Wurster aza-crown ethers with *N-para*-phenylene-phenothiazine or -phenoxazine groups

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Abstract

N-Phenylaza-15-crown-5 **3** reacts with phenothiazine **1a**, 2-chlorophenothiazine **1b**, or phenoxazine **1c** in the presence of mild oxidizing agents (I_2, Fe^{3+} or Cu^{2+}) affording new Wurster aza-crown-ethers **4a**–**4c**. Homolytic processes for the formation of compounds **4a-4c** were discussed. Redox properties of these compounds were investigated by cyclic voltammetry. In concentrated sulfuric acid as solvent and oxidant, these compounds give stable radical-cations as proved by electron paramagnetic resonance (EPR). Ionophoric properties of the new compounds **4a-4c** were evidenced by cyclic voltammetry with lithium and sodium cations. The relative hydrophobic/hydrophilic character of these compounds was determined by reverse-phase thin-layer chromatography (RP-TLC). Redox and ionophoric properties of the new compounds **4a**–**4c** may lead to analytical and bioanalytical applications.

Keywords: Phenothiazine, phenoxazine, Wurster's crown analogs, cyclic voltammetry, spectrophotometry, EPR, RP-TLC

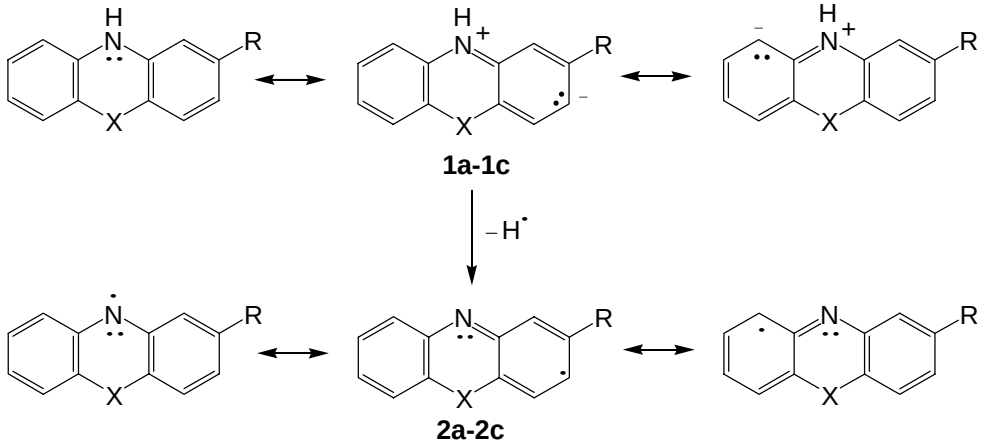
Introduction

"Wurster's Blue" (*N*,*N*,*N*′,*N*′-tetramethyl-1,4-benzenediamine radical-cation) was described in 1879.[1-3]A spectacular reaction is shown on the web, and takes place between a colorless solution

of tetramethyl *para*-phenylenediamine on treatment with bromine gas affording a deep blue solution that becomes colorless again with an excess of bromine due to the sequential formation of the radical-cation and the dication.[4] "Wurster's aza-crown-ethers" that have been described so far exhibit interesting chromophoric, ionophoric and redox properties, but their synthesis involves several steps.[5-17]

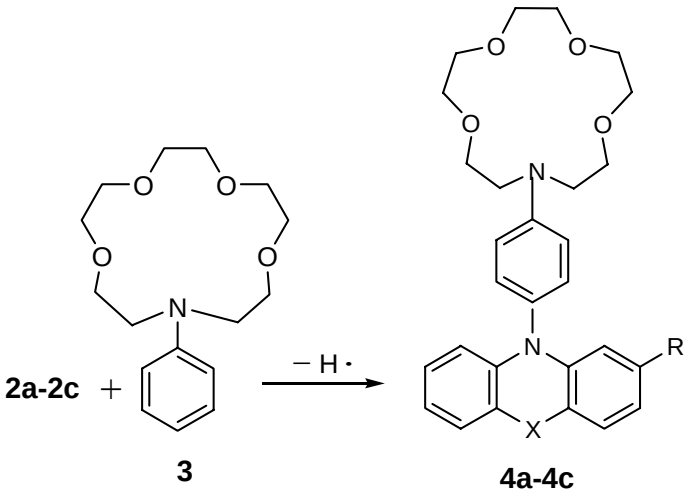
Derivatives of phenothiazine **1a** and 2-chlorophenothiazine **1b** have remarkable biological activities and medical applications,[2,18] e. g.: Chlorproethazine, Chlorpromazine, Levomepromazine, Methophenazine, Methiazinic acid, Piperacetazine, etc. For **1a** derivatives one can also mention dyestuffs [2] such as Methylene Blue, Azur A, B and C. Among analogous phenoxazine **1c** derivatives with various uses,[19] one can mention natural antibiotics such as actinomicines, dyes such as Meldola`s Blue and gallocyanine, and reagents for analytical or bioanalytical uses such as Amplex Red Reagent (10-acetyl-3,5-dihydroxy-phenoxazine), Resorufine (7-hydroxyphenoxazine-3-one-*N*-oxide) and its sodium salt as well as 6-chloro-9-nitro-5-oxo-5*H*-benzo[*a*]phenoxazine.[19,20]

Till now, no "Wurster's crowns" coupled with heterocycles **1a**, **1b** or **1c** have been described. We present here a straightforward pathway for obtaining "Wurster's aza-crown-ethers" **4**, involving a simple *homolytic aromatic substitution* of *N*-phenylaza-15-crown-5 **3** by a free radical **2** resulting from **1a**, **1b** or **1c** (Schemes 1 and 2).



Scheme 1. A few of the resonance structures of phenothiazines **1a**, **1b** and phenoxazine **1c** and of the corresponding neutral free radicals **2a–2c**: **a**, X=S, R=H; **b**, X=S, R=Cl; **c**, X=O, R=H.

The yield in the "Wurster's aza-crown-ethers" **4a–4c** is satisfactory (above 50%) for this direct synthetic approach (Scheme 2). The present communication describes the synthesis and properties of these new "Wurster's aza-crown-ethers" **4**, combining the ionophoric affinity for Li^+ and Na^+ with the chromophoric and redox properties of the Wurster moiety.[8,9]

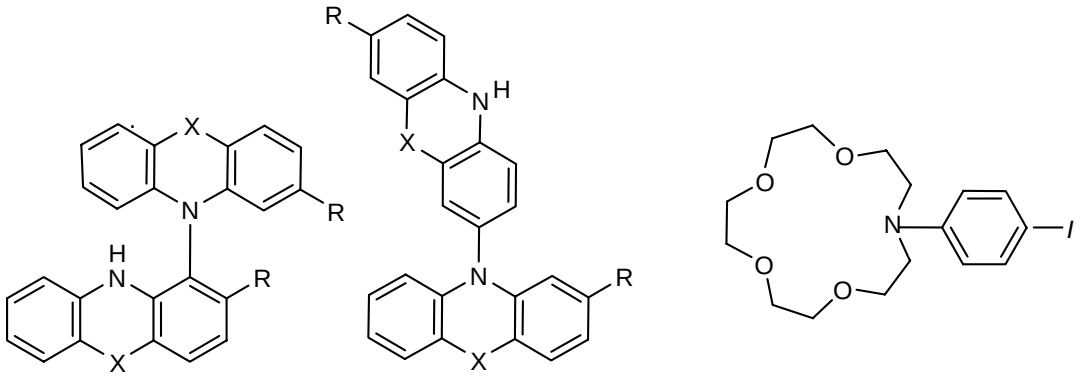


Scheme 2. One-step synthesis of Wurster aza-crown-ethers **4**: *homolytic aromatic substitution* of N-phenylaza-15-crown-5 **3** by free radicals **2a**–**2c** (with **a**, R=H, X=S; **b**, R=Cl, X=S; **c**, R=H, X=O) resulting from the oxidation of phenothiazine or phenoxazine derivatives.

