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# Macrocycles with a phenothiazine core: synthesis, structural analysis, and electronic properties

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### ABSTRACT

New phenothiazine macrocycles with polyethyleneoxy chains were synthesized in good yields by reacting 10-ethyl-10*H*-3,7-di(3-hydroxyphenyl)phenothiazine with diiodurated or ditosylated polyethyleneglycols. Their structures were investigated by NMR spectroscopy and single crystal X-ray crystallography in the case of one compound. The electronic properties were determined by absorption spectroscopy and cyclic voltammetry and their complexation ability for alkali cations was investigated by ES-HRMS.

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Phenothiazine is an important nitrogen-sulfur heterocycle and its derivatives exhibit broad pharmacological and biological activities, being used as sedatives, tranquilizers, antituberculotics, antipyretics, antitumor agents, bactericides, or parasiticides.<sup>1</sup> Phenothiazine derivatives have good donor abilities and low oxidation potential and form stable radical cations<sup>2</sup> and their physiological activities can be attributed to these properties.<sup>1,3</sup> Phenothiazine has a 'butterfly structure',<sup>4</sup> and on oxidation to radical cation adopts a planar geometry. Due to its interesting properties, phenothiazine has become a popular heterocyclic unit used in material sciences<sup>5</sup> and also in biology and biochemistry as a marker for proteins, DNA, or other biochemical systems.<sup>6</sup> Phenothiazine is found as a core unit in redox-active alkylated<sup>7</sup> and heteroarylated<sup>8</sup> bi- and terphenothiazines, oligophenothiazine-fullerene dyads,<sup>9</sup> cruciform fluorophores,<sup>10</sup> molecular wires,<sup>11</sup> or ligands for surface modification.<sup>12</sup> There are very few reported macrocycles with phenothiazine units, the most representative being the cyclophanes with phenothiazine and bipyridinium or with two phenothiazine units.<sup>13</sup>

Herein we report the synthesis, structural analysis, and complexation studies of the first phenothiazine macrocycles embedded in ethylenoxide chains of various lengths (Scheme 1).

The building block for the synthesis of the target macrocycles was the diphenol **5** which was obtained via a multistep procedure

starting from 10*H*-phenothiazine **1** (Scheme 1). The alkylation of **1** with ethyl iodide was followed by core bromination of 10-ethyl-10*H*-phenothiazine **2** to afford **3** in 76% yield.<sup>14</sup> The diboronic diester **4** was synthesized according to the literature,<sup>15</sup> and further subjected to Suzuki cross-coupling<sup>16</sup> with 3-bromophenol to give 10-ethyl-10*H*-3,7-di(3-hydroxyphenyl)phenothiazine **5** in good yield (60%). Next, diphenol **5** was reacted with either diiodurated or ditosylated polyethyleneglycols in acetonitrile at high dilution, to afford the macrocycles **6** with different cavity sizes (Scheme 1, yields up to 32%).<sup>17</sup>

The structure of the macrocycles **6** was confirmed by their mass and NMR spectra and also by single crystal X-ray diffraction for **6b** (Fig. 1).<sup>18</sup>

The solid state molecular structure shows the butterfly conformation of the phenothiazine core with a boat conformation for the six-membered heterocycle and a bowsprit orientation of the ethyl substituent located on the N atom (Fig. 1). On the other hand, there are four types of molecules in the lattice (Fig. 2a), which exhibit differences between the torsion angles of the aromatic units and between the torsion angles in the chains. The angles between the planes of the benzene units of the phenothiazine core have different values in the four types of molecules ( $\alpha = 28.6^{\circ}$ ,  $32.1^{\circ}$ ,  $41.4^{\circ}$ , and  $46.7^{\circ}$ ). The aromatic substituents at positions 3 and 7 are not coplanar with the benzene rings of the phenothiazine units and the dihedral angles between their planes are all different, the eight values varying from  $13.15^{\circ}$  to  $34.47^{\circ}$ . This peculiar situation occurs as the result of numerous C–H…p and C–H… $\pi$  contacts, which





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Scheme 1.



Figure 1. Molecular structure of macrocycle 6b.

ensure the favorable packing in the lattice. Thus, one can consider the lattice to be formed by pairs of macrocycles (highlighted in different colors: blue–orange and green–pink) exhibiting perpendicular phenothiazine cores (Fig. 2a).

