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The template synthesis and complexation properties of methoxypyrogallo[4]arene

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Abstract—A template method for the synthesis of methoxypyrogallo[4]arene was presented. A complexation of MPA with strong electron acceptors was observed. The ESI-MS analysis showed strong complexing properties of MPA towards alkali metal cations. The ionophore properties of MPA were investigated. The quantum-mechanical calculations were performed for the resulting complexes.

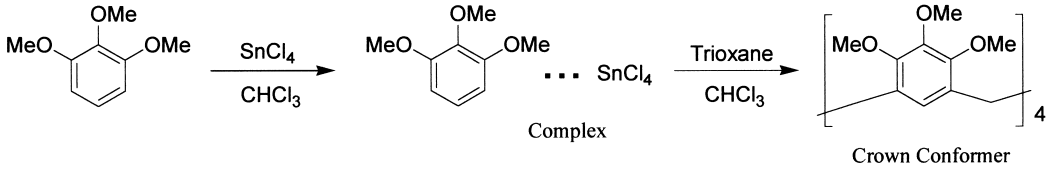
1. Introduction

Extensive studies on the application of Lewis acids in organic synthesis have been conducted for many years. They have also found application in the synthesis of calixarenes.[1–5] Our former investigation concerned the Lewis acid-catalysed synthesis of octamethoxyresorc[4]-arene from 1,3-dimethoxybenzene and aliphatic aldehydes.[6] Among the many Lewis acids tried, only $SnCl_4$ catalyses this reaction selectively, to give the octamethoxy-resorc[4]arene crown conformer. This is very important from the synthetic viewpoint, thus allowing the synthesis of the methoxyresorc[4]arene crown conformers in a one-step procedure. This paper demonstrates novel possibilities of using $SnCl_4$ as a catalyst for the reaction of 1,2,3-trimethoxybenzene (TMB) with trioxane. This reaction affords the methoxypyrogallo[4]arene (MPA) crown conformer via the charge-transfer (CT) complex of TMB and $SnCl_4$, according to Scheme 1. The complexing properties of this compound were studied.

The reaction of TMB with other aliphatic aldehydes failed to give the expected results. Only the reaction with trioxane gives methoxypyrogallo[4]arene in 75% yield. This reaction appears to be a typical template reaction. The TMB–$SnCl_4$ complex precipitates during the synthesis. Following addition of trioxane to the chloroform solution of this complex, the complex dissolves and the reaction solution—initially yellowish—turns violet. After a minute or two, the dark violet complex of calixarene with $SnCl_4$ precipitates. Following addition of methanol the complex dissolves again, and MPA precipitates from the solution after several hours of stirring. The ^1H NMR spectra indicate formation of the crown conformer of MPA only. The signal for the methylene bridge is a broad singlet that indicates a dynamic effect typical for high-molecular mass compounds with strong dipolar interactions of the nuclei and steric hindrance of the rotation. The signals of other groups are singlets only.

2. Complexation with strong electron acceptors

The complexing properties of MPA towards tetracyano-ethylene (TCNE), tetrachlorobenzoquinone (TClQ) and tetracyanoquinodimethane (TCNQ) were tested. Only in the case of TCNE, was a distinct absorption band



Scheme 1.

Keywords: pyrogallo[4]arene; template reaction; ESI-MS; complexation; ion-selective membrane electrodes.
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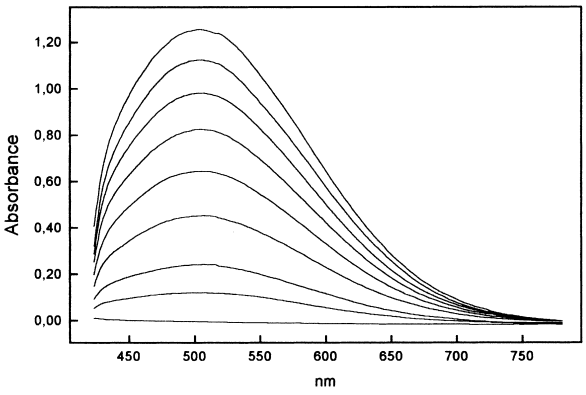


Figure 1. Changes in the absorption spectrum of TCNE in chloroform resulting from addition of MPA. The TCNE concentration is 0.0109 M, the MPA concentration varies from 0.0054 to 0.0758 M. The spectra were taken at 20°C.

(λ_{max}=504 nm) observed in the long-wave part of the UV–vis spectrum after addition of MPA to the solution of TCNE in chloroform (Fig. 1).

