexible [3.3.3]metacyclophane-2,11,20-trione **1** and -2,11-dione **3** into rigid host compounds to be used for complexation studies, sulfuration reactions were carried out on them. Thus ketones **1** and **3** were converted into cyclic thioketals **2** and **4** (Scheme 1). From dynamic ^1H NMR studies, the cyclic thioketal **2** which was found to be slightly flexible in solution at 27°C was fixed in a “partial-cone” conformation below -10°C by the observation of two pairs of doublets for the benzylic protons (relative intensity 2:1) in the ^1H NMR spectrum, Figure 2. Besides other changes in both the aromatic and aliphatic regions of the proton ^1H NMR spectra Figure 2, the aromatic protons gave two slightly broad singlets in the region δ 7.0 - 7.6 ppm below 0°C.

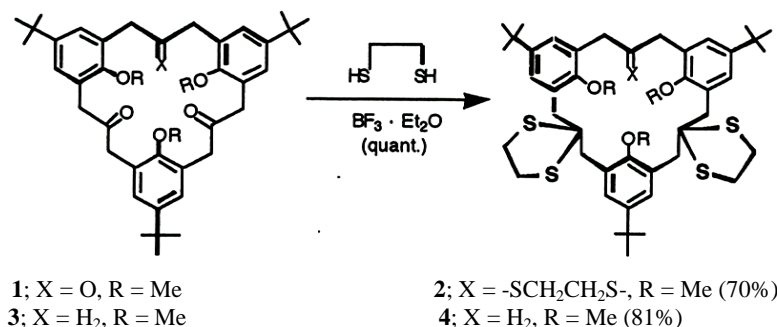
This could be interpreted to mean the inversion of one of the benzene rings, precisely the signal up-field. A further confirmation of this arrangement of the benzene rings could also be deduced from the intensities of the two sets of aromatic signals. The two broad signals have been integrated and show 4 protons at 7.6 ppm and 2 protons at 7.2 ppm which can be interpreted as one of the three benzene rings undergoing inversion.

The coalescence temperature (T_c) for the benzylic protons was found to be 0°C and the free energy of activation for the ring inversion was estimated to be 13.2 kcal/mol. The rate of inversion at the coalescence temperature was calculated from the expression; $K_{\text{coalescence}} = \pi(\Delta\nu^2 + 6J^2)^{1/2}/2^{1/2}$ where $\Delta\nu$ is the difference in chemical shift between the centres of the two doublets arising from the benzylic protons, and J is the coupling constant. Substituting this value into the Eyring rate equation³⁵ gives the expression; $\Delta G^\ddagger = RT \ln(6.62 \times 10^{12}/K_{\text{coalescence}})$ which was used for the estimation of the free energy of activation for ring inversion.

Titration of the cyclic thioketal **2** with $\text{CF}_3\text{SO}_3\text{Ag}$ in acetone- d_6 / CDCl_3 (3:1 v/v), monitored by ^1H NMR, Figure 3, clearly demonstrates that a 1:3 complex with “partial-cone” conformation is formed which is quite stable on the NMR time scale.

This ratio of complexation for the cyclic thioketal **2** with Ag^+ was experimentally confirmed by the mole ratio method, Figure 4. A two-phase solvent extraction experiment indicated that the cyclic thioketal **2** shows a strong affinity for the Ag^+ making it possible for a high Ag^+ selectivity to be observed, Figure 5. The lone pairs of electrons on the sulfur atoms and the π -electrons of the benzene rings might be responsible for the binding of the silver ions. Thus these two groups arrange themselves in a manner forming pockets into which the silver ions enter, Figure 6.

On the contrary, the parent triketone **1** shows a rather poor metal affinity, Figure 5. Shinkai and his co-workers have reported the intramolecular tunneling of Ag^+ through the cavity of 1,3-alternate conformer of calix



Scheme 1. Synthesis of [3.3.3]metacyclophane cyclic thioketals **2** and **4**.