In each pair considered, the benzene rings of the phenothiazine cores and one phenol ring exhibit edge-tilted to face (T) structures (Fig. 2b and c). Thus, in the green–pink assembly, the dihedral angles between the similar aromatic rings are  $\alpha = 76.83^{\circ}$  and  $84.36^{\circ}$  for the rings of the phenothiazine core and  $\alpha = 62.14^{\circ}$  for the phenol rings, while the C–H··· $\pi$  contacts correspond to the H-centroid of aromatic ring distances d = 2.941, 2.823, and 3.039 Å. The similar data for the orange–blue assembly are:  $\alpha = 79.15^{\circ}$ ,  $84.95^{\circ}$ , and  $67.92^{\circ}$  and d = 2.904, 2.814, and 3.093 Å, respectively. Additionally, C–H··· $\pi$  contacts between H atoms of the chains and aromatic units of the neighboring macrocycles could also be observed in both assemblies [d = 2.893 Å (Fig. 2b) and d = 2.806 Å (Fig. 2c)].

Some relevant interactions can be also noticed between molecules belonging to different assemblies. For the green–blue (Fig. 2d) and pink–orange (Fig. 2e) pairs, T structures involving one of the benzene rings of the phenothiazine cores could be observed. The characteristic data are:  $\alpha = 85.09^{\circ}$  and  $84.28^{\circ}$ ; d = 2.759 and 2.960 Å, respectively. C–H··· $\pi$  contacts involving the H atoms of the methyl groups of the orange and green molecules respectively, and the phenol units of their partners were also revealed (distances from the H atom to the centroid of the aromatic unit d = 2.905 and 3.110 Å, respectively). Other details of the intermolecular C–H··· $\pi$  contacts in the lattice are given in the SI. The oxygen atoms of the chains exhibit intra- and intermolecular C– $H \cdots p$  contacts involving the H atoms of the polyethyleneoxide units (see the Supplementary data).

The <sup>1</sup>H NMR spectra of **6a–c** exhibit characteristic patterns for the phenothiazine core and for the polyethyleneoxide chains with four, five, and six ethyleneoxy units, respectively. The similar aromatic units as well as the similar parts of the ethyleneoxy chains are magnetically equivalent showing unique sets of signals. However, a certain flexibility of the chains and a partial rotation of the aromatic substituents of the heterocyclic core have to be taken into consideration, and these motions, at the average of the conformational equilibria, render the similar groups of the macrocycles equivalent in the NMR.

The electronic properties of the macrocycles **6a-c** were investigated by UV-Vis absorption spectra and cyclic voltammetry. The electrochemical data of the compounds **6a-c** were obtained by cyclic voltammetry at room temperature in the anodic region, and the redox potentials calculated against ferrocene are summarized in Table 1. The one-electron reversible oxidation potentials of phenothiazine derivatives 6a-c are in the expected regions for phenothiazine derivatives and correspond to the formation of stable phenothiazine radical cations. Compared to N-methyl-phenothiazine  $(E_0^{0/+1} = 767 \text{ mV})^{7c}$  and *N*-hexyl-phenothiazine  $[(E_0^{0/+1} = 10^{-1} \text{ mV})^{7c}]$ 728 mV),<sup>7c</sup> *N*-ethyl-phenothiazine has, most probably, an intermediate value of  $E_0^{0/+1}$ ], anodic shifts being observed for macrocycles **6a–c**. This is consistent with the electrochemical behavior of other 3,7-aryl substituted phenothiazines bearing electronwithdrawing groups.<sup>14</sup> The difference in  $E_0^{0/+1}$  of the three macrocycles is probably due to the enclosure of the macrocycles which favors the increase of the torsion angle of the benzene rings belonging to the phenoxy units with respect to the phenothiazine core. The quasi-orthogonal orientation of the benzene rings reduces the influence of the phenoxy substituents to the -I effect. The higher observed value of the  $E_0^{0/+1}$  (824 mV) for the

Table 1					
Selected	electronic	properties	of	macrocycles	6a-6

$E_0^{0/+1b}$ (mV)	
824 777 786	

<sup>a</sup> Adsorption spectra were recorded at room temperature in CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Cyclic voltammetry measurements were performed in CH<sub>2</sub>Cl<sub>2</sub> at rt,  $\nu = 100$  mV/ s, electrolyte: <sup>n</sup>Bu<sub>4</sub>N<sup>+</sup>PF<sub>6</sub><sup>-</sup>, Pt working electrode, Pt counter electrode, and Ag/AgCl pseudo reference electrode.



**Figure 2.** (a) Part of the crystal structure of **6b** showing the four different types of molecules; view of the lattice showing selected C-H···π interactions between the pair of molecules, (b) green–pink assembly, (c) orange–blue assembly, (d) green–blue assembly, (e) pink–orange assembly.

macrocycle with the shortest chain **6a**, could be attributed to a nearly coplanar disposition of the phenolic rings with respect to the phenothiazine unit (conformation in which both -I effect of OH group and -E effect of the phenyl ring can operate). A coplanar disposition of the aromatic rings ensures the shortest distance between the oxygen atoms of the phenoxy substituents. The increasing number of the ethyleneoxy units leads to an increase of the torsion of the phenoxy substituents of the phenothiazine core hav-

ing as result the decrease of the  $E_0^{0/+1}$  values. A similar trend was observed for the variation of  $\lambda_{\max}$  (in these cases diminishing of the  $\lambda_{\max}$  values) when the spectra of **6b** and those of **6a** and **6c** were compared.

