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Chemical oxidative polymerization of benzocaine

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ABSTRACT

Novel electroactive paramagnetic *ortho*-coupled aniline oligomers functionalized with ethyl ester groups were synthesized by the oxidation of the 4-carbethoxyaniline, well known anesthetic benzocaine, with ammonium peroxydisulfate in an acidic aqueous medium at room temperature. Oligobenzocaines were characterized by elemental analysis, gel-permeation chromatography, conductivity measurements, FTIR, Raman and EPR spectroscopies, and scanning electron microscopy. Theoretical study of the mechanism of benzocaine oxidation has been based on the AM1 and RM1 semi-empirical quantum chemical computations of the heat of formation and ionization energy of the benzocaine, protonated benzocaine, generated reactive species and reaction intermediates, taking into account influence of pH and solvation effects. Electroactivity of the oligobenzocaines was studied by the cyclic voltammetry.

1. Introduction

Polyaniline (PANI) is one of the most studied conducting electroactive polymers because of its simple and cost-effective synthesis by the chemical and electrochemical oxidation of aniline [1], unique acid/base doping/dedoping chemistry [2], environmental stability, and versatile applicability in rechargeable batteries, erasable optical information storage, shielding of electromagnetic interference, microwave/radar absorbing materials, sensors, indicators, catalysts, fuel and solar cells, electronic and bioelectronic components, membranes, electrochemical capacitors, electrochromic devices, non-linear optical and light-emitting devices, electromechanical actuators, antistatic and anticorrosion coatings. The commercial use of PANI is mainly limited by its poor processability. In order to obtain a more processable material, the modification of the PANI molecular and/or supramolecular structure is necessary. This can be achieved by ionic (incorporation of amphiphilic functionalized dopant anions) or covalent derivatization (incorporation of hydrophobic or hydrophilic ring/*N*-substitutents into PANI backbone) of PANI, as well as by the preparation of PANI nanostructures [3].

Oxidative polymerization of ring/*N*-substituted anilines has been extensively studied during the past three decades. Investigations were focused on the oxidation of *ortho*/*meta*- and *N*-substituted anilines since it was expected that *ortho*/*meta*- and *N*-substituted anilines can prevalently give N—C4 coupled oligomers/polymers upon the oxidation, similarly to PANI. Considerable attention has also been paid to the oxidative polymerization of *para*-substituted anilines [4–46], e.g., CH_3— (*p*-toluidine) [4,5], CH_3CH_2— [6], $(CH_3)_3C$— [7], C_6H_5— [8], H_2N—C_6H_4— (benzidine) [9–13], N≡C— [7,14], HOOC— (4-aminobenzoic acid) [14–16], F— [7,17–19], Cl— [5–7,14,18,20,21], Br— [7,14,18,21], J— [21], H_2N— (*p*-phenylenediamine) [10,12,22–36], C_6H_5—NH— (4-aminodiphenylamine) [37–39], H_2N—$C_6H_4(CH_3)$— (*o*-tolidine) [40], O_2N— [7,14,41], HO— (4-aminophenol) [42–44], CH_3O— (*p*-anisidine) [14], CH_3CH_2O— (*p*-phenetidine) [14], HO_3S— (sulfanilic acid) [15,45], and H_2NO_2S-substituted aniline (sulfanilamide) [46]. Electrochemical oxidative polymerizations have been widely used for the synthesis of the poly(*p*-substituted anilines) [4,7–11,14–18,24–26,39,43,45]. Peroxydisulfates (NH_4^+, K^+) are most frequently used as oxidants [5,6,12,13,19,21,25,29,30,38,40,41,44]. Bromine [23], iodine [29], Fe(III) compounds [6,28,37], metal chelate/O_2 [27], tetrachloroauric acid [35], hydrogen peroxide without catalyst [31] and with horseradish peroxidase [32,42], *cis*-bisglycinato Cu(II)-monohydrate/Co(II)-dionemonoxime [34], silver nitrate [36], and sodium dichromate [46] are occasionally employed. The enzyme-catalyzed oxidative polymerization has also been studied [20,32,33,42]. Molecular-weight distribution measurements revealed that the products of oxidative polymerization of *p*-substituted anilines are low- to high-molecular-weight oligomers

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rather than polymers. To our knowledge no work has yet been published on the oxidative polymerization/oligomerization of benzocaine (4-carbethoxyaniline), well known *p*-substituted aniline anesthetic [47] (Scheme 1). This is particularly interesting because it was shown by Hoffmann-La Roche Inc. research team that polymers comprising repeating procaine (benzocaine derivative) units exhibit local anesthetic and anti-arrhythmic activity similar to anesthetic monomer but of significantly longer duration [48].

In the present communication, products of the oxidation of benzocaine with ammonium peroxydisulfate (APS) in an aqueous solution of hydrochloric acid were characterized by gel-permeation chromatography (GPC), conductivity measurements, scanning electron microscopy, cyclic voltammetry, elemental analysis, and FTIR, Raman, and EPR spectroscopies. The mechanism of the oxidation of benzocaine is computationally modeled by the AM1/COSMO and RM1/COSMO methods. The results of quantum mechanical calculations are correlated with the experimental analysis of molecular structure of oxidation products.

2. Experimental

2.1. Materials

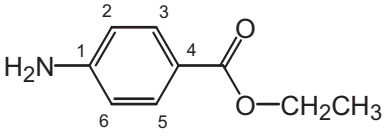
Benzocaine (extra pure, 99.9%, Centrohem, Serbia), APS (p.a., ⩾99%, Centrohem, Serbia), hydrochloric acid (0.1 M standard solution, Centrohem, Serbia), sulfuric acid (p.a., 96%, Centrohem, Serbia), and dimethyl sulfoxide (DMSO) (p.a., 99.9%, Centrohem, Serbia) were used as received.

