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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.

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.[1] Phenothiazine derivatives have good donor abilities and low oxidation potential and form stable radical cations[2] and their physiological activities can be attributed to these properties.[1,3] Phenothiazine has a 'butterfly structure',[4] 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[5] and also in biology and biochemistry as a marker for proteins, DNA, or other biochemical systems.[6] Phenothiazine is found as a core unit in redox-active alkylated[7] and heteroarylated[8] bi- and terphenothiazines, oligophenothiazine-fullerene dyads,[9] cruciform fluorophores,[10] molecular wires,[11] or ligands for surface modification.[12] There are very few reported macrocycles with phenothiazine units, the most representative being the cyclophanes with phenothiazine and bipyridinium or with two phenothiazine units.[13]

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.[14] The diboronic diester **4** was synthesized according to the literature,[15] and further subjected to Suzuki cross-coupling[16] 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%).[17]

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).[18]

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 ($\alpha = 28.6°$, 32.1°, 41.4°, and 46.7°). 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° to 34.47°. This peculiar situation occurs as the result of numerous C–H···p and C–H···π contacts, which

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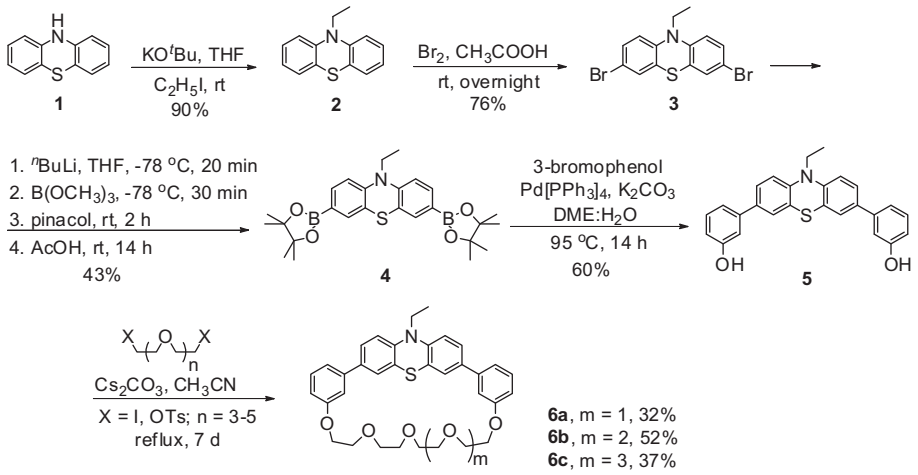

Scheme 1.

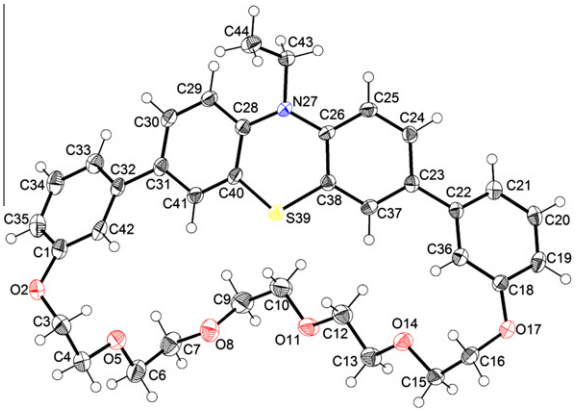

Figure 1. Molecular structure of macrocycle **6b**.

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 $\alpha = 76.83°$ and 84.36° for the rings of the phenothiazine core and $\alpha = 62.14°$ for the phenol rings, while the C–H···π 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: $\alpha = 79.15°$, 84.95°, and 67.92° and $d = 2.904$, 2.814, and 3.093 Å, respectively. Additionally, C–H···π 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: $\alpha = 85.09°$ and 84.28°; $d = 2.759$ and 2.960 Å, respectively. C–H···π 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···π contacts in the lattice are given in the SI. The oxygen atoms of the chains exhibit intra- and intermolecular C–H···p contacts involving the H atoms of the polyethyleneoxide units (see the Supplementary data).

The ^{1}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 ($E_0^{0/+1} = 767$ mV)[7c] and *N*-hexyl-phenothiazine [($E_0^{0/+1} = 728$ mV),[7c] *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 electron-withdrawing groups.[14] 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–c**

Compd	Absorption $\lambda_{max,\ abs}$[a] (nm)	$E_0^{0/+1}$[b] (mV)
6a	276, 327	824
6b	280, 335	777
6c	280, 333	786

[a] Adsorption spectra were recorded at room temperature in CH_2Cl_2.
[b] Cyclic voltammetry measurements were performed in CH_2Cl_2 at rt, $v = 100$ mV/s, electrolyte: $^nBu_4N^+PF_6^-$, Pt working electrode, Pt counter electrode, and Ag/AgCl pseudo reference electrode.