Using the Job method, it was found that the complexes of MPA with TCNE in chloroform had the 1:1 stoichiometry (Fig. 2). The formation constants of the discussed complex were evaluated by the Benesi–Hildebrand method.[7] The results are presented in Table 1. These calculations confirm the 1:1 stoichiometry of the complex.

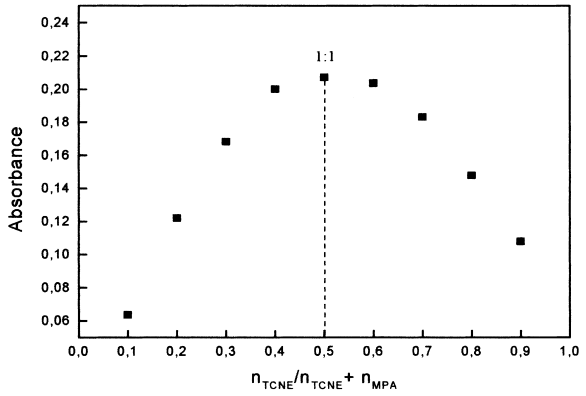


Figure 2. Determination of the composition of TCNE–MPA crown conformer complex by the Job method. The total concentration of MPA and TCNE is 1.1×10^{-3} M.

Table 1. The values of formation constant (K), molar absorption coefficient (ε) and goodness of fit parameter (R^2) at the temperature of 293–333 K, calculated from the Benesi–Hildebrand equation. The last row shows the changes in the formation enthalpy (ΔH) and formation entropy (ΔS) of the MPA–tetracyanoethylene complex in chloroform.

T (K)	K (M^{-1})	ε (M)	R
293	6.49±0.24	341.96	0.9998
303	5.24±0.63	385.43	0.9996
313	4.38±0.38	398.54	0.9999
323	3.45±0.20	464.99	0.9999
333	2.60±0.15	556.93	0.9999
ΔH=−18.17±1.24 kJ mol^{-1}, ΔS=−46.21±0.40 J mol^{-1} K^{-1}			

Table 1 also shows the thermodynamic parameters of the complex formed, which were calculated using the vant' Hoff equation.

These results indicate formation of the 1:1 complex between MPA and TCNE. The ^{1}H NMR spectra of MPA in the presence of the equimolar amount of TCNE in chloroform do not exhibit any considerable change ($\Delta\delta_{max.}$=0.002) in relation to free MPA. Therefore, this technique does not allow us to suggest the structure of the complex formed. In order to suggest its structure a quantum-mechanical calculation was performed. Our previous work[6] demonstrated that the TCNE–OMRA complexes are of the external type, i.e. the TCNE molecule binds to OMRA from the outside. Therefore, the AM1 calculation (MOPAC 6.0[8]) was performed for such an external complex.

Fig. 3 presents the calculated changes in heat of formation of the MPA–TCNE complex vs the distance of the complex components.

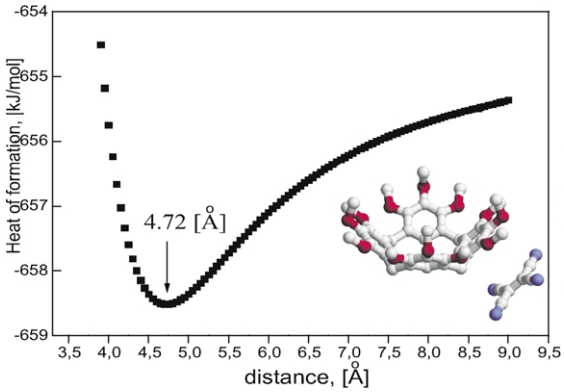


Figure 3. Heat of formation of the MPA–TCNE complex in relation to the distance between the complex components.

The results of the calculation for the external complex show only slight charge transfer from the MPA crown conformer molecule to the TCNE molecule. This is reflected by the slight changes in the π-electron density of MPA compared to the free molecule and by ionisation potentials of the complex formed. The equilibrium distance in this complex is 4.72 Å and it is slightly greater than that for the OMRA–TCNE complex.[6] This results from the larger steric hindrance caused by the OMe groups in MPA in relation to OMRA. These data indicate that a stable external complex is formed due to the π···π interaction between TCNE and one of the aromatic rings of the crown conformer of OMRA. Besides, the 'sandwich-type' arrangement, which is observed for the CT-complexes of TCNE, favours such a type of a complex being formed.