2.2. Oxidation of benzocaine

The oxidation of benzocaine has been carried out with APS at oxidant-to-monomer mole ratio 1.25. The oxidant solution (2.85 g APS dissolved in 20 ml of distilled water) was poured into the monomer solution (1.65 g of benzocaine dissolved in 100 ml of 0.1 M HCl), and the reaction mixture was left for 48 h with stirring, at 20 °C. The dark brown precipitate was collected on a filter, rinsed with 0.01 M HCl, and dried in vacuum at 60 °C for 3 h.

2.3. Characterization of oxidation products

Molecular weights were assessed with a GPC/SEC apparatus using a 8 × 500 mm Labio GM 1000 column operating with *N*-methyl-2-pyrrolidone and calibrated by polystyrene standards, with a spectrophotometric detection at the wavelength of 546 nm. The sample was dissolved in *N*-methyl-2-pyrrolidone containing 0.025 g cm^{-3} triethanolamine for deprotonation and 0.005 g cm^{-3} lithium bromide to prevent aggregation. Flow rate was 1 ml min^{-1}. The electrical conductivity of oligobenzocaine powder compressed between stainless steel pistons, within an isolating hard-plastic die, was measured at room temperature by means of an AC bridge (Waynne Kerr Universal Bridge B 224), working at fixed frequency of 1.0 kHz. During the measurement, the pressure was kept constant at 124 MPa. A scanning electron microscope JEOL JSM 6460 LV has been used to characterize the morphology of the oligobenzocaines. Powdered material was deposited on an adhesive tape fixed to specimen tabs and then coated by ion sputtered gold using a BAL-TEC SCD 005 Sputter Coater prior to SEM measurements. Elemental analysis (C, H, N, S, Cl) was performed using Perkin Elmer CHNS/O Analyzer 2400. Infrared spectra of the powdered samples dispersed in KBr pellets were recorded in the range 400–4000 cm^{-1} at 64 scans per spectrum at 2 cm^{-1} resolution using a Thermo Nicolet NEXUS 870 FTIR spectrometer with a DTGS TEC detector. The spectra were corrected for the presence of carbon dioxide and humidity in the optical path. Raman spectra excited with a diode-pumped solid state high-brightness laser (532 nm) were collected on a Thermo Scientific DXR Raman microscope, equipped with a research optical microscope and a CCD detector. The laser beam was focused on the sample using objective magnification 50×. The powdered sample was placed on an X–Y motorized sample stage. The scattered light was analyzed by a spectrograph with grating 1800 lines mm^{-1}. Laser power was kept at 0.1 mW on the oligobenzocaine sample in order to avoid its degradation. The correction of fluorescence was automatically done for oligobenzocaine sample during the measurement with 532 nm laser. The EPR spectra of solid-state samples were obtained at room temperature using a Varian E104-A EPR spectrometer operating at X-band (9.3 GHz), using the following settings: 1 G modulation amplitude, 100 kHz modulation frequency, and 10 mW microwave power. Spectra were recorded and analyzed using EW software (Scientific Software). Cyclic voltammetry measurements were conducted at room temperature using Gamry PCI4/750 potentiostat (Gamry Instruments, USA) controlled by Gamry Framework v4.35. Measurements were performed in a standard three-electrode electrochemical cell using square shaped Pt electrode with geometrical surface area of 0.25 cm^2 as a working electrode and a saturated calomel electrode (SCE) as a reference electrode. As a counter electrode, large surface platinum plate was used. The oxidation products of benzocaine were dissolved at a concentration of 2.5 g dm^{-3} in dimethyl sulfoxide (DMSO) solution of H_2SO_4 (0.2 M), and this solution was studied by cyclic voltammetry. Prior to, and during each experiment, the solutions were purged with high purity nitrogen gas.



Scheme 1. Benzocaine.

2.4. Theory: computational methods

A semi-empirical AM1 method [49] (included in the molecular orbital program [50] MOPAC 97, part of the Chem3D Pro 5.0 package, CambridgeSoft Corporation), and RM1 method [51] (improved/reparameterized version of AM1, included in the MOPAC 2009) have been used to assess the heat of formation (ΔH_f) of individual species. The AM1 method was proved to be accurate enough to have useful predictive power, and fast enough to allow the processing of large molecules such as aromatic amine oligomers and their intermediates [38c,52]. Solvation effects were taken into account using the conductor-like screening model (COSMO) to approximate the effect of water surrounding the molecule [53]. Conformational analysis of all intermediates was done. The steric energy was minimized using MM2 molecular mechanics force-field method [54]. Input files for the semi-empirical quantum chemical computations of all intermediates were the most stable conformers of investigated molecular structures. The geometry optimization was performed by the EigenvectorFollowing procedure [55]. Restricted Hartree–Fock method has been used.

3. Results and discussion

3.1. Molecular-weight distribution, conductivity and morphology

The oxidation products of benzocaine are proved to be low-molecular-weight oligomers, as revealed by GPC (Fig. 1). Benzocaine oligomers show bimodal molecular-weight distribu-

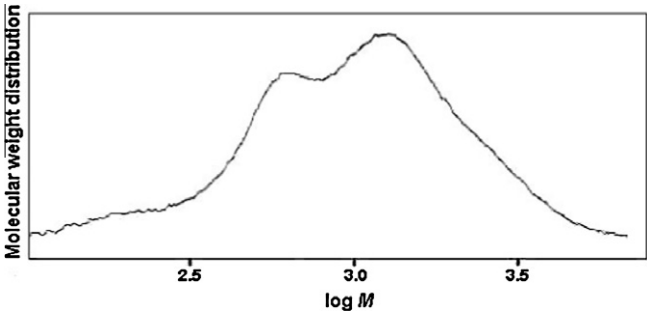


Fig. 1. Molecular-weight distribution of the oxidation products of benzocaine, determined by gel-permeation chromatography in *N*-methyl-2-pyrrolidone.