Results and Discussion

Synthesis of compounds 4a–4c. Reaction conditions and mechanism

Oxidation of the three heterocycles[3,18,19] **1a–1c** converts them into free radicals **2a–2c**, as seen in Scheme 1, which dimerize rapidly to **5** and **6**[18,19,21,22] (with an N–C bond).



a, X=S, R=H; **b**, X=S, R=Cl; **c**, X=O, R=H.

Some oxidative reactions of phenothiazine **1a** and phenoxazine **1c** involve *heterolytic* reactions in the presence of nucleophiles and afford colored products with quinonoid structures (by substitution of the heterocyclic ring), which can be reduced to the corresponding leuco-derivatives.[23-25] In the present case, however, the reaction mechanism in methanol at room

temperature in the presence of mild oxidizing agents (I_2, Fe^{3+} or Cu^{2+}) is a *homolytic aromatic substitution*, involving the *N*-phenylaza-15-crown-5 **3** and the nitrogen atom of the free radicals **2a–2c** (Scheme 1), affording compounds **4a–4c** (Scheme 2). This statement is based on the following experimental observations:

i. as seen in Table 1 for the first oxidation step, compounds **1a**–**1c** are oxidized more easily than N-phenylaza-15-crown-5 **3**;
ii. irrespective of the oxidizing agent (I_2, Fe^{3+} or Cu^{2+}), the dimers **5a**, **5c** and **6a**, **6c** (evidenced by TLC, along with other side-products), proved the formation of the neutral free radicals **2a–2c**;
iii. since the literature mentions that dimers **5a** and **6a** are formed from phenothiazine **1a** and the stable free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) or solid PbO_2,[3,26,27] we investigated the reaction between **1a** and **3** in methylene chloride and each of these two oxidizing agents at room temperature for 24 hrs; along with dimers **5a** and **6a** in significant amounts, TLC showed the presence of **4a** in low concentration;
iv. on monitoring by cyclic voltammetry the reaction of **1a** with **3** in acetonitrile, one reversible major peak was detected (Figure 1), and TLC of the oxidation products evidenced the electrochemical formation of **1a**, **3**, **4a** and dimers **5a** and **6a** in the absence of chemical oxidants (see Experimental Part);
v. no reaction occurs when phenothiazine **1a** is replaced by N-methylphenothiazine; this experiment proves that the N-centered stable free radical **2a** is essential for the formation of **4a**;
vi. sodium acetate, which favors heterolytic processes,[24] lowers the yield in products **4a** or **4c**, as one can see in Table 2 (the ratios between the aromatic heterocycle, **1a** or **1c**, N-phenylaza-15-crown-5 **3** and oxidizing agent are also displayed in Table 2).

Table 1. Peak potentials (V vs. Ag/Ag^+) for oxidation (EpaI and EpaII) and reduction (EpcI and EpcII) of compounds **1a–1c** and **3** (10^{-3}M) in acetonitrile in the presence of tetra-n-butylammonium perchlorate, TBAP (10^{-1}M)

Compound	EpaI	EpcI	EpaII	EpcII
1a	0.30	0.18	0.71	-
1b	0.41	0.31	0.71	-
1c	0.36	0.22	0.85	-
3	0.50	-	-	-

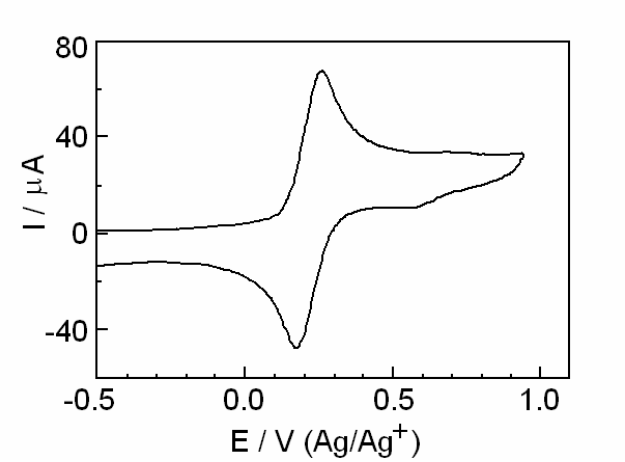


Figure 1. Cyclic voltammogram recorded for a mixture of **1a** and **3** in acetonitrile with TBAP (10^{-1}M) as supporting electrolyte in concentrations of 10^{-3} M, at a scan rate of 0.5 V/s; Epa=0.27 V and Epc=0.16V.

Table 2. Yields of compounds **4a**, **4c** as a function of experimental conditions [a]

Reactants (molar ratio)	CH_3COONa (moles relative to **1a**, **1c**)	%[b] relative to **1a**, **1c**	
		4a	**4c**
1a+**3**+I_2 (1:1:1)		29	
1a+**3**+I_2 (1:1:1.5)		52	
1a+**3**+I_2 (1:1:2.2)		48	
1a+**3**+I_2 (1:1:1)	2.2	17	
1a+**3**+I_2 (1:1:1.5)	2.2	33	
1a+**3**+I_2 (1:1:2.2)	2.2	25	
1a+**3**+ $FeCl_3$ anh. (1:1:1.5)		31	
1a+**3**+$FeCl_3$ anh. (1:1:1.5)	2.2	26	
1a+**3**+$FeCl_3.6H_2O$ (1:1:1.5)		24	
1a+**3**+$FeCl_3.6H_2O$ (1:1:1.5)	2.2	22	
1a+**3**+$CuCl_2.2H_2O$ (1:1:1.5)		50	
1a+**3**+$CuCl_2.2H_2O$ (1:1:1.5)	2.2	32	
1c+**3**+I_2 (1:1:1.5)			51
1c+**3**+I_2 (1:1:1.5)	2.2		23
1c+**3**+$FeCl_3$ anh. (1:1:1.5)			30
1c+**3**+$FeCl_3$ anh. (1:1:1.5)	2.2		10

[a] solvent methanol at room temperature for 24 hrs under stirring;
[b] after work-up and isolation by TLC (see Experimental Part).

When iodine was used as an oxidizing agent for the reaction between **1a-1c** and **3**, another product (**7** in 10-15% yield relatively to **3**) was identified, in addition to **4a–4c**, **5a–5c**, and **6a–6c**. The iodo-derivative **7** has been described in the literature as the reaction product between **3** and *N*-iodosuccinimide, involving probably also a homolytic process.[28] We have obtained it as the main reaction product from **3** and iodine in methanol (74% yield, see Experimental Part).

An excess of oxidizing agent (iodine) up to 50% increases the yield in compounds **4** but a larger excess lowers it (the first six experiments in Table 2), so that the other experiments were carried out with equimolar amounts of reactants **1a**, **1c** and **3**, and with 1.5 moles of oxidant per mole of each reactant (Table 2).