3. The complexation properties of MPA towards the metal cations

The crown conformers of calixarenes are often used as receptors in complexation studies.[1,9] Due to the presence of 12 OMe groups, MPA may resemble a crown ether in its characteristics. This compound was tested for complexation with alkali metal cations by ESI-MS. Fig. 4 shows an

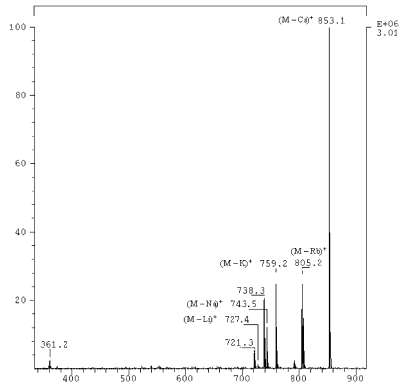


Figure 4. ESI-mass spectrum of MPA in the presence of alkali metal cations in the mixed solvent acetonitrile–water.

ESI-mass spectra (ESI-MI) for equal concentrations (5×10^{-4} M) of MPA and the appropriate alkali metal cations in acetonitrile–water (9:1). The Na^+, K^+, Rb^+, and Cs^+ cations are approximately 8, 20, 21 and 70 times more complexed, respectively, than the least complexed Li^+ cation. This trend is confirmed also by the quantum-mechanical calculation. The heats of formation of complexes of MPA with Li^+, Na^+, and K^+ cations were computed using MNDO (MOPAC 6.0).[8]

Fig. 5 shows the heat of formation in relation to distance of the metal cation from the reference point. This reference point was selected arbitrarily inside the MPA molecule, between the hydrogen atoms of the pyrogalloarene ring.

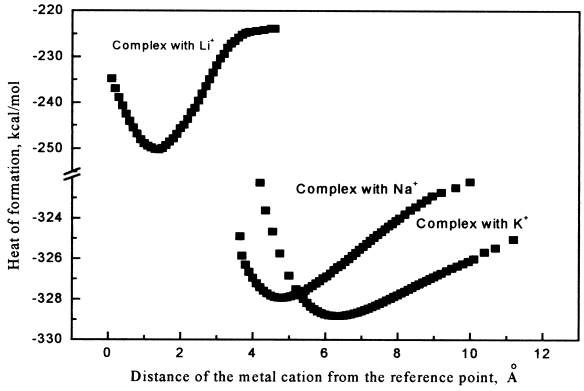


Figure 5. Heat of formation of the complexes of MPA with Li^+, Na^+ and K^+ cations versus distance of the metal cation from the reference point.

The calculation indicates that the K^+ cation is the most strongly complexed, the Na^+ cation is the next, and the Li^+ cation is the least complexed one. The Rb^+ and Cs^+ cations were excluded from the calculation because of lack of parameterisation. The distances calculated for the Li^+, Na^+, and K^+ cations in the complex were 1.36, 4.77 and 6.35 Å, respectively. Theoretical calculation indicates that the most stable conformation of calixarene in the complex is the crown conformation for the K^+ cation, next the crown conformation for the Na^+ cation and the boat conformation for the Li^+ cation (Scheme 2). The conformation of the complex with the potassium, rubidium and caesium ions is stabilised mainly by the interactions of the cation with the OMe groups. These interactions, as well as the interactions with the π-electron system are observed for the sodium ion. In the case of the lithium ion, which is located near the lowest pyrogalloarene ring carbons, the interactions with the π-electron system predominate.

4. The ionophore properties of MPA

Additional studies were conducted in order to estimate the complexation properties of MPA. This compound was used as an ionophore in the ion-selective membrane electrodes made of PVC plasticised with bis(1-butylpentyl) adipate (BPPA). The complexation with alkali metal cations: Li^+, Na^+, K^+, Rb^+, Cs^+; alkaline earth metal cations: Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}; several transition metal cations: Ni^{2+}, Cu^{2+}, Zn^{2+}; and tetramethylammonium cation (TMA^+), guanidinium chloride (G^+Cl^-), and ammonium chloride NH_4Cl was investigated.