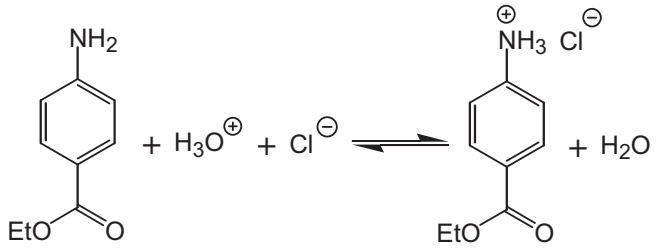
tion with peak molecular weights $M_{p1} = 630$ and $M_{p2} = 1330$, weight-average molecular weight $M_w = 1370$, number-average molecular weight $M_n = 820$, and polydispersity $M_w/M_n = 1.7$.

Oligobenzocaines are non-conducting ($\sigma = 8.4 \times 10^{-9}$ S cm^{-1}). They have fragmental morphology accompanied with submicro- and microspheres (Fig. 2).

3.2. Computational study of the oxidative oligomerization of benzocaine

The pK_a of protonated benzocaine is 2.54 [56], indicating that benzocaine exists prevalently (86.6%) in hydrochloride salt form (Scheme 2), while 13.4% of benzocaine remains to be nonprotonated, upon the reaction with equimolar quantity of HCl in an aqueous solution (pH of the *in situ* prepared 0.1 M benzocaine hydrochloride solution is 1.73), because of the hydrolysis of benzocaine hydrochloride (Scheme 2).

A lower value of the ionization energy, *i.e.* increased oxidizability, of benzocaine ($E_i = 8.72$ eV AM1/COSMO, 8.51 eV RM1/COSMO) in aqueous solution, compared with a protonated benzocaine ($E_i = 10.36$ eV AM1/COSMO, 10.25 eV RM1/COSMO) in acid solutions, is confirmed computationally. It can be concluded that



Scheme 2. Formation of benzocaine hydrochloride by the acid/base (HCl/benzocaine) neutralization, and hydrolysis of formed acidic salt benzocaine hydrochloride.

nonprotonated benzocaine molecule is primary target of peroxydisulfate ($S_2O_8^{2-}$) as a powerful two-electron oxidant (2.0–2.1 V *vs.* NHE) [57]. It has recently been shown that arylnitrenium cations are formed in the initiation phase of the oxidation of primary arylamines with $S_2O_8^{2-}$ in an aqueous solution, whenever the formation of *para*/*ortho*-iminoquinonoid intermediate and/or product is not possible [38c,58–62]. It follows that two-electron oxidation of benzocaine with peroxydisulfate leads to the formation of benzocaine nitrenium cation, hydrated proton and sulfate anions:

$$EtO_2CC_6H_4NH_{2(aq)} + S_2O_{8(aq)}^{2-} \rightarrow [EtO_2CC_6H_4NH]_{(aq)}^{+} + H_{(aq)}^{+} + 2SO_{4(aq)}^{2-} \quad (1)$$

Generated benzocaine nitrenium cation is highly reactive electrophilic species. The positive charge distribution on the benzocaine nitrenium cation, represented by its resonance hybrid (**1**, Scheme 3), indicates that N and C2(6) are the main benzocaine nitrenium cation reactive centers (C4 is blocked by carbethoxy substituent). The oxidative dimerization of benzocaine proceeds through the electrophilic aromatic substitution reaction of nonprotonated benzocaine molecule with its nitrenium cation in the bulk of a solution (Scheme 3). The Boyland–Sims oxidation [62] of benzocaine, i.e., the formation of corresponding soluble

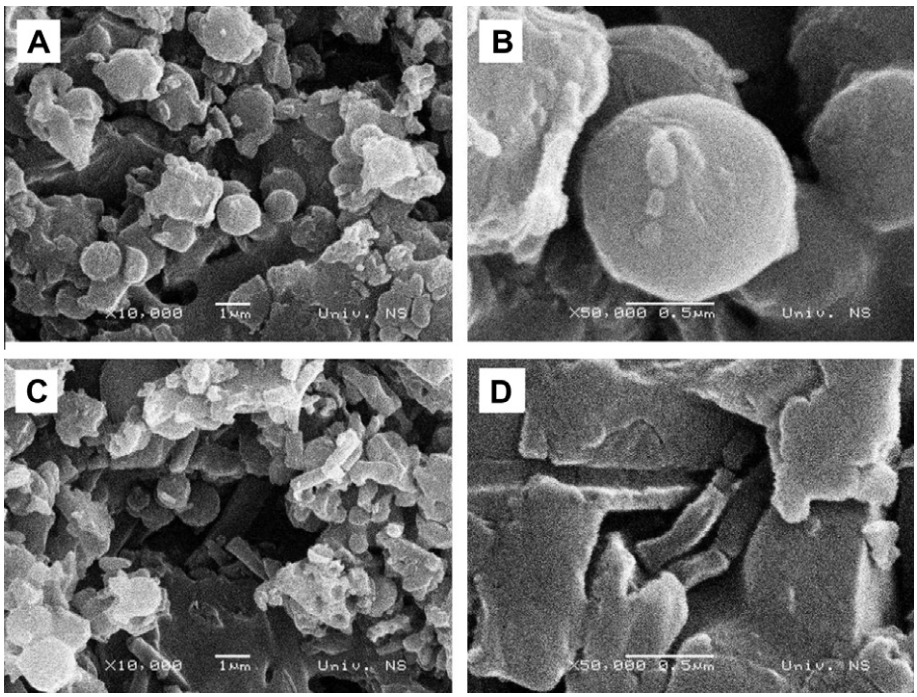
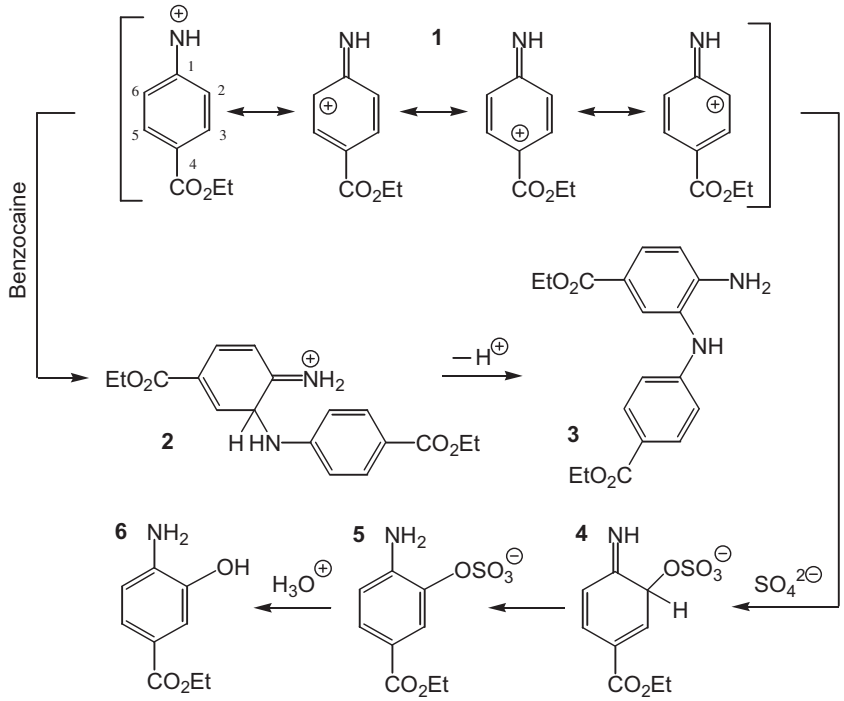