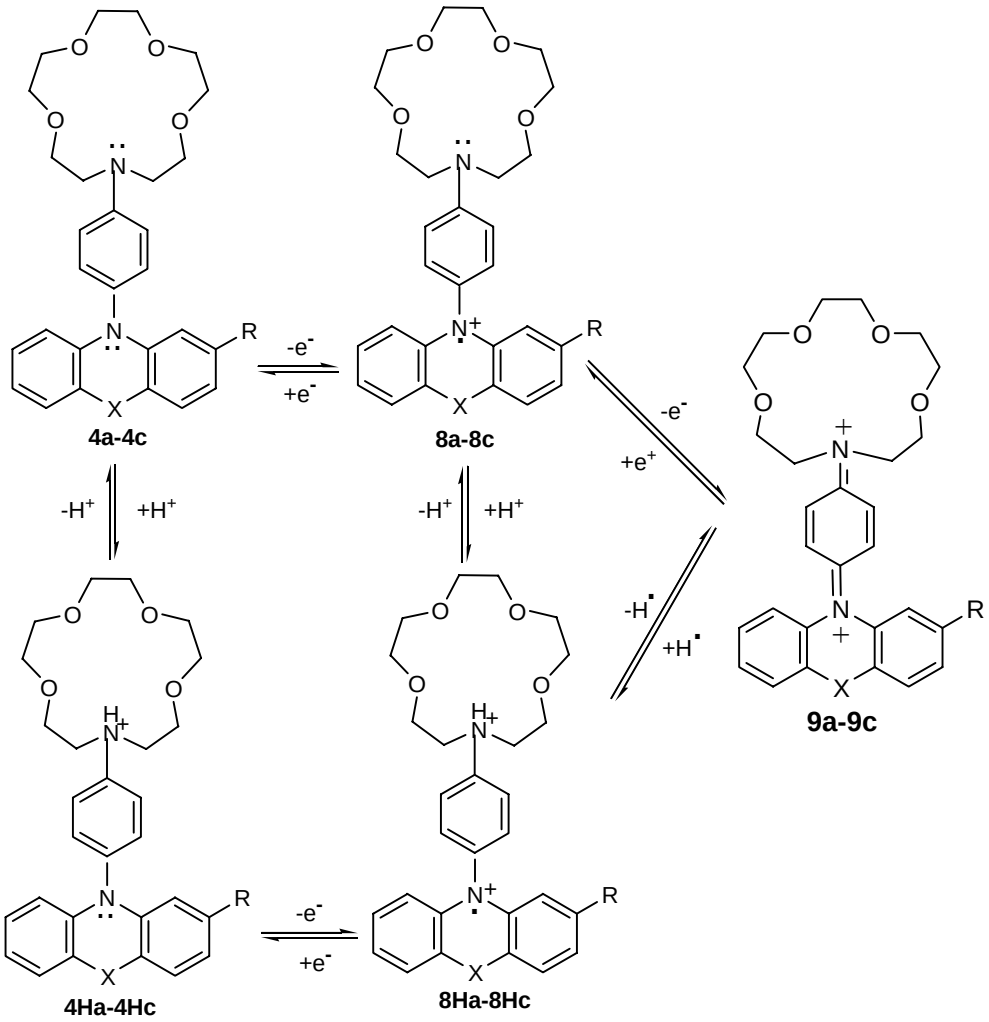
When iodine was used as oxidant, about half of the unreacted crown ether **3** could be recovered (20%).

The reaction involving 2-chlorophenothiazine **1b** with molar ratios **1b**:**3**:I_2 = 1:1:1.5 yielded the product **4b** in 53% yield, indicating that substituted derivatives of these aromatic heterocycles can also be used satisfactorily.

In the presence of water (or hydrated oxidizing agents, Table 2) one obtains from **1a** or **1c**, along with other side-products, phenothiazin-3-one or phenoxazin-3-one (these products may also be observed when the first step of the work-up involves aqueous solutions[18,19]).

Owing to the basicity of the tertiary aminic groups, compounds **4a**–**4c** can be protonated to **4Ha**–**4Hc** in acidic media (Scheme 3). The initial mixture of the two reactants *N*-phenylaza-15-crown-5 (**3**) and the aromatic heterocycle **1a**–**1c** in methanol is yellow, but on adding an excess of oxidizing agent the mixture becomes deeply colored. Compounds **4a**–**4c** can be oxidized to cation-radicals **8a**–**8c** ("Wurster's aza-crown-ethers") and dications **9a**–**9c**, similarly to "Wurster's Blue" cation-radical (*N*,*N*,*N*′,*N*′-tetramethyl-1,4-benzenediamine radical-cation[4,18,19]), see the Redox reactions paragraph. In acid and oxidative medium, dication-radicals **8Ha**–**8Hc** and dications **9a**–**9c** may also be formed (Scheme 3), see EPR spectra paragraph. On adding reducing agents to this reaction mixture (ascorbic acid for Fe^{3+} or Cu^{2+}, or ascorbic acid and sodium thiosulfate for I_2), the color returns gradually to yellow, reforming compounds **4a**–**4c** (see Experimental Part).

Two less likely alternatives to the *homolytic aromatic substitution* mechanism presented in Scheme 2 are: (i) a coupling of two radicals formed by oxidation of both reactants **1** and **3** (as seen from Table 1, whereas **1a**–**1c** have oxidation potentials of 0.3–0.4 V, the macrocyclic amine **3** has a higher oxidation potential, 0.5 V); (ii) a *homolytic ipso-substitution*[29] for the case when iodine was the oxidizing agent, involving the formation of the iodo-derivative **7** that would react with radical **2a**–**2c** displacing the iodine; actually, on reacting in methanol for 24 hrs. at room temperature an equimolar mixture of **1a** and **7** with an excess of anhydrous $FeCl_3$ and then extracting the mixture with methylene chloride and analyzing the products by TLC, **4a** was detected in 40% yield.



a, X=S, R=H; **b**, X=S, R=Cl; **c**, X=O, R=H.

Scheme 3. Reversible processes converting compounds **4a**–**4c** into conjugate acids **4Ha**–**4Hc**, and redox processes affording radical-cations **8a**–**8c** or their conjugate acids **8Ha**–**48c**, and dications **9a**–**9c**.

NMR and IR Spectra of the new Wurster aza-crown-ethers 4a-4c

Both by ^{1}H-NMR and ^{13}C-NMR spectra (see Experimental Part), the structures of the new compounds **4a**–**4c** were confirmed. The following remarks should be noted:

i. the symmetry of the unsubstituted heterocycle **4a** and **4c** is reflected by the pairwise equality of δ values for H-1-9, H-2-8, H-3-7, H-4-6 and for C-1-9, C-2-8, C-3-7, C-4-6; however, this symmetry is broken by the 2-chloro-substituent in **4b**;

ii. ^{1}H- and ^{13}C-NMR chemical shift δ values for positions 4 and 6 decrease on replacing the sulfur heteroatom by the more electronegative oxygen heteroatom **4a**>**4c**;

iii. for compound **7**, NMR data are similar to those reported in the literature[28] and confirm the *para*-position of the iodo substituent in N-phenylaza-15-crown-5, **3**.

Infrared absorption spectra of compounds **4a**–**4c** confirm the absence of the NH stretching frequency in these products.