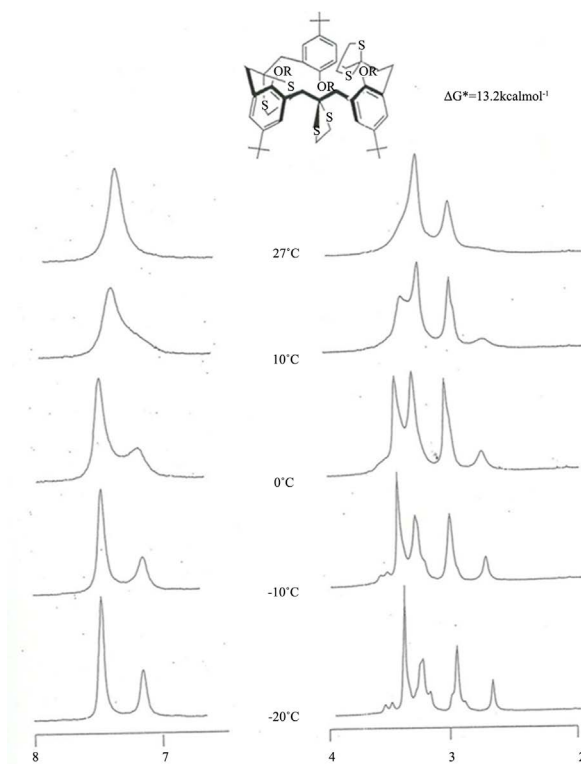


Figure 2. Partial variable temperature ^1H NMR spectra of **2** in $\text{CS}_2/\text{CDCl}_3$ [3:1 v/v] at 270 MHz, δ (ppm) [4] [5].

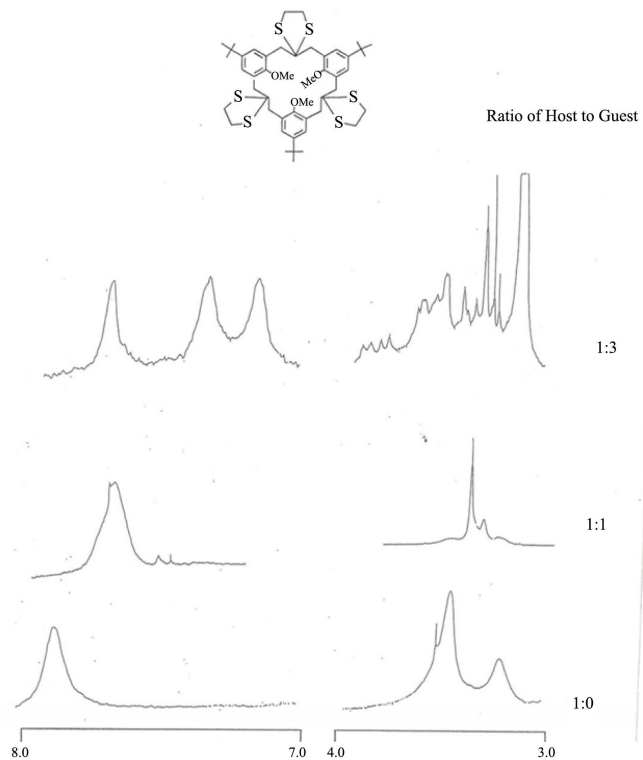


Figure 3. Partial ^1H NMR spectra of the titration of **2** in $\text{Acetone-D}_6/\text{CDCl}_3$ [3:1 v/v] against Ag^+ at 270 MHz, δ (ppm), 27°C.

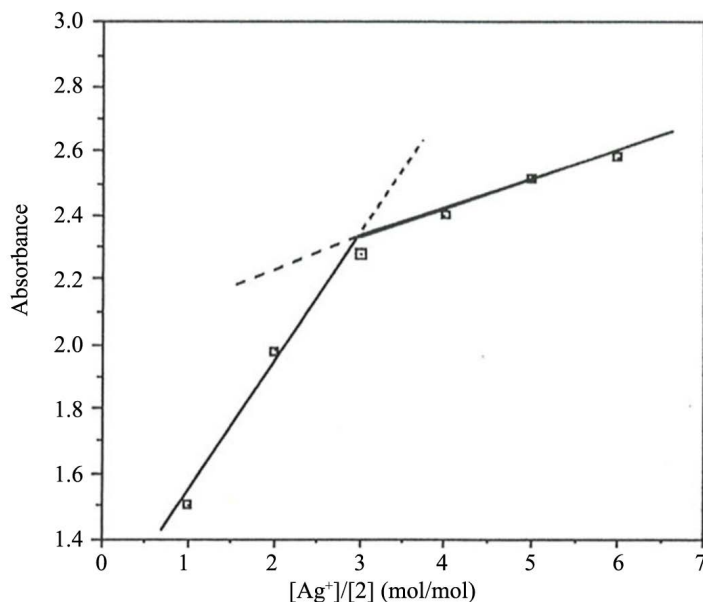


Figure 4. Complexation involving host **2** and silver picrate (mole ratio method).