Fig. 2. Scanning electron micrographs of oligobenzocaines (A, C, and D different parts of the same sample in two magnifications; B is magnified part of A).



Scheme 3. Formation of prevalent products (**3** and **5**) in reactions of benzocaine nitrenium cation (**1**) with benzocaine and sulfate anion.

ortho-aminoaryl sulfate (**5**) through the reaction between benzocaine nitrenium cation and sulfate anion, is possible side oxidation process (Scheme 3).

According to the Hammond postulate [63], the regioselectivity of these reactions is not governed by the stability of final products (**3** and **5**, Scheme 3) but it is governed by the stability of intermediates (**2** and **4**, Scheme 3) resembling structurally the corresponding transition states. For that reason the quest for the most stable intermediates is performed (Tables 1 and 2).

It is proved by both AM1/COSMO and RM1/COSMO computations that $N_{(ArNH^+)}$—$C2_{(ArNH2)}$ coupled dibenzocaine intermediate (**2**, Scheme 3, Table 1) is prevalently formed by the electrophilic aromatic substitution reaction of benzocaine nitrenium cation with benzocaine, while C2-OSO_3^- coupled intermediate (**4**, Scheme 3, Table 2) is prevalent in the case of the reaction between benzocaine nitrenium cation and sulfate anion. These intermediates further undergoes rapid transformations to the N—C2 coupled dibenzocaine (**3**, Scheme 3) and 2-amino-5-carbethoxy-phenyl sulfate (**5**, Scheme 3), which is susceptible to hydrolysis (**5** → **6**) under applied acidic reaction conditions. We propose that further growth of oligobenzocaine chain, similarly to the polyaniline chain growth [60,61], occurs through the oxidation of benzocaine with fully oxidized iminoquinonoid oligobenzocaines which contain an even number of benzocaine units, as well as through the electrophilic aromatic substitution reaction of benzocaine with fully oxidized oligobenzocaine nitrenium cations containing an odd number of benzocaine units. Our computational results indicate that oligobenzocaines contain N—C2 coupled dibenzocaine unit as the major structural segment which can exist in both reduced (aminobenzenoid) and oxidized (iminoquinonoid) form. Formation of substituted phenazine unit by the intramolecular oxidative cyclization of N—C2 coupled dibenzocaine unit, as well as the oxidative incorporation of 2-amino-5-carbethoxy-phenyl sulfate (**5**) and its product of hydrolysis (**6**) into the oligobenzocaines is also possible.

Table 1
Heat of formation, ΔH_f (kcal mole^{-1}), of the intermediates formed in the reaction of benzocaine ($ArNH_2$) with its nitrenium cation ($ArNH^+$) in an aqueous solution, computed by AM1/COSMO and RM1/COSMO methods.

Coupling mode $ArNH^+ + ArNH_2$	ΔH_f (kcal mole^{-1})	
	AM1	RM1
N—N	−3.81	−14.22
N—C2(6)	−26.46	−35.08
C2(6)—N	−9.24	−16.92
C2(6)—C2(6)	−10.17	−11.57

Table 2
Heat of formation, ΔH_f (kcal mole^{-1}), of the intermediates $[EtO_2CC_6H_4NH]OSO_3^-$ formed in the reaction of nitrenium cation of benzocaine with SO_4^{2-} in an aqueous solution, computed by AM1/COSMO and RM1/COSMO methods.

ΔH_f (kcal mole^{-1}) $[EtO_2CC_6H_4NH]OSO_3^-$			
AM1		RM1	
N—O	C2(6)—O	N—O	C2(6)—O
−355.54	−366.74	−328.09	−341.78

3.3. Molecular structure of the oligobenzocaines

3.3.1. Elemental analysis

The elemental composition of oligobenzocaines (Table 3) indicates the presence of sulfur and chlorine due to the incorporation of sulfate/hydrogen sulfate and chloride anions as counter ions of positively charged oligobenzocaine chain. The lower N/C mole ratio in synthesized oligobenzocaine (0.097) compared with that

Table 3
Elemental composition of benzocaine oligomers, determined by the elemental analysis (C, H, N, S and Cl) and by difference (O), and calculated elemental composition of monomer benzocaine.

Sample	Content (wt.%)					
	C	H	N	O	S	Cl
Benzocaine	65.44	6.71	8.48	19.37	–	–
Oligobenzocaine	58.06	4.90	6.58	27.08	2.54	0.84

of benzocaine (0.11) is most probably due to the partial hydrolysis of C=NH$^+$ bond to C=O bond in iminoquinonoid segments.