In order to investigate their ability to complexation of alkali metal cations, which is characteristic for the crown ether class,<sup>19</sup> the macrocycles **6a–c** were subjected to ES-HRMS experiments that revealed high affinities for Li<sup>+</sup>, Na<sup>+</sup>, and K<sup>+</sup> cations. The investigations

#### Table 2

Relative intensity peaks of complexes of macrocycles 6a-c and alkali metal cations (samples of equimolecular amounts of  $1.5 \times 10^{-4}$  M solution of **6** dissolved in acetonitrile and 1:1:1:1:1 mixture of LiCl, NaSCN, KSCN, Rb<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub>, each salt  $1.5 \times 10^{-4}$  M solution dissolved in acetonitrile).

	<b>6a</b> (%)	<b>6b</b> (%)	<b>6c</b> (%)
[M+Li] <sup>+</sup>	100	37	6
[M+Na] <sup>+</sup>	78	100	59
[M+K] <sup>+</sup>	78	60	100
[M+Rb] <sup>+</sup>	-	-	_
[M+Cs] <sup>+</sup>	-	-	2
[2M+K] <sup>+</sup>	11	21	4

were performed with solutions containing equimolecular amounts of multicomponent mixtures formed by the macrocyclic host and the five guest cations as well as samples containing the macrocycle and a single guest cation. Thus, the mass spectra of the solutions of equimolecular amounts of macrocycle 6 and LiCl, NaSCN, KSCN, Rb<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub> showed the highest preference to formation of  $[6a+Li]^+$ ,  $[6b+Na]^+$ , and  $[6c+K]^+$  complexes, respectively (Table 2), according to the macrocycle cavity size. Macrocycles **6a** and **6b**, with four and five ethyleneoxy units, also exhibited a peak corresponding to sandwich<sup>20</sup> [2M+K]<sup>+</sup> complexes, besides the 1:1 complex with  $K^+$  (Table 2). There were no traces of the  $[M+Rb^+]$  or  $[M+Cs^+]$  peaks for macrocycles **6** even in the samples containing only the macrocycle and rubidium or cesium carbonate, except for **6c** which exhibited a peak corresponding to the complex with Cs<sup>+</sup> (Table 2). However, the experiments conducted with lithium chloride revealed some interesting aspects. The ES-HRMS spectra of the samples of macrocycles 6 and LiCl showed no affinity for the lithium cation, while in the samples of 6 with equimolecular amounts of the alkali metal salts, the corresponding [M+Li]<sup>+</sup> peak was present (Table 2). This noticeable change in complexation ability can be explained by the change in pH to slightly basic,<sup>21</sup> since in the samples containing all alkali metal salts the corresponding carbonates (for Rb and Cs) or thiocyanates (for Na and K) were used and chloride for Li.

In summary, we report here the synthesis, structural analysis, and complexation ability of new phenothiazine macrocycles. To the best of our knowledge these are the first examples of crown ethers embedding phenothiazine units. Macrocycles 6 exhibit an electrochemical behavior similar to N-alkyl phenothiazine. The ES-HRMS experiments performed in order to determine the affinity of **6** for alkali cations, revealed a high affinity of **6a** for Li<sup>+</sup>, **6b** for  $Na^+$ , and **6c** for  $K^+$ , respectively. In the case of **6b**, the solid state molecular structure investigations showed numerous intra- and intermolecular C–H···p and C–H··· $\pi$  interactions.

## Acknowledgements

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# Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2012.12.068.

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- 17. General procedure for the synthesis of macrocycles 6a-c: A solution of 1 mmol of diiodurated tetraethylene glycol (for 6a), ditosylated pentaethylene glycol (for 6b), and ditosylated hexaethylene glycol (for 6c) in dry acetonitrile was added over 3 days to a solution of diphenol 5 (1 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (5 mmol) in dry acetonitrile at reflux. The stirring under reflux was continued for additional 4 days. After cooling to room temperature, water (100 ml) and dichloromethane (50 ml) were added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2  $\times$  50 ml). The combined organic layers were washed with brine, dried with sodium sulfate and the solvents were removed in vacuum. The residue was adsorbed on silica gel and was purified by column chromatography

29-Ethyl-7,10,13,16,19-pentaoxa-37-thia-29-aza-hexacyclo [23.7.5.1.<sup>2.6</sup>1.<sup>20.24</sup>0.<sup>28,36</sup>0.<sup>30,38</sup>]-nonatriconta-1(32),2,4,6(33),

- 20(34),21,23,25,27,30,35,37-dodecaene (6a)