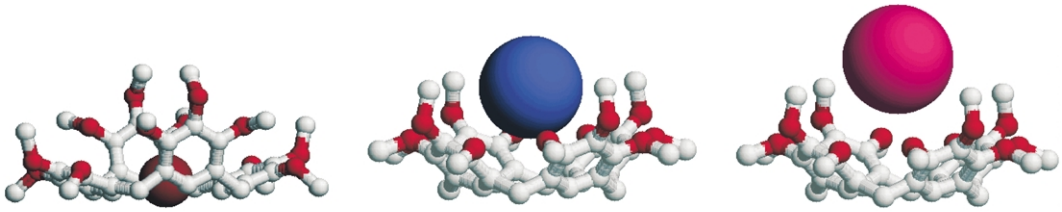
4.1. The electrode characteristics and selectivity coefficients

The characteristics of the studied electrode #1 containing MPA and blank electrode #2 containing no ionophore but the same amount of other components are shown in Table 2.

The selectivity coefficients ($\log K_{A,M}^{pot}$) were determined by the separate solution method (SSM)[10] and calculated using the Nicolsky–Eisenman[11] equation:

$$E = E_0 + S\log\left[(a_A) + K_{A,M}^{pot}\right](a_M)^{z_A/z_M}$$

where E is the measured potential; E_0 is a constant that includes the standard potential of the electrode, the reference electrode potential and the junction potential; z_A and z_M are charges of primary ion A and of the interfering ion M; a_A



boat conformation for Li^+ *crown conformation for Na^+* *crown conformation for K^+*

Scheme 2.

Table 2. The characteristics of the studied membrane electrodes

Electrode	Ion A	S (mV)	Linear range ($-\log a_A$)
#1	TMA^+	50	−6.0 to −1.0
	G^+	57	−6.5 to −1.0
	Cs^+	59	−4.5 to −1.0
	H^+	45	−5.2 to −1.0
#2	TMA^+	48	−5.5 to −1.0
	G^+	50	−6.0 to −1.0
	Cs^+	45	−4.8 to −1.0
	H^+	45	−4.5 to −1.0

and a_M are the activities of the primary ion A and interfering ion M; $K_{A,M}^{pot}$ is the potentiometric selectivity coefficient for the primary ion A against the interfering ion M; S, the slope, is defined as $S = 2.3RT/zF$ where R, T and F have usual meanings.

The calculation was made using the equation:

$$\log K_{A,M}^{pot} = [(E_M - E_A)/S] + (1 - z_A/z_M)\log a_A$$

The potential of the cell was measured with two separate solutions. Table 3 shows the values of the selectivity coefficients for these two electrodes.

Table 3. The selectivity coefficients for two membrane electrodes #1 and #2

Ion A	$\log K^{pot}_{TMA,A}$	
	Electrode #1	Electrode #2
G^+	+1.46	+0.54
TMA^+	0	0
H^+	–	−0.74
Li^+	−0.6	−1.82
Na^+	−0.67	−1.52
K^+	−0.27	−1.34
Rb^+	−0.12	−1.26
Cs^+	−0.04	−1.2
NH_4^+	−0.11	−1.47
Mg^{2+}	−2.4	−3.7
Ca^{2+}	−2.0	−3.9
Sr^{2+}	−2.07	−3.6
Ba^{2+}	−0.7	−3.06
Cu^{2+}	−1.2	−2.42
Ni^{2+}	−1.1	−2.4
Zn^{2+}	−1.4	−2.44

The investigated ionophore shows some selectivity for the guanidinium cation. The importance of guanidinium derivatives such as creatinine, creatine or arginine and methylguanidine in biology and medicine is the reason for search for guanidinium ion (G^+) sensors.[12,13] The suitable size of the macrocyclic ring of the ligand and possibility of hydrogen bond formation between guanidinium NH_2 groups and phenolic OMe might stabilise such a complex. The selectivity of the electrode is $\log K^{pot}_{G,Na} = -2.1$ and $\log K^{pot}_{G,K} = -1.73$. In the series of alkali metal ions, the softer acids (Cs^+) are better complexed then the harder ones (Li^+, Na^+). The order of selectivity is: $Cs^+ > Rb^+ > K^+ > Li^+ > Na^+$. This agrees well with the findings resulting from ESI-MI. The membrane electrode is almost as selective for the Cs^+ ion as for the TMA^+ cation, which is softer acid than the caesium cation. The studied ligand does not fulfil all requirements for ionophoric behaviour in the membrane electrode. One should not expect to find a good selectivity for the MPA ligand, which possesses four aromatic rings ($\pi-\pi$) and eight OMe groups as electron donors. On the other hand, the membrane with no ionophore (#2) exhibits quite a similar selectivity order. One can conclude that it is rather an ionic additive (KTClPB) that facilitates ion transfer across the membrane/solution interface. Stabilisation of some of the formed complexes by the MPA ligand (for example: G^+MPA, Cs^+MPA) is responsible for a better selectivity of electrode #1.