Redox reactions of the new Wurster aza-crown-ethers 4a–4c

Cyclic voltammetry of compounds **4a**–**4c** using tetra-n-butylammonium perchlorate (TBAP) as supporting electrolyte evidenced two redox reactions (peaks I and II) in reversible processes (Figure 2), corresponding to Scheme 3, similarly to other Wurster compounds.[3,5-9]

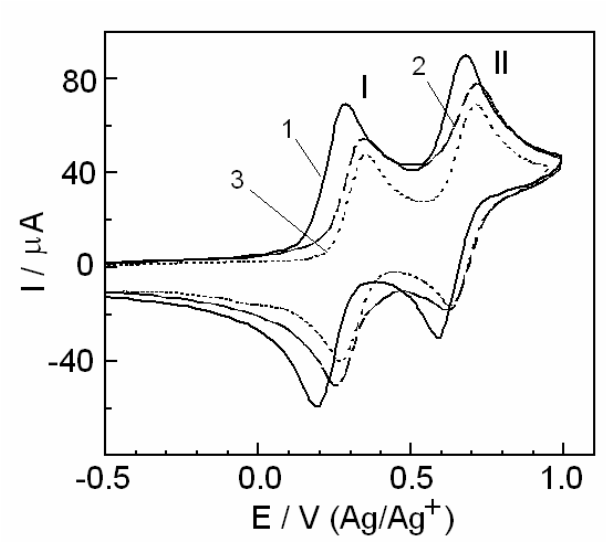


Figure 2. Cyclic voltammograms recorded for a concentration of 10^{-3} M in acetonitrile of compounds **4a** (full line, 1), **4b** (dotted line, 3) and **4c** (dashed line, 2); scan rate 0.5 V s^{-1}, supporting electrolyte TBAP (10^{-1}M).

The oxidation potentials (Figure 2) increase in the order **4a**<**4b**≈**4c**, for each of the oxidation steps (Table 3).

Table 3. Peak potentials (V vs. Ag/Ag^+) for oxidation (EpaI and EpaII) and reduction (EpcI and EpcII) of compounds **4a-4c** (10^{-3}M) in acetonitrile in the presence of tetra-n-butylammonium perchlorate, TBAP (10^{-1}M)

Compound	EpaI	EpcI	EpaII	EpcII
4a	0.25	0.18	0.68	0.60
4b	0.36	0.27	0.72	0.64
4c	0.35	0.25	0.72	0.62

When $LiClO_4$ or $NaClO_4$ are used as a support electrolyte, the voltammograms indicated also a reversible system (Figure 3).

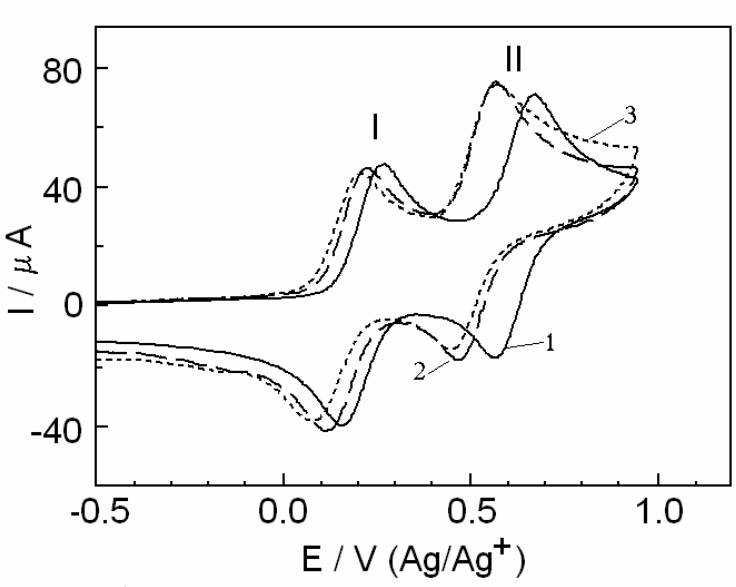


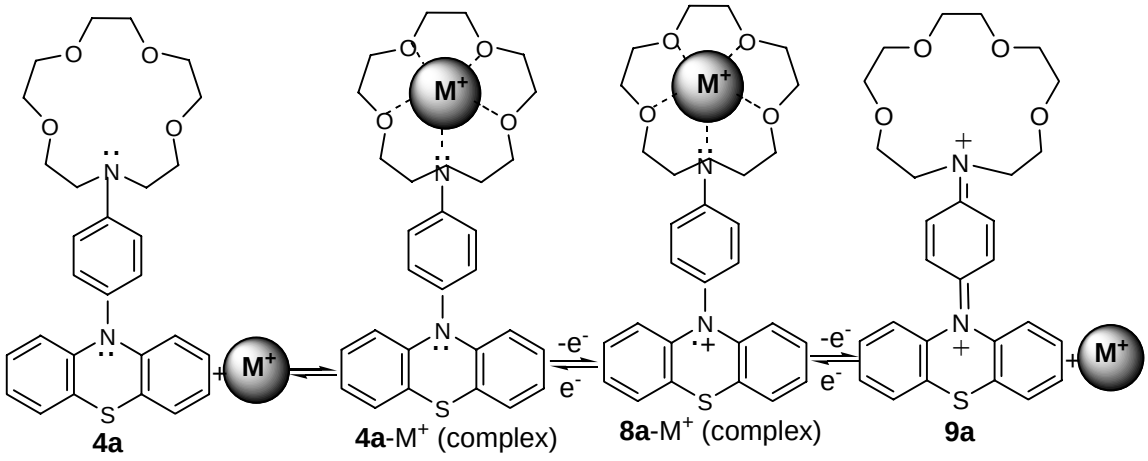
Figure 3. Characteristic voltammetric patterns for **4a** (10^{-3}M in acetonitrile) in the presence of different supporting electrolytes: TMAP (full line, 1), $NaClO_4$ (dashed line, 2), $LiClO_4$ (dotted line, 3); concentration of the supporting electrolyte is 10^{-1}M; scan rate 0.5 V s^{-1}.

With tetramethylammonium perchlorate (TMAP) as reference, Table 4 indicates that the oxidation potentials decrease with these cations (Li^+ or Na^+). This fact proves that the lone electron pair of the nitrogen atom in the macrocycle becomes involved in the complex formation.

Table 4. Oxidation (EpaI and EpaII) and reduction (EpcI and EpcII) peak potentials (V vs. Ag/Ag^+) of **4a** in acetonitrile (10^{-3}M) in the presence of various supporting electrolytes (10^{-1}M)

Electrolyte	EpaI	EpcI	EpaII	EpcII
TMAP	0.26	0.17	0.68	0.60
$NaClO_4$	0.23	0.11	0.58	0.47
$LiClO_4$	0.22	0.08	0.58	0.44

Cyclic voltammograms (Figure 3) and peak potentials (Table 4) demonstrated that the resulting supramolecular assembly (**4a**-M^+complex) is stable, and so is also its mono-oxidation product (**8a**-M^+complex); however, the next oxidation step no longer has a lone electron pair at the macrocyclic nitrogen atom, and therefore this is no longer stable,[8,9] but forms the dication **9a** releasing the alkaline metal cation (Scheme 4).



Scheme 4. Reversible redox ionophoric process of **4a** in the presence of alkali metal ions (M^+=Li or Na)

The complexation of Li^+ or Na^+ with **4a** (Table 4) is in agreement with data reported in the literature,[30] regarding the fitting between the ionic diameter and the macrocyclic cavity size (1.2-1.5 Å) of the *N*-phenylaza-15-crown-5 **3** and the ionic diameters for Li^+ (1.36 Å) and Na^+ (1.94 Å) respectively. In the case of K^+ with larger ionic diameter (2.66 Å),[30] our investigations revealed no complex formation.