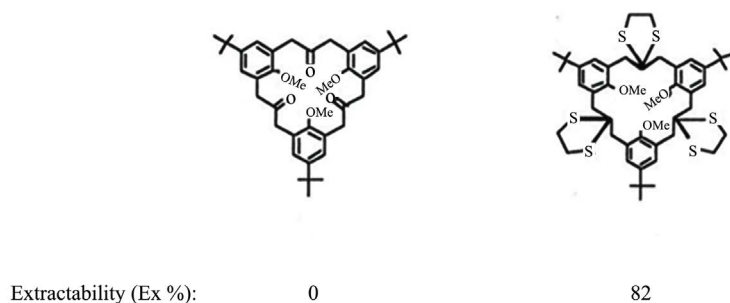


Figure 5. Extraction of silver ions with [3.3.3]metacyclophane derivatives.

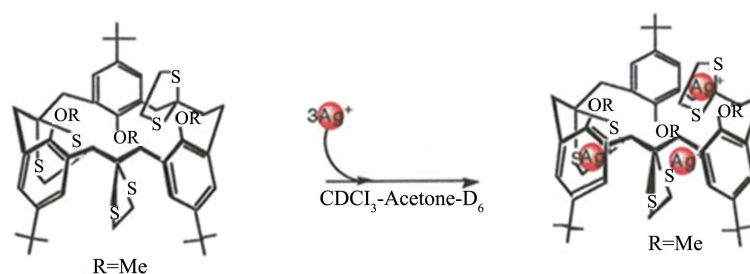


Figure 6. Silver ions filling pockets in compound **2**.

[4] arene, a motion that they named “Metal Tunnelling” [36].

Extraction conditions: Aqueous phase (5 ml) contains AgNO_3 [Guest] (2.5×10^{-4} M) for Ag^+ . Organic phase (CH_2Cl_2 , 5 ml) contains [3.3.3]metacyclophane derivative (Host) (2.5×10^{-4} M). Extractabilities were determined by U. V. spectroscopy.

Interestingly, an intramolecular Ag^+ rolling phenomenon in which the Ag^+ rolls from one binding site to the other in a circular motion like a “Molecular Roulette” was observed for the first time by ^1H NMR spectroscopy in the 1:1 complex between the cyclic thioketal **2** and Ag^+ above room temperature, **Figure 7** and **Figure 8**. A mole ratio of 1:1 of the cyclic thioketal **2** and Ag^+ seems to portray a picture in which the Ag^+ undergoes an in-