5. Experimental

5.1. General

^{1}H NMR spectra of solutions in $CDCl_3$ (internal standard: Me_4Si) were recorded with a Bruker AM-300 spectrometer. ESI-mass spectra were recorded with Finigan-Mat 312. UV–vis spectra were taken on an Specord 500 spectrophotometer.

5.2. Reagents

1,3-Dimethoxybenzene, trioxane and tin tetrachloride were from Acros. Poly(vinyl chloride) (PVC), and bis(2-butylpentyl)adipate (BBPA), potassium tetrakis(4-chlorophenyl)borate (KTClPB) and chloroform for spectroscopy were from Fluka. Tetrahydrofuran (THF), from POCh, was dried and freshly distilled before use. All aqueous solutions were prepared with redistilled water (conductivity<2 μS cm^{-1}). The salts LiCl, NaCl, KCl, NH_4Cl, $MgCl_2$, $SrCl_2$, $BaCl_2$, $NiCl_2$, $CuCl_2$, $ZnCl_2$, (POCh) and $CaCl_2$, tetramethylammonium chloride (TMA)Cl, guanidinium chloride (GCl) (Fluka), RbCl and CsCl (Ubichem Ltd), were of p.a. grade. TCNE, TClQ and TCNQ were purified by sublimation.

5.3. Spectroscopic measurements

The continuous variation method was employed to estimate the stoichiometry of the complexes at 25°C. The concentration of [MPA+TCNE] was kept constant (5×10^{-2} M). For the determination of formation constants, a series of solutions containing TCNE (5.0×10^{-2} M) and varying concentrations of crown conformer MPA (4.3×10^{-3}–3.8×10^{-2} M) were prepared in a cell of 1.0 cm path length.

5.4. Preparation of the membranes and measurement of the cell potential

The components of membrane #1 (2.5 wt% of ionophore, 33 wt% PVC, 65 wt% plasticiser and 20 mol% KTClPB (with respect to the ionophore), about 200 mg in total, were dissolved in 1.5 ml of freshly distilled THF. The solution was poured into a glass ring as described previously[14]. The membrane #2 (blank) had the same composition except the ionophore. After evaporation of the solvent the membranes were used for making the electrodes. The plasticiser BBPA was used in both membranes. The membranes were incorporated into Ag/AgCl electrodes IS

561 (Fluka). 0.01 M KCl was used as an internal electrolyte. A double-junction reference electrode Radelkis 0P0820P was used with 1 M NH_4NO_3 solution in a bridge cell. The potentials were measured at 20°C using a METROHM 654 pH-meter. All measurements were carried out at room temperature (20°C) with cells of the type:

Ag|AgCl|1 M KCl|1 M NH_4NO_3|sample||membrane||

0.01 M KCl|AgCl|Ag

The measured salt solutions were prepared by successive dilution of initial 5×10^{-2} mol dm^{-3} stock solution. The sample was diluted until further dilution gave no change of potential. The activity coefficients were calculated according to the Debye–Hückel approximation.[15] The selectivity coefficients were determined by the separate solution method (SSM).

5.4.1. The synthesis of MPAV. In a typical experiment, TMB (1 g) was dissolved in 10 ml of $CHCl_3$, after which $SnCl_4$ (1 equiv.) was added to the solution. The TMB–$SnCl_4$ complex precipitated after a minute or two. Then trioxane (1 equiv.) in $CHCl_3$ (5 ml) was added to the reaction mixture, after which the complex dissolved, and the reaction mixture, initially colourless, turned dark-violet. After stirring for 3 h at room temperature, the MPA–$SnCl_4$ complex precipitated. Chloroform was decanted, and methanol (20 ml) was added to the precipitate. After several hours of stirring, MPA precipitated from the solution. The resulting precipitate was collected by filtration and crystallised from ethanol to give the crown conformer in 75% yield. Mp 181–183°C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 3.747 (s, 24H, OCH_3), 3.790 (s, 8H, CH_2), 3.877 (s, 12H, OCH_3), 6.190 (s, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 29.056, 60.513, 125.023, 129.208, 146.082, 149.977; ESI-MS, 721.3 ($1-H^+$), 727.4 ($1-Li^+$), 743.5 ($1-Na^+$), 759.2 ($1-K^+$), 805.2 ($1-Rb^+$), 853.1 ($1-Cs^+$); HRMS: 720.31397, Calcd: 720.31458.

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