Spectrophotometry of the new Wurster aza-crown-ethers 4a–4c

The electronic absorption spectra in the 230-325 nm range of methanol solutions of **1a–1c**, **3** and **4a–4c** are displayed in Table 5. The following observations hold:

i. all seven compounds present two distinct absorption maxima at 238-259 nm and 302-323 nm. In addition, compounds **4a**–**4c** have a third band at 265nm appearing as a shoulder for **4a** and **4b** (on the 257 nm or 259 nm absorption band, respectively), but as distinct maximum for **4c**;
ii. taking into account that compounds **4a**–**4c** possess both molecular moieties of **1a**–**1c** and **3**, one expects the presence of electronic transitions characterizing these moieties, and in addition a band that would be similar to that of *para*-phenylenediamine;
iii. in solution and as TLC spots, compounds **1a**–**1c** and the new Wurster aza-crown-ethers **4a**–**4c** are weakly fluorescent at 366 nm; at present, this property was not investigated more closely.

Table 5. Spectrophotometric behavior of compounds **1**, **3** and **4** in methanol

Compounds	$\lambda_{1\ max}$ (nm)(logε)	$\lambda_{2\ max}$ (nm)(logε)	$\lambda_{3\ max}$ (nm)(logε)
1a[a]	252 (4.515)		318 (3.620)
1b[b]	256 (5.023)		323 (4.025)
1c[b]	238 (5.282)		317 (4.593)
3[b]	257 (5.174)		302 (4.330)
4a[c]	257 (4.651)	265 (sh)	312 (3.716)
4b[b]	259 (5.083)	265 (sh)	313 (4.082)
4c[b]	239 (4.733)	265 (4.206)	322 (4.012)

[a]concentration 10^{-4}M; [b]concentration 10^{-5}M; [c]concentration 5×10^{-5}M.

EPR Spectra of radicals formed from the new Wurster aza-crown-ethers 4a–4c

In concentrated sulfuric acid as solvent and oxidant, compounds **4a**–**4c** give stable radicals, but the resolution of the EPR spectra is low due to high viscosity of the solvent (Figure 4). We assume that under these conditions, in agreement with Scheme 3, radicals **8Ha**–**8Hc** become protonated affording radical-dications **8Ha-8Hc**.

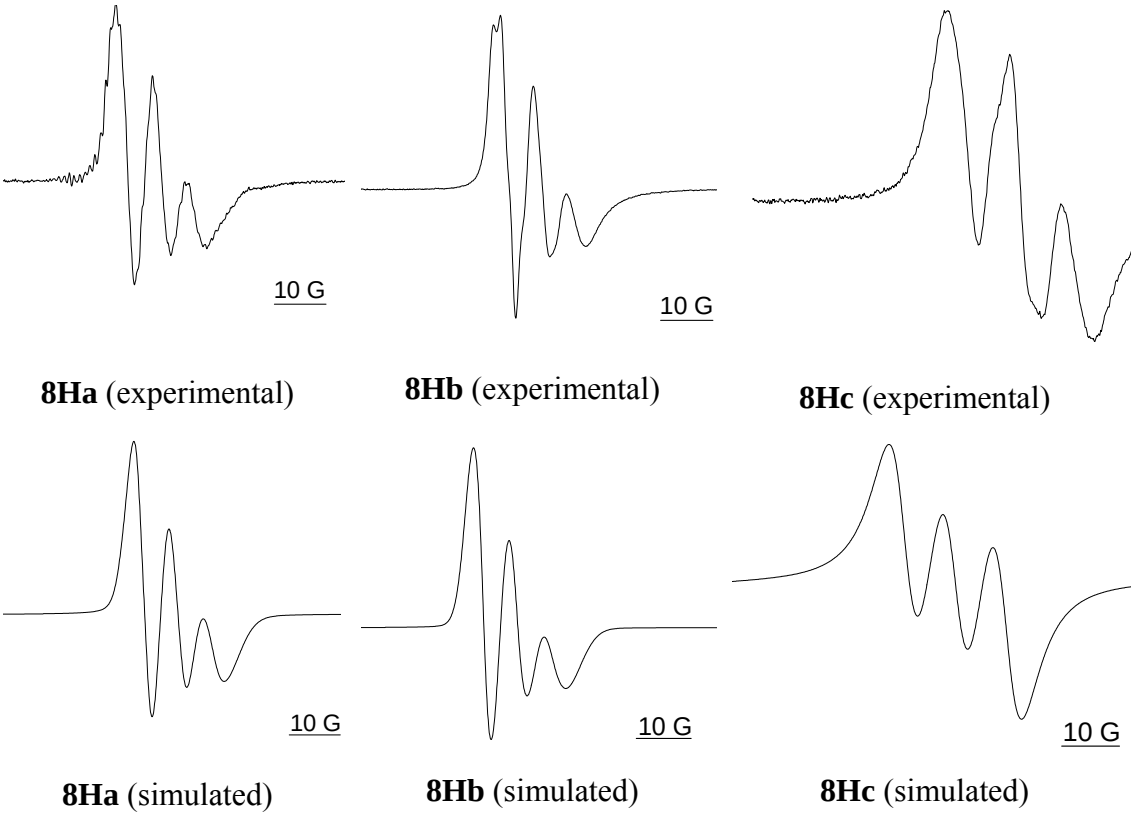
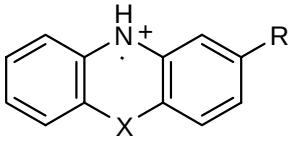


Figure 4. EPR spectra of stable radical-dications **8Ha-8Hc**, in sulfuric acid.

The experimental a_N values for radical-dications **8Ha**–**8Hc** and literature a_{NH} values for radical-cations **10a**–**10c** corresponding to compounds **1a** and **1c** (by oxidation in acid medium[3,18,31-37] or in molten salts[32]) are presented in Table 6 and its footnotes.



10a-10c

a, X=S, R=H;
b, X=S, R=Cl;
c, X=O, R=H.

We can assume that the EPR spectra, λ_{max} and color of the new radical-dications **8Ha-8Hc** should be comparable to those of the radical-cations **10a-10c**[3,18,31-37] (Table 6).

Table 6. EPR a_N (or a_{NH}) and g values, as well as electronic absorption data for radical-dications **8Ha**–**8Hc** (experimental values) and radical-cations **10a-10c** (experimental and/or literature data values)

Radicals	g	a_N (gauss)	a_{NH} (gauss)	λ_{max}(nm)	Color[b]
8Ha	2.0076	6.66		520[b]	Orange-red
8Hb	2.0082	6.36		534[b]	Red
8Hc	2.0057	8.90		540[b]	Red-violet
10a	2.0050[33]	6.52[33] 6.41[33] 6.50[33]	7.07[a] 6.52[3,18,31] 7.10[32] 7.5[32,33,36]	519[b] 515[32,34]	Orange-red
10b			7.10[a]	529[b]	Red
10c	2.0049[33]	7.90[33] 7.83[33]	9.23[a] 9.83[33] 9.02[32,37]	530[b] 529[32,35]	Red-violet

[a] our experimental values in concentrated sulfuric acid.
[b] the color in a mixture of benzene-acetone (1:1 v/v) with five drops of concentrated H_2SO_4.

The red solutions of **4a**–**4c** in concentrated sulfuric acid presenting the EPR spectra shown in Figure 4 reform these compounds on diluting with a 20-times larger amount of water. The work-up was extraction with dichloromethane, drying of the colorless organic layer, and evaporating the solvent in vacuum. The pink-colored aqueous phase was neutralized with $NaHCO_3$, and then the same procedure was followed. Analysis of both residues by TLC revealed only the presence of compounds **4a-4c**, proving that no degradation takes place in H_2SO_4 and that radicals **8Ha-8Hc** have no structural modifications.