3.3.2. FTIR spectroscopy

The monomer spectrum displays very strong, sharp bands at 3423 and 3342 cm^{-1} (Fig. 3), which correspond to the asymmetric and symmetric free N—H stretching vibrations, ν_{as}(N—H) and ν_s(N—H), respectively, and the band at 1635 cm^{-1} (Fig. 4) due to the N—H scissoring vibration, δ(NH_2), of a primary aromatic amino group [38c,58,64–66]. The oxidative transformation of primary amino group of benzocaine during the polymerization into the secondary amino and imino groups is confirmed by the appearance of new, broad band at 3460 cm^{-1} in the spectrum of benzocaine oligomers, assigned to the N—H stretching vibrations of secondary amino groups and imino groups. The contribution of ν_{asym}(N—H) vibration of remaining terminal NH_2 groups in low-molecular-weight oligomers to this band is also possible. The presence of remaining free NH_2 and NH_3^+ groups in the structure of benzocaine oligomers is revealed by the bands at 3351, 3320, 1644 cm^{-1} due to ν_{sym}(N—H), ν(N—H$^+$), and δ(NH_2) vibrations (Tables 4 and 5) [38c,58,64–66]. They are broader and show shifted positions related to the corresponding bands of monomer. Later feature is due to the influence of hydrogen bonding on N—H vibrations. The pronounced broadening of the bands in the spectral region 3700–3000 cm^{-1} for benzocaine oligomers is connected with strong hydrogen bonding which involves different types of intra- and intermolecular hydrogen-bonded N—H stretching vibrations in oligomers (*e.g.* N—H···N, NH$^+$···N, N—H···O=C) [38c,58,64,66,67].

The transformation of 1,4-disubstituted pattern on aromatic ring of monomer to 1,2,4-trisubstituted and 1,2,3,5-tetrasubstituted patterns in oligobenzocaines rings, due to polymerization reaction, is proved by the disappearance of monomer band at 846 cm^{-1} and the appearance of new bands at 914, 859 and 830 cm^{-1} in the spectrum of oligobenzocaines (Fig. 4 and Table 5) [64,65].

The characteristic bands of carbethoxy group (O=C—OEt) are observed in the spectrum of benzocaine at 2985, 2957, 2942, 2899, 2872, 1684, 1475, 1451, 1442, 1391, 1367, 1281, 1125, 1110, 773, and 701 cm^{-1} and in the spectrum of oligobenzocaines at 2981, 2938, 2905, 2873, 1715, 1475 sh, 1463, 1445 sh, 1392, 1368, 1277, 1105, 770, and 700 cm^{-1} (Tables 4 and 5), demonstrating that this group was not participated in the process of polymerization. The wavenumber of C=O stretching vibration [ν(C=O)] in the benzocaine spectrum (1684 cm^{-1}) is lowered compared to the general wavenumber region of this vibration for aryl esters (1740–1705 cm^{-1}), due to the conjugation with the benzene ring and additionally due to the presence of C=O···H—N intermolecular hydrogen bonding [64,66]. For oligobenzocaines, such type of hydrogen bonding is less pronounced as they show ν(C=O) band at 1715 cm^{-1}.

In the spectral region where the bands due to the C—N stretching vibrations of aromatic amines appear (~1360–1250 cm^{-1}), an overlapping with the strong/very strong bands due to the asymmetric C—O—C stretching vibration of aryl ester, ν_{asym}(C—O—C), is expectable (Table 5) [64]. It can be seen that the band at 1277 cm^{-1} for oligobenzocaines is significantly stronger than corresponding band of monomer, and this is most probably caused by the contribution of C—N stretching vibration of newly formed secondary amine in oligobenzocaines (the band which usually appeared in polyanilines at ~1304 cm^{-1}) to the band of ν_{asym}(C—O—C).

The bands due to the benzenoid (B) ring stretching vibrations are observed at 1598, 1575, and 1515 cm^{-1} in the spectrum of monomer, and at 1604 and 1524 cm^{-1} in the spectrum of oligobenzocaines, with possible contributions of the quinonoid (Q) ring stretching and δ_{as}(NH_3^+) vibrations to the band at 1604 cm^{-1} [64,66,68]. The spectral features associated with high electrical conductivity and high degree of electron delocalization in polyanilines, *c.f.* strong band at ~1140 cm^{-1} due to the B—NH$^+$=Q stretching vibration and broad strong absorption tail at wavenumbers >2000 cm^{-1} [69], are not observed for oligobenzocaines.

The presence of hydrogen sulfate counter-ions in the structure of oligobenzocaines is proved by the bands at 1041 and

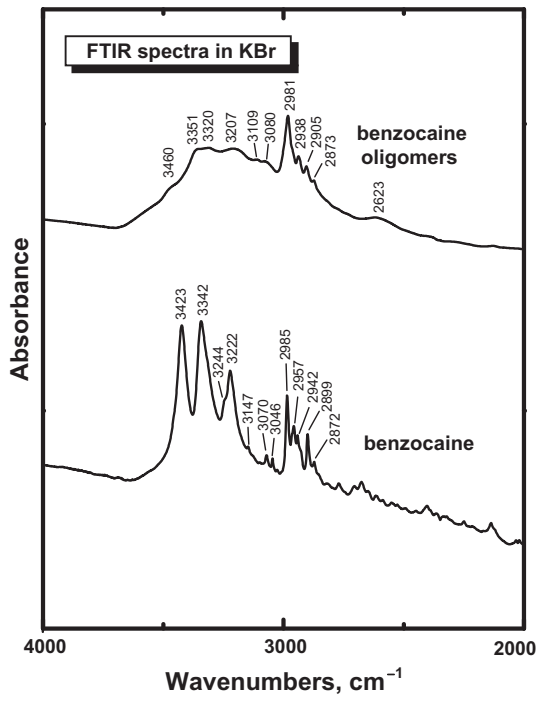


Fig. 3. FTIR spectra of benzocaine and its oligomers in the wavenumber region 4000–2000 cm^{-1}.