Yield 32% (182 mg), light green solid, mp = 195–196 °C;  $R_f$  = 0.59 (pentane: ethyl acetate = 3:1); ES-HRMS: calcd for  $C_{34}H_{36}NO_5S [M+H]^+$ : 570.2303, found: 570.2309. <sup>1</sup>H NMR (300 MHz,  $CD_2Cl_2$ )  $\delta$  ppm: 1.49 (3H, t, J = 6.9 Hz), 3.68 (8H, s), 3.81 (4H, t, J = 6.6 Hz), 4.01 (2H, q, J = 6.9 Hz), 4.24 (4H, t, J = 6.3 Hz), 6.83 (2H, dd, J = 8.1; J' = 2.4 Hz), 7.03 (2H, d, J = 8.1 Hz), 7.16-7.21 (4H, overlapped peaks), 7.29 (2H, t, J = 7.8 Hz), 7.42 (2H, dd, J = 8.4, 1.8 Hz), 7.53 (2H, d, J = 1.8 Hz).<sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  ppm: 13.44 (CH<sub>3</sub>), 41.67 (N–CH<sub>2</sub>), 67.65, 70.13, 71.10, 71.19 (CH2), 112.69, 115.95, 116.05, 118.75, 126.24, 127.51, 130.11 (CH; aromatic), 125.74, 136.65, 141.85, 145.96, 159.72  $(C_{quaternary}; aromatic)$ . ES(+)-HRMS:  $m/z = 570.23 [M+H]^+; 576.24 [M+Li]^+;$ 592.21 [M+Na]<sup>+</sup>; 608.19 [M+K]<sup>+</sup>; 1139.46 [2M+H]<sup>+</sup>; 1177.41 [2M+K]<sup>+</sup>. 32-Ethyl-7,10,13,16,19,22-hexaoxa-40-thia-32-aza-hexacyclo [26.7.5.1.<sup>26</sup>1.<sup>23,27</sup>0.<sup>31,39</sup>0.<sup>33,41</sup>]-dotetraconta-1(35),2,4,6(36),

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23(37),24,26,28,30,33,38,41-dodecaene (6b)
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Yield 52% (319 mg), light green solid, mp = 114–115 °C;  $R_f$  = 0.51 (pentane:ethyl acetate = 1:2); ES-HRMS: calcd for  $C_{36}H_{40}NO_6S$  [M+H]\*: 614.2573, found: 614.2571. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 1.51 (3H, t, J = 7.0 Hz), 3.70–3.78 (12H, overlapped peaks), 3.86 (4H, t, J = 5.8 Hz), 4.02 (2H, q, J = 7.0 Hz), 4.24 (4H, t, J = 5.8 Hz), 6.87 (dd, 2H, J = 8.0, 1.8 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.14–7.19 (4H, overlapped peaks), 7.32 (t, 2H, J = 8.0 Hz), 7.41 (4H, dd, J = 7.4 Hz, 2.0 Hz), 7.48 (2H, d, J = 2.0 Hz). <sup>13</sup>C NMR (75 MHz, DMSO- $d_6$ )  $\delta$ ppm: 13.16 (CH<sub>3</sub>), 41.65 (N-CH<sub>2</sub>), 67.48, 69.72, 70.78, 70.92, 76.67 (CH<sub>2</sub>), 112.71, 114.87, 115.38, 118.84, 125.98, 128.45, 129.77 (CH, aromatic), 124.82, 133.56, 135.83, 141.34, 159.26 ( $C_{quaternary}$ ; aromatic). ES(+)-HRMS: m/z = 614.26 [M+H]<sup>+</sup>; 620.36 [M+Li]<sup>+</sup>; 636.24 [M+Na]<sup>+</sup>; 652.21 [M+K]<sup>+</sup>; 1227.51 [2M+H]+; 1265.46 [2M+K]+.

35-Ethyl-7,10,13,16,19,22,25-heptaoxa-43-thia-35-aza-hexacy clo[29,7,5,1,<sup>2,6</sup>1,<sup>26,30</sup>0,<sup>34,42</sup>0,<sup>36,44</sup>]-pentatetraconta-1(38),2,4,6 (39),26(40),27,29,31,33,36,41,44-dodecaene (**6**c) Vield 37% (243 mg) light green solid mp = 108-10

 ES(+)-HRMS: m/z = 658.28 [M+H]<sup>+</sup>; 664.29 [M+Li]<sup>+</sup>; 680.27 [M+Na]<sup>+</sup>; 696.24 [M+K]<sup>+</sup>; 790.18 [M+Cs]; 1353.52 [2M+K]<sup>+</sup>.

- 18. Crystallographic data of the structure reported in this Letter have been deposited at the Cambridge Crystallographic Data Center as supplementary publication no CCDC-278084. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or as Supplementary data of this Letter.
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