Hydrophobicity/hydrophilicity balance of the new Wurster aza-crown-ethers 4a–4c

The hydrophobicity/hydrophilicity property of compounds **4** is important for their possible chemical and biomedical applications. The octanol-water partition coefficient (*P*) and its logarithm (*logP*) are the usual parameters[38] for estimating quantitatively these characteristics, and they can be measured or computed. In our case, this property for compounds **4a**–**4c** was studied experimentally by reversed phase TLC[39-43] (RP-TLC) and compared with this property for the starting compounds **1a**–**1c**, **3**, and the side-reaction compound **7**. Thus, R_f values were measured using precoated C_{18}-chain layers (RP-18F_{254S}, Merck), as stationary phases and different acetonitrile-water mixtures as mobile phases (Table 7). The molecular hydrophobicity, R_{M0}, appreciated as a result of experimental data depending on R_{M0} values and calculated[39-43] with eqs. 1 and 2, is the R_M value extrapolated to zero concentration of the organic component in the acetonitrile–water mixture; *b* is the change in the R_M value caused by increasing the concentration (*K*) of the organic component in the mobile phase. Statistical analysis involved the correlation coefficient (*R*), the Fisher parameter (*F*), and the standard deviation (*SD*) (Table 7).

$$R_M = \log(1/R_f - 1) \quad \text{eq. 1}$$

$$R_M = R_{M0} + bK \quad \text{eq. 2}$$

Table 7. R_f values, hydrophobic characteristics (R_{M0} and *b*) and calculated *logP* of the new compounds **4**, of the starting compounds **1**, **3** and of the secondary reaction product **7**. RP-TLC results[a,b] for acetonitrile-water mixtures (A–E)

No.	R_f					Hydrophobicity characteristics		Statistical parameters			*logP* calc.
	A	B	C	D	E	R_{M0}	*b*	*R*	*F*	*SD*	
1a	0.789	0.717	0.650	0.584	0.487	2.190	–0.029	–0.998	902.1	0.015	4.150
1b	0.679	0.615	0.513	0.410	0.346	2.639	–0.031	–0.997	505.8	0.022	5.180
1c	0.831	0.769	0.669	0.641	0.512	2.379	–0.032	–0.988	129.1	0.044	3.840
3	0.743	0.692	0.675	0.623	0.602	0.879	–0.013	–0.984	95.8	0.022	0.950
4a	0.428	0.333	0.289	0.205	0.161	2.925	–0.029	–0.995	323.1	0.025	4.830
4b	0.342	0.220	0.189	0.129	0.103	3.336	–0.031	–0.986	106.7	0.048	5.420
4c	0.460	0.350	0.297	0.246	0.168	2.866	–0.029	–0.991	177.5	0.034	4.430
7	0.717	0.679	0.644	0.615	0.597	0.731	–0.011	–0.988	127.0	0.016	2.350

[a]Five determinations on silica gel RP-18F_{254S} (Merck), with percent of acetonitrile in mixture acetonitrile-water: A = 95%, B = 90%, C = 85%, D = 80% and E = 75%; [b]R_{M0}, *b*, *R*, *F*, and *SD* are defined by the preceding text and by eqs. 1 and 2.

On attempting to calculate log*P* values using fragmental constants,[44] a satisfactory correlation with experimental data for R_{M0} was obtained (Figure 5).

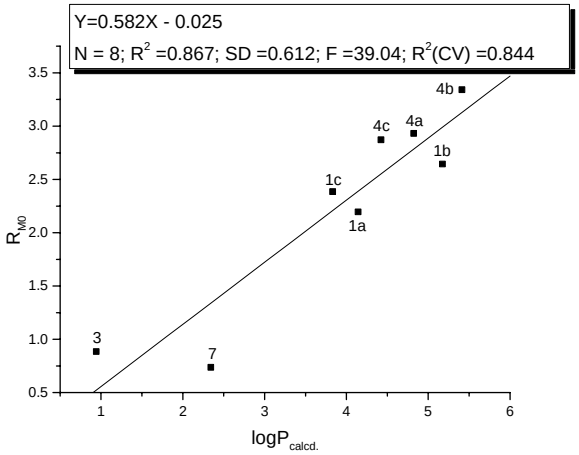


Figure 5. R_{M0} *vs* $logP_{calcd}$ for compounds **1a-1c**, **3**, **4a-4c** and **7**.

The experimental results concerning the hydrophobic/hydrophilic character (R_{M0} values, Table 7) indicate that the starting heterocycles **1a**–**1c** have a higher hydrophobicity than the compounds **3** and **7** containing the *N*-phenylaza-15 crown-5, and that the new Wurster aza-crown-ethers **4a**–**4c** are the most hydrophobic of all.

Conclusions

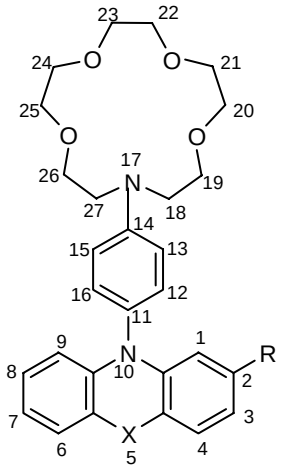
In a one-step synthesis, the free radicals **2a**–**2c** obtained by oxidizing (with I_2, Fe^{3+} or Cu^{2+}) phenothiazine **1a**, 2-chlorophenothiazine **1b**, or phenoxazine **1c** afford by *homolytic aromatic substitution* of *N*-phenylaza-15-crown-5 **3** new "Wurster's aza-crown-ethers" **4a**–**4c**. The structures were confirmed by mass spectrometry, ^{1}H-NMR and ^{13}C-NMR spectra. Redox reactions yielding the Wurster radical-cations **8a**–**8c** and the corresponding dications **9a**–**9c** were explored by cyclic voltammetry. In the presence of lithium and sodium cations, oxidation potentials of **4a** decrease, proving the ionophoric character of this new "Wurster's aza-crown-ether". In concentrated sulfuric acid stable radical-dications **8Ha**–**8Hc** are formed, as proved by EPR spectra. The hydrophobicity of the new "Wurster's aza-crown-ethers" **4a**–**4c** was determined experimentally by RP-TLC. Compounds **4a**–**4c** may lead to analytical and bioanalytical applications.

Experimental Section

General. Phenothiazine **1a**, 2-chlorophenothiazine **1b**, phenoxazine **1c**, N-methylphenothiazine, iodine, ascorbic acid, $CuCl_2.2H_2O$, anhydrous sodium acetate, sodium thiosulfate, anhydrous sodium sulfate, and lead dioxide were from Aldrich; N-phenylaza-15-crown-5 **3**, anhydrous $FeCl_3$, $NaClO_4.H_2O$, PLC plates Silica Gel 60 F_{254} (for Preparative TLC), TLC plates Silica Gel 60 F_{254} (for analytical TLC), and silica gel RP-18 F_{254S} (for RP-TLC), were from Merck; $FeCl_3.6H_2O$, tetra-n-butylammonium perchlorate (TBAP) and tetramethylammonium perchlorate (TMAP) were from Fluka.