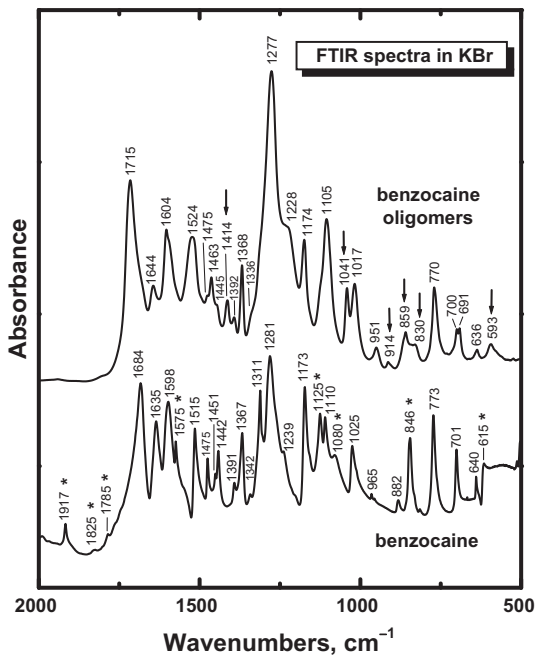


Fig. 4. FTIR spectra of benzocaine and its oligomers in the wavenumber region 2000–500 cm^{-1}. The new bands which appeared in the spectrum of oligomers in comparison with the spectrum of monomer are marked with an arrow; the bands of monomer which disappeared in the spectrum of oligomers are marked with an asterisk.

Table 4
Main FTIR bands of benzocaine and its oligomers in the frequency region 4000–2000 cm^{-1}, and their assignments.

Wavenumbers, cm^{-1}		Assignments[a]	References
Benzocaine	Benzocaine oligomers		
	3460 m	ν(N—H) in Ar—NH— and —C═NH/ν_{asym}(N—H) in Ar—NH_2	[38c,58,64–66]
3423 vs		ν_{asym}(N—H) in Ar—NH_2	[38c,58,64–66]
3342 vs	3351 s	ν(N—H^+) in NH_3^+/ν_{sym}(N—H) in Ar—NH_2/overtone of $\delta(NH_2)$	
	3320 s		[38c,58,64–66]
3222 s		H-bonded ν(N—H)/ν(N—H^+) in —NH_3^+/overtone of $\delta(NH_2)$	[38c,64,66]
	3207 s	H-bonded ν(N—H)/H-bonded —NH^+═ stretching/ν(N—H^+) in NH_3^+	[38c,64,66]
3147 w–m		H-bonded ν(N—H)/ν(N—H^+) in NH_3^+	[58,64]
	3109 m	H-bonded ν(N—H)	[58]
3070 w–m	3080 m	H-bonded ν(N—H)/ν(C—H) on Ar ring	[38c,58]
3046 w–m		H-bonded ν(N—H)/ν(C—H) on Ar ring	[58,67]
2985 s	2981 vs	$\nu_{asym}(CH_3)$	[64]
2957 m		$\nu_{asym}(CH_3)$ and its interaction with overtone of $\delta(CH_3)$	[64,66]
2942 m	2938 m–s	$\nu_{asym}(CH_2)$	[64,66]
2899 m	2905 m	$\nu_{sym}(CH_3)$	[64]
2872 m	2873 m	$\nu_{sym}(CH_2)$	[64]
	2623 m	Combination band enhanced by Fermi resonance, involving def. vibrations, in Ar—NH_3^+ salt	[66]

Abbreviations: ν – stretching; δ – in-plane bending; vs – very strong; s – strong; m – medium; w – weak; sym – symmetric; asym – asymmetric; Ar – aromatic.

Table 5
Main FTIR bands of benzocaine and its oligomers in the frequency region 2000–500 cm^{-1}, and their assignments.

Wavenumbers, cm^{-1}		Assignments[a]	References
Benzocaine	Benzocaine oligomers		
1684 vs	1715 vs	ν(C═O)	[64]
1635 s	1644 m–s	$\delta(NH_2)$ (scissoring) with H-bonding	[64–66]
1598 s–vs	1604 s	Aromatic ν(C═C) with contributions of Q ring stretching (in N═Q═N) and $\delta_{asym}(NH_3^+)$ in oligobenzocaines	[64,66,68]
1575 m–s		Aromatic ν(C═C)	[64]
1515 s	1524 s	Aromatic ν(C═C), with contribution of $\delta_{sym}(NH_3^+)$ in oligobenzocaines	[64,66,68]
1475 m	1463 m–s	—CH_2— scissoring/aromatic ν(C═C)/	[64]
	1475 sh	—OCH_2— deformation	
1451 m, 1442 m	1445 sh	$\delta_{asym}(CH_3)$	[64]
	1414 m	Ring-stretching in phenazine-type unit	[69]
1391 w–m	1392 w	—OCH_2–wagging	[64]
1367 s	1368 s	$\delta_{sym}(CH_3)$	[64]
1342 w		—CH_2— wagging	[64]
1311 vs		ν_{asym}(C—O—C)	[64]
1281 vs	1277 vs	ν_{asym}(C—O—C)	[64]
1239 sh	1228 sh	ν(C—N)	[69]
1173 vs	1174 s	Aromatic δ(C—H)	[64]
1125 s		ν_{sym}(C—O—C)	[64]
1110 s	1105 s	ν_{sym}(C—O—C)/aromatic δ(C—H)	[64]
1080 m		Aromatic δ(C—H)	[64]
	1041 s	$\nu_{sym}(SO_3)$ in HSO_4^-	[64]
1025 m–s	1017 s	Aromatic δ(C—H)	[64]
	914 w	γ(C—H) 1,2,3,5-tetrasubstituted ring (1H)	[65]
882 w		ν(C—C)/ν(C—O) in carbethoxy group	[64]
	859 m	γ(C—H) 1,2,4-trisubstituted ring (1H)	[65]
846 s		γ(C—H) 1,4-disubstituted ring (2H)	[65]
	830 w–m	γ(C—H) 1,2,4-trisubstituted ring (2H)/ring deformation (phenazine-type ring)	[65]
773 s	770 s	CH_2 rocking	[64]
701 m–s	700/691 m	o.p. C═O wag mixed with the aryl CH wag in aryl benzoate esters	[66]
640 m	636 w	NH_2 wagging/rocking or i.p. def. vib. of CO_2 group of aromatic ester	[64]
	593 w–m	HSO_4^- ions	[64]

Abbreviations: ν – stretching; δ – in-plane bending; γ – out-of-plane bending; Q – quinonoid; vs – very strong; s – strong; m – medium; w – weak; sh – shoulder; i.p. – in-plane; o.p. – out-of-plane; sym – symmetric; asym – asymmetric.