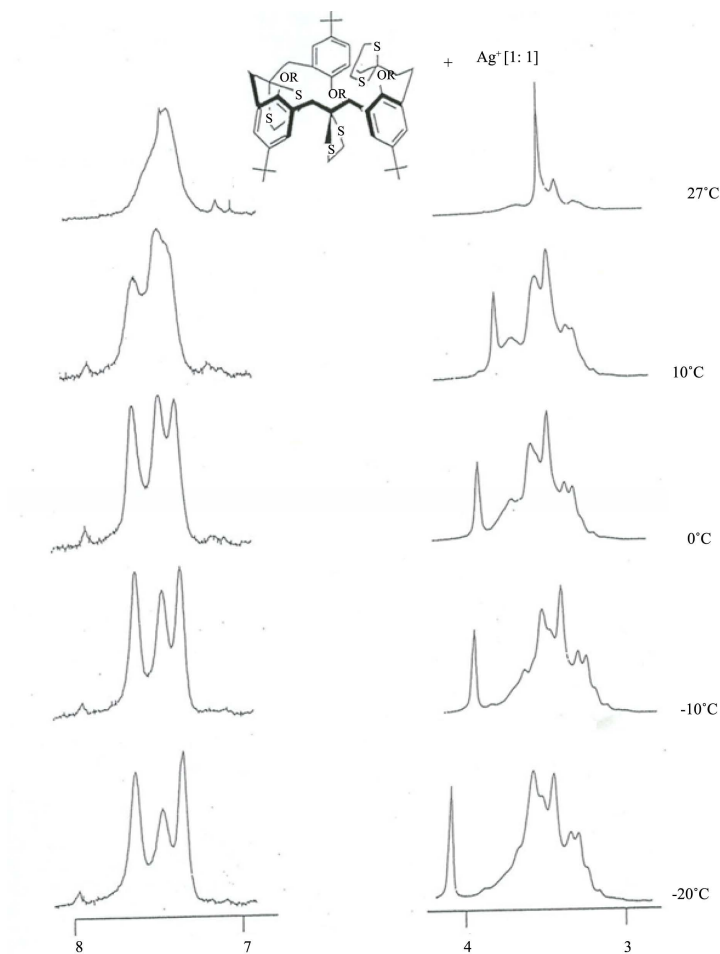


Figure 7. Partial variable temperature ^1H NMR spectra of the titration of **2** + $\text{CF}_3\text{SO}_3\text{Ag}$ [1:1 mol/mol] in acetone- D_6/CDCl_3 [3:1 v/v] at 270 MHz, δ (ppm) [4] [5].

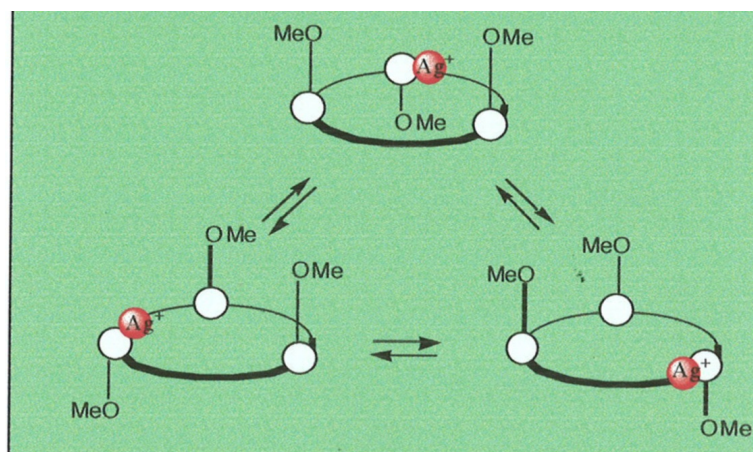


Figure 8. Intramolecular Ag^+ rolling phenomenon like a “Molecular Roulette”.

termolecular motion between the uncomplexed cyclic thioketal **2** and the complexed, **Figure 9**. One cannot rule out the possibility of the intramolecular motion, like that of the “Molecular Roulette”, also occurring in this sys-

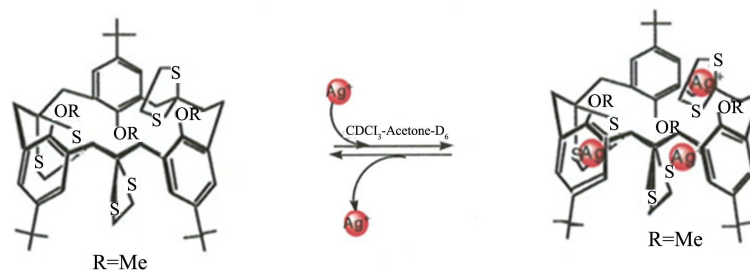


Figure 9. The inter- and intramolecular motion between uncomplexed and complexed cyclic thioketal **2**.

tem. Similar studies involving the cyclic thioketal **4** are currently going on.

4. Conclusion

We have synthesized 2,11,20-tris(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **2** and 2,11-bis(ethanedithia)-9,18,27-trimethoxy-6,15,24-tri-tert-butyl[3.3.3]metacyclophane **4** in yields of 70% and 81% respectively. Solution Proton Nuclear Magnetic Resonance (^1H NMR) studies revealed the conformations of **2** and **4** to be partial-cone. The affinity of compound **2** for silver ions was found to be 82% high. The multi-membered carbon skeleton of the [3.3.3]metacyclophane system was very stable as it allowed the introduction of the thio functional groups into the carbonyl units without ring-opening side reactions. The studies so far have shown an Intramolecular Motion by the silver ions within compound **2** that we have named “**Molecular Roulette**”, the first of its kind within the [3.3.3]metacyclophanes and their derivatives.

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