Instrumentation. *^{1}H-NMR* (300 MHz) *and ^{13}C-NMR spectra* (100 MHz) were recorded with a Varian Inova 400 with an ASW-SW headprobe at 30 ºC. using unidimensional techniques (Dept, Apt) and bidimensional sequences (Gcosy, Ghmqc, Ghmbc, Ghsqc, where G means gradient). *IR spectra* were recorded with an FT-IR Bruker Vertex 70 equipped with ATR diamond cell. *ESI-MS spectra* were recorded with a QMD 1000 Carlo Erba instrument. *Cyclic voltammetric* measurements were performed with a conventional three-electrode glass cell by means of a PAR-273-A potentiostat, and all solutions were prepared by using acetonitrile. As reference electrode, a silver wire immersed in a 0.1M $AgNO_3$ solution was used, linked to the main compartment of the cell by means of a Vycor plug. A platinum disk (surface area, 0.07 cm^2) and a platinum wire were used as the working and counter electrode, respectively. The voltammograms were recorded at a concentration of the investigated compounds of 10^{-3} M, within the potential range –0.5 to 1.0 V. As supporting electrolyte, tetra-n-butylammonium perchlorate (TBAP), tetramethylammonium perchlorate (TMAP), $NaClO_4$ or $LiClO_4$, were used, at a concentration of 0.1M. *EPR spectra* were recorded at room temperature on a JEOL FA 100 spectrometer with 100 kHz modulation frequency, 0.998 mW microwave power, 480 s sweep time, 0.2 G modulation amplitude, time constant 0.3 s. Compounds **1a-1c** and **4a**–**4c** were oxidized in H_2SO_4 to give the corresponding radical-dications **8Ha**–**8Hc** and radical-cations **10a**–**10c**, respectively.

Synthesis of compounds 4a–4c with various oxidizing agents.



4a-4c

a, R=H, X=S; **b**, R=Cl, X=S; **c**, R=H, X=O

A. Oxidation with iodine. Equimolar amounts of aromatic heterocyc1es **1a**–**1c** and N-phenylaza-15-crown-5 **3** were dissolved in methanol (30 mL for one gram of mixture) at room temperature. The pale yellow solution was treated with a solution of iodine in methanol (molar ratio 1:1.5 for **1**:I_2, i. e. 40 mL methanol for one gram of iodine) and left for 24 hrs with stirring at room temperature. Then distilled water (about ten times larger volume) was added to the green-brown solution, when a fine brown precipitate was formed. A solution of sodium thiosulfate was added for completely removing iodine, followed by adding ascorbic acid till the pH was 3.5. Solid sodium chloride was added to the grey suspension for obtaining an almost saturated solution in order to facilitate the precipitation. After keeping overnight at 5°C, the precipitate was filtered off with suction on a G3 glass filter and washed with distilled water (from the filtrate one may isolate unreacted N-phenylaza-15-crown-5 **3** with 20% yield, by extraction with methylene chloride, evaporation of the solvent, and purification by TLC). The precipitate was dissolved in methylene chloride and the extract was washed with 2% aqueous thiosulfate, and then with 2% aqueous ascorbic acid. The yellow-green organic phase was dried over sodium sulfate and then the solvent was removed under reduced pressure. The crude compounds **4a**–**4c** were purified by preparative TLC (PLC plates Silica Gel 60 F_{254}, dichloromethane: toluene: methanol, 5:5:0.2 v/v, four times). The extraction from silica gel was performed in a Soxhlet with dichloromethane: methanol (9:1 v/v). Yields: 52% for **4a**, 53% for **4b** and 51% for **4c**.

B. **Oxidation with anhydrous iron(III) chloride**. With the same molar ratios as in the previous procedure, the methanol solution was kept for 24 hrs at room temperature under stirring. Then distilled water (a 10-times larger volume) was added, followed by ascorbic acid to pH = 3.5 and by solid sodium chloride to reach an almost saturated solution. After keeping at 5°C overnight, the solution was extracted with methylene chloride, the organic phase was dried over Na_2SO_4,

the solvent was removed and the products were isolated as indicated above. Yields: 31% for **4a** and 30% for **4c**.

C. **Oxidation with $CuCl_2.2H_2O$.** The procedure was similar to that outlined above under B. Yield: 50% for **4a.**

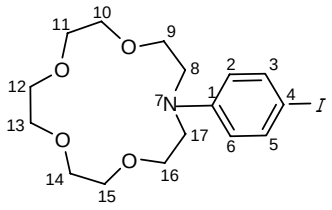
10-(*N,N'*-4-Phenylene-aza-15-crown-5)-phenothiazine, **4a.** Off-white crystals, m.p. 162-164°C; ESI-MS, 492, calculated for $C_{28}H_{32}N_2O_4S$, 492; Anal.: Calcd.%: C, 68.26; H, 6.54; N, 5.68; found% C, 68.21; H, 6.50; N, 5.61.^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.16(d, 2H, H-12, H-16, 9.0); 6.80(d, 2H, H-13, H-15, 9.0); 6.95(dd, 2H, H-4, H-6, 1.6, 7.4); 6.84(td, 2H, H-2, H-8, 7.3, 1.6); 6.75(td, 2H, H-3, H-7, 7.4, 1.2); 6.26(dd, 2H, H-1, H-9, 1.2, 8.2); 3.82(t, 4H, H-22, H-23, 6.1); 3.72÷3.64(m, 12H, H-19, H-20, H-21, H-24, H-25, H-26); 3.64(t, 4H, H- 18, H-27, 5.9).^{13}C-NMR ($CDCl_3$, δ ppm): 147.21(C-14); 145.04(C-1a, C-9a); 128.49(C-11); 119.38(C-C-4a, C-6a); 131.74(C-12, C-16); 112.76(C-13, C-15);126.78(C-2, C-8); 126.44(C-4, C-6); 121.94(C-3, C-7); 115.73(C-1, C-9); 71.32(C-22, C-23); 70.26(C-21, C-24); 69.95(C-20, C-25); 68.47(C-19, C-26); 52.83(C-18, C-27). FT-IR (ATR in solid, ν cm^{-1}): 3055w; 2891s; 2868s; 1605m; 1571w; 1514vs; 1458vs; 1439s; 1384m; 1348m; 1299s; 1231s; 1204w; 1189w; 1127vs; 1109s; 1087m; 1062m; 1044m; 1007w; 977m; 944m; 755m; 739s; 618w; 549w;

10-(*N,N'*-4-Phenylene-aza-15-crown-5)-2-chloro-phenothiazine, 4b. White-yellow crystals, m.p. 171-172°C; ESI-MS, 527, calculated for $C_{28}H_{31}O_4N_2SCl$: 527; Anal.: Calcd.%: C, 63.80; H, 5.92; N, 5.31; found% C, 63.78; H, 5.89; N, 5.28; ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.14(d, 2H, H-12, H-16, $^3J(H^{12(16)}\text{-}H^{13(15)})$=9.0); 6.81(d, 2H, H-13, H-15, $^3J(H^{13(15)}\text{-}H^{12(16)})$=9.0); 6.94(dd, 1H, H-6, $^4J(H^6\text{-}H^8)$=1.8, $^3J(H^6\text{-}H^7)$=7.4); 6.78(td, 1H, H-7, $^3J(H^7\text{-}H^6$, $H^7\text{-}H^8)$=7.4, $^4J(H^7\text{-}H^9)$=1.4); 6.82(m, 1H, H-8); 6.24(dd, 1H, H-9, $^4J(H^9\text{-}H^7)$=1.4, $^3J(H^9\text{-}H^8)$=8.2);;6.85(d, 1H, H-4, $^3J(H^4\text{-}H^3)$=8.2); 6.73(dd, 1H, H-3, $^4J(H^3\text{-}H^1)$=2.1, $^3J(H^3\text{-}H^4)$=8.2); 6.26(d, 1H, H-1, $^4J(H^1\text{-}H^3)$=2.1); 3.83(t, 4H, H-22, H-23, 6.2) 3.72÷3.64(m, 16H, H-18÷H-21, H-24÷H-27).^{13}C-NMR ($CDCl_3$, δ ppm): 147.58(C-14); 146.22(C-1a); 144.47(C-9a); 132.65(C-11); 127.90(C-2); 119.19(C-6a); 117.98(C-4a); 131.46(C-12, C-16); 113.01(C-13, C-15);116.12(C-9); 115.70(C-1); 121.72(C-3); 122.46(C-7); 126.98(C-6); 127.04(C-8 or C-4); 126.47(C-4 or C-8); 71.36(C-22, C-23); 70.31(C-21, C-24); 70.07(C-20, C-25); 68.55(C-19, C26); 52.82(C-18, C-27).FT-IR(ATR in solid, ν cm^{-1}): 3069w; 2970m; 2846w; 1603m; 1566m; 1513s; 1483w; 1458vs; 1441m; 1389s; 1361m; 1349m; 1291s; 1251m; 1138s; 1109vs; 1043m; 992m; 956m; 927m; 823m; 743s; 561w.