593 cm^{-1}, which are absent in the spectrum of monomer (Table 5) [64]. The new band at 1414 cm^{-1} in the spectrum of benzocaine oligomers is assignable to the ring stretching vibration of substituted phenazine units, formed by the intramolecular oxidative cyclization reaction [70].

3.3.3. Raman spectroscopy

The Raman spectrum of the oligobenzocaines sample shows significant differences when compared with the spectrum of benzocaine (Fig. 5). Many new bands at 1643, 1589, 1547, 1523, 1428, 1398, 1349, 1217, and 1044 cm^{-1} appear in the Raman spectrum of oligobenzocaines, which are not present in the monomer spectrum. The band located at 1589 cm^{-1} is attributable to the C═C and C∼C stretching vibrations of the Q and semi-Q rings, respectively (where '∼' denotes the bond intermediate between the single and double bond) [71]. The new band at 1349 cm^{-1} can be assigned to the C—$N^{+\cdot}$ stretching vibration of localized cation radicals and/or to C∼N^+ stretching vibration in phenazine-type of segments [71]. Raman spectroscopy revealed the formation of new C—N bonds in oligobenzocaines by the occurence of new band at

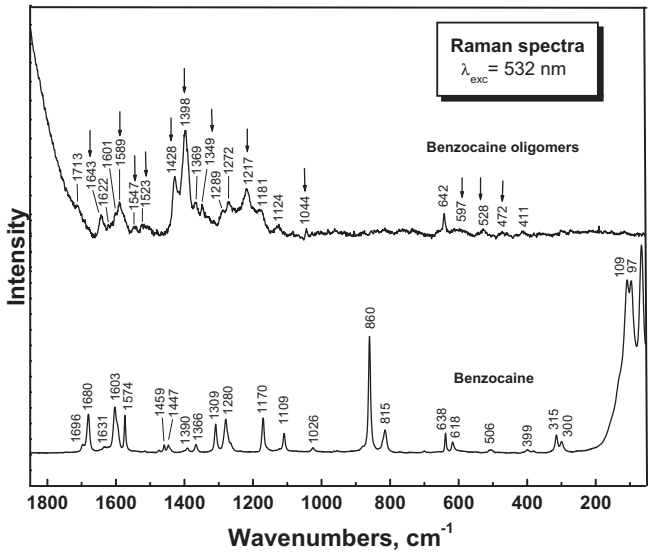


Fig. 5. Raman spectra of benzocaine and its oligomers in the wavenumber region 1850–50 cm^{-1}; excitation wavelength 532 nm. The new bands which appeared in the spectrum of oligomers in comparison with the spectrum of monomer are marked with an arrow.

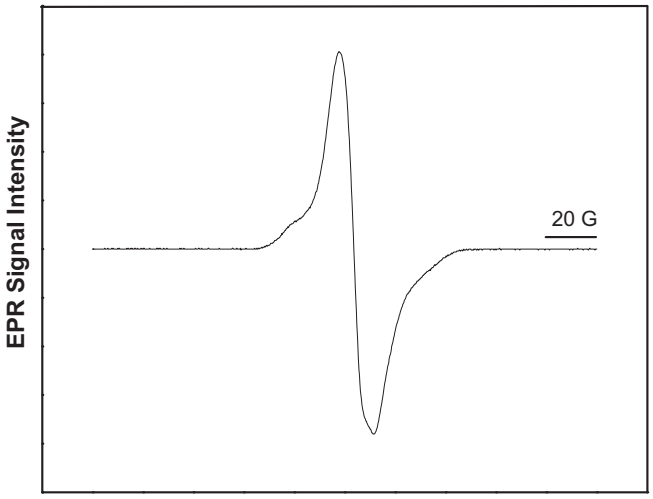


Fig. 6. EPR spectrum of benzocaine oligomers.

1217 cm^{-1} assigned to the C—N stretching vibration in B units [71]. The band at ~1523 cm^{-1} can be assigned to the N—H bending vibration. Phenazine-like segments are revealed by the band a 1428 cm^{-1}, attributed to the ring-stretching vibration of phenazine [71]. The band at 1643 cm^{-1} is due to the C~C stretching vibration of B ring, mixed with C~C ring-stretching vibration in phenazine-type units. Resonantly enhanced band at 1398 cm^{-1} can be attributed to phenazine- and phenoxazine-type rings, with the contribution of $—OCH_2$ wagging in carbethoxy group [64,71]. Oligobenzocaine spectrum shows the band at 1547 cm^{-1} which is assignable to the C—C stretching vibration in Q rings and/or stretching vibration of phenazine-type rings. The characteristic bands of carbethoxy group of the benzocaine are preserved in the Raman spectrum of oligobenzocaines.

3.3.4. EPR spectroscopy

The existence of paramagnetic (cation radical) segments in benzocaine oligomers, indicated by FTIR, is proved by the EPR spectroscopy, Fig. 6.

Based on elemental analysis and FTIR, Raman and EPR spectroscopy, it can be concluded that oligobenzocaines represent N—C2 coupled oligoanilines, functionalized with ethyl ester groups, which contain both reduced (aminobenzenoid) and oxidized (paramagnetic semiquinonoid, diamagnetic quinonoid, substituted phenazine) segments (Scheme 4). Precipitated oligobenzocaines contain sulfate/hydrogen sulfate and chloride anions as counter ions of the positively charged oligomeric chains. The experimental findings are in excellent agreement with computational predictions of the molecular structure of prevalent benzocaine dimer units.