10-(*N,N'*-4-Phenylene-15-crown-5)-phenoxazine, **4c.** Yellow crystals, m.p. 125-126°C; ESI-MS, 476, calculated for $C_{28}H_{32}O_5N_2$: 476; Anal.: Calcd.% C, 70.56; H, 6.76; N, 5. 87; found% C, 70.52; H, 6.74; N, 5.80; ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.10(d, H-12, H-16, 8.6); 6.78(d, H-13, H-15, 8.6); 6.65÷6.55(m, 6H, H-1, H-2, H-3, H-7, H-8, H-9); 5.99(m, 2H, H-4, H-6); 3.81(t, 4H, H-22, H-23, 6.0); 3.78÷3.65(m, 12H, H-19, H-20, H-21, H-24, H-25, H-26); 3.64(t, 4H, H-18, H-27, 5.9). ^{13}C-NMR ($CDCl_3$, δ ppm): 147.35(C-14); 144.02(C-4a, C-6a); 135.18(C-1a, C-9a); 126.48(C-11);131.22(C-12, C-16); 123.18(C-3, C-7); 120.74(C-2, C-8); 115.10(C-1, C-9); 113.32(C-4, C-6); 113.15(C-13, C-15);71.31(C-22, C-23); 70.26(C-21, C-24); 69.97(C-20, C-25); 68.48(C-19, C-26); 52.82(C-18, C-27). FT-IR (ATR in solid, ν cm^{-1}): 3057w; 2935w;

2891m; 2871m; 1624w; 1604w; 1590w; 1516s; 1479vs; 1387w; 1350m; 1323s; 1289m; 1265s; 1207w; 1129m; 1111s; 1091m; 1065w; 980w; 945w; 861w; 754m; 740m; 584w;

Synthesis of compound 7



7

A 10% w/w solution of *N*-phenylaza-15-crown-5 **3** in methanol was treated with a solution of iodine in methanol (40 mL for one gram of I_2, molar ratio 1:1.5 for **3**:I_2). The brown solution was stirred at room temperature for 24 hrs. A tenfold larger volume of distilled water was added, when a fine brown precipitate separated. Then solid sodium thiosulfate was added under stirring till the solution became colorless. After bringing the pH to 3.5 with solid ascorbic acid, the suspension was kept overnight at 5°C. Solid sodium chloride was added to saturation, and the solution was extracted with methylene chloride. After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification was carried out by preparative TLC as outlined above. Yield 74%.

***N*-(4-Iodophenyl)-aza-15-crown-5**, **7.** Waxy product. ESI-MS, 421, calculated for $C_{16}H_{24}O_4NI$: 421; Anal.: Calcd.% C, 45.61; H, 5.74; N, 3.32; found% C, 45.59; H, 5.71; N, 3.30; ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.43(d, 2H, H-3, H-5, 9.1); 6.44(d, 2H, H-2, H-6, 9.1); 3.72(t, 4H, H-12, H-13, 6.2); 3.68÷3.63(m, 12H, H-9÷H-11, H-14÷H-16); 3.55(t, 4H, H-8, H-17, 6.2); ^{13}C-NMR ($CDCl_3$, δ ppm): 147.09(C-1); 137.71(C-3, C-7); 113.81(C-2, C-6); 76.30(C-4); 71.31(C-12, C-13); 70.18(C-11, C-14); 70.09(C-10, C-15); 68.23(C-9, C-16); 52.50(C-8, C-9).

Monitoring the reaction between 1a and 3 by cyclic voltammetry. An equimolar mixture of compounds **1a** and **3** in acetonitrile in the presence of TBAP was monitored analytically by cyclic voltammetry following the redox processes (Figure 1). Then, on adding a tenfold volume of distilled water to the solution, the milky liquid phase was extracted L/L with methylene chloride. The lower phase was separated, dried over Na_2SO_4, and concentrated under reduced pressure to about 0.1 mL. The TLC analysis confirmed the mechanism described by Scheme 2 by identifying the starting materials **1a**, **3**, of the reaction product **4a** (traces), and of traces of dimers **5a**, **6a** resulting from the free radical **2a**.

TLC behavior. TLC analyses (Table 8) were employed for identification, purification, and purity determination. For the dimers **5a–5c** and **6a–6c**[22,28] the "*fingerprint*" test had used as standard the solution obtained by treating compounds **1a–1c** with solid PbO_2 in methylene

chloride; this solution contained unreacted compounds **1a–1c** and the dimers (**5a–5c + 6a–6c**). On analytical silica gel 60 F_{254} (Merck) plates the three mobile phases (A–C) allowed the identification of unreacted starting materials (**1a–1c**), reaction products **4a–4c**, dimeric side-products **5a–5c**, **6a–6c**, and compound **7**. Detection of spots employed UV light (254 nm for non-fluorescent background, or 366 nm for fluorescent background) as well as iodine vapor yielding various colors indicated in Table 8.

Table 8. TLC data of compounds **1**, **3-7** on silica gel analytical plates

Comp.	R_f			Detection		
	A	B	C	UV 254 nm	UV 366 nm	Iodine vapor
1a	0.625	0.964		Grey	Fl [b]	Green
1b	0.750	0.964		Grey	Fl [b]	Green
1c	0.650	0.964		Grey	Fl [b]	Blue
3	0	0.317	0.285	Grey		Yellow
4a	0	0.329		Grey	Fl [b]	Purple-green
4b	0	0.353		Grey	Fl [b]	Green
4c	0	0.341		Grey	Fl [b]	Orange
5a [a]	0.525	0.964		Grey	Fl [b]	Green
6a [a]	0.337	0.964		Grey	Fl [b]	Green
5b [a]	0.675	0.964		Grey	Fl [b]	Green
6b [a]	0.587	0.964		Grey	Fl [b]	Green
5c [a]	0.550	0.964		Grey	Fl [b]	Green-blue
6c [a]	0.475	0.964		Grey	Fl [b]	Green-blue
7	0	0.470	0.380	Grey		Yellow-brown

(A) toluene: *n*-hexane=6:4 (v/v) twice; (B) CH_2H_2:toluene:MeOH=5:5:0.2 (v/v) four times; (C) $CHCl_3$:MeOH=10:0.2 (v/v); [a]order of migration (R_f) by analogy with literature data;[22,27] [b] Fl = weakly fluorescent.

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