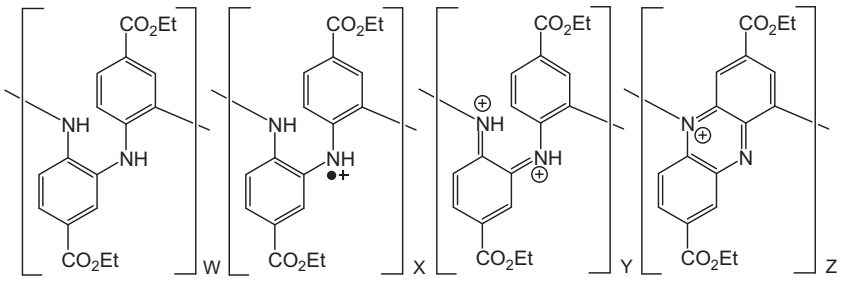
3.4. Electroactivity of the oligobenzocaines

Benzocaine oligomers, which are soluble in DMSO, show electroactivity expressed on the cyclovoltammetric curves by two anodic peaks at potentials 0.38 V (1A) and 0.65 V (2A), as well as by two cathodic peaks occurring at potentials 0.33 V (1C) and 0.07 V (2C), determined at scan rate of 200 mV s^{-1} (Fig. 7) in 0.2 M H_2SO_4/DMSO. The anodic peak potentials increase while cathodic peak potentials decrease (Fig. 7) with the increase of scan rate from 20 to 500 mV s^{-1}.

As demonstrated for cathodic peak 2C (Fig. 7), peak current density was found to be proportional to a square root of the scan rate and the linear dependence of the peak potential *vs.* logarithm of the scan rate was confirmed. This indicates a complex irreversible/quasi-reversible behavior which cannot be fully assessed at the present stage.

4. Conclusions

Benzocaine oligomers, with weight-average molecular weight M_w = 1370 and number-average molecular weight M_n = 820, were synthesized for the first time by the oxidation of the benzocaine with ammonium peroxydisulfate in a hydrochloric acid aqueous solution at room temperature. Oligobenzocaines protonated by both hydrochloric acid and *in situ* formed sulfuric acid, as revealed by the elemental analysis, are nonconducting (8.4×10^{-9} S cm^{-1}) and have fragmental morphology accompanied with submicro- and microspheres. Molecular orbital AM1 and RM1 computations,



Scheme 4. Molecular structure of oligobenzocaines.

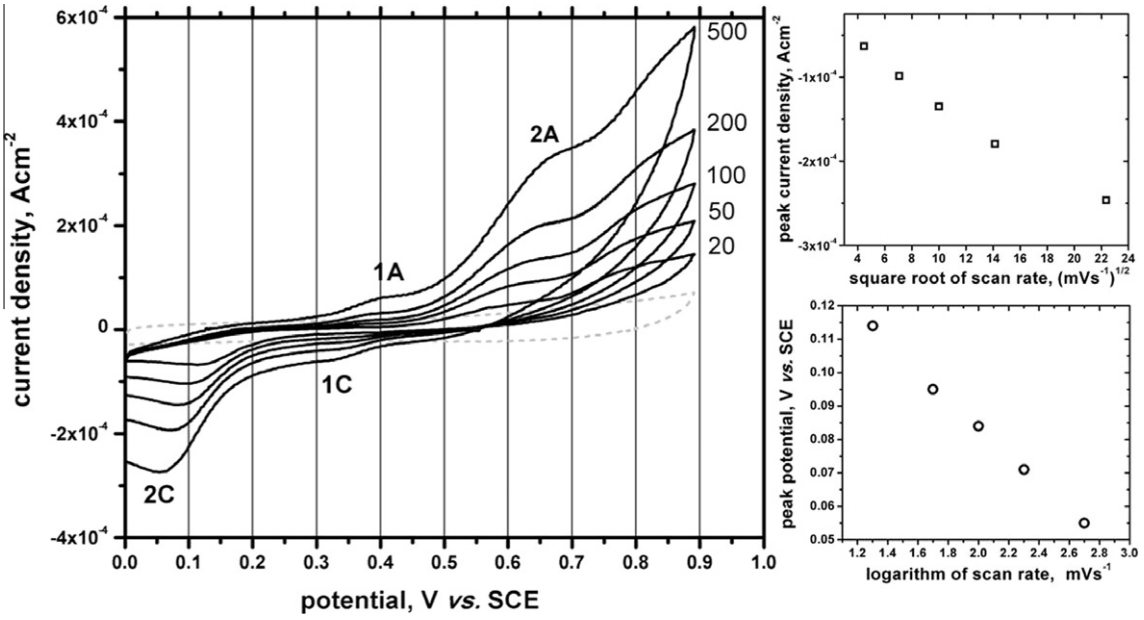


Fig. 7. Cyclic voltammograms (left) of the solution of benzocaine oligomers (2.5 g dm^{-3}) in 0.2 M H_2SO_4/DMSO, recorded at various scan rates (v = 20, 50, 100, 200 and 500 mV s^{-1}, as denoted in figure). A background cyclic voltammogram of the supporting electrolyte 0.2 M H_2SO_4/DMSO recorded at 500 mV s^{-1} is presented by dotted line. The dependence of the peak current density (□) and peak potential (○) on the scan rate for 2C peak (right) is demonstrated following the theory of cyclic voltammetry.

combined with MM2 molecular mechanics force-field method and conductor-like screening model of solvation, indicate that oligobenzocaines contain N—C2 coupled dibenzocaine unit as the major structural segment which can exist in both reduced (aminobenzenoid) and oxidized (iminoquinonoid) form. Quantum chemical prediction of benzocaine oligomerization pathway is consistent with the results from FTIR spectroscopic analysis, which confirmed the transformation of 1,4-disubstituted benzene ring of monomer to 1,2,4-trisubstituted and 1,2,3,5-tetrasubstituted rings in oligobenzocaines containing unchanged carbethoxy ester group. The FTIR and Raman spectroscopies also proved the presence of phenazine-like units in benzocaine oligomers. Paramagnetism, caused by the existence of cation radical dibenzocaine structural segments, and electroactivity of the oligobenzocaines were proved by the EPR and cyclic voltammetry, respectively.

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