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SYNTHESIS AND PROPERTIES OF PHENOTHIAZINE DERIVATIVES. 2*. SPECTRAL (ESR AND IR) CHARACTERISTICS OF THE RADICAL-CATIONS OF THE PHENOTHIAZINE N-DERIVATIVES

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The temperature dependence of the ESR spectra of the radical-cations of the N-derivatives of phenothiazine were studied in the range of 200-393 K (o-xylene). It was established that at temperatures of 323-333 K the nature of the HFS varies from doublet to quartet with approximate intensity ratios of 1:2:2:1, and this transformation is irreversible. A hypothesis explaining the results is proposed. IR spectroscopy was used to confirm the proposed mechanism of localization of the unpaired electron.

Keywords: phenothiazine, radical-cation, IR spectroscopy, ESR spectroscopy.

The reactivity of stable radicals is largely determined by the nature of the localization of the unpaired electron in the molecular system. The localization of the unpaired electron at an individual atom of the molecule can be regarded as the limiting case. Nitroxyl radicals can serve as examples illustrating such a type of "rigid" localization.

A different situation is found in free radical systems in which the atom that is the formal carrier of the unpaired electron is included in a heterocyclic ring. Such examples are phenothiazine and its derivatives, oxidation of which under fairly mild conditions leads to the formation of stable radical-cations with formal localization of the unpaired electron at the nitrogen atom. Earlier [1-3] we studied the reaction of phenothiazine and its N-substituted derivatives with a series of oxidizing agents (concentrated nitric acid in perchloric acid, *o*-chloranil, *o*-bromanil, aluminum chloride, stannic chloride, halogen-containing solvents chloroform, carbon tetrachloride) and showed that radical-cations stable both in solution and in the solid state are formed in all cases.

In order to assess the mobility of the unpaired electron at the nitrogen atom phenothiazine (**1**), N-methylphenothiazine (**2**), N-ethylphenothiazine (**3**), N-benzylphenothiazine (**4**), and N-propargylphenothiazine (**5**) were synthesized, and the temperature dependence of the ESR spectra of the series of radical-cations of N-substituted phenothiazines was studied. The temperature dependence of the ESR spectra was investigated in the region of 200-393 K.

By studying the ESR spectra of the obtained radical-cations in various solvents it was possible to reveal a series of special features connected with the nature of the substituent at the nitrogen atom of the heterocyclic ring, i.e., whether this substituent is methyl group or group of the CH_2R (R = Me, Ph, C≡CH) type. In the first case the

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hyperfine structure (HFS) in the ESR spectrum corresponds to well-known published data [4, 5] and represents a sextet with the intensities of the components in ratios of 1:4:7:7:4:1 and with additional splitting of each component of the sextet into a series of lines on account of the coupling of the unpaired electron with the ring protons (Fig. 1). In the second case, where there is a methylene group at the nitrogen atom in the radical-cations, the hyperfine structure in the ESR spectra did not receive an unambiguous interpretation either in our investigations [1, 2] or in the work of other authors [4, 6].

To explain the nature of the HFS in the ESR spectra in this case we put forward a hypothesis about nonequivalence of the protons of the methylene group, due to the more significant steric hindrance of conformational rotation of the CH_2R group around the N–C bond compared with the CH_3 group.

A specific method of checking this hypothesis may be investigation of the ESR spectra of the studied series of radical-cations at temperatures above room temperature. If the hypothesis were correct, changes due to the appearance of two equivalent protons could be expected in the ESR spectra at high temperatures. It should be noted that the high-temperature investigations did not support this idea. Thus, the HFS in the ESR spectra, observed for the radical-cation of N-propargylphenothiazine in the indicated temperature range, changed from a doublet at room temperature (Fig. 2a) to a quartet at temperatures above 320 K (Fig. 2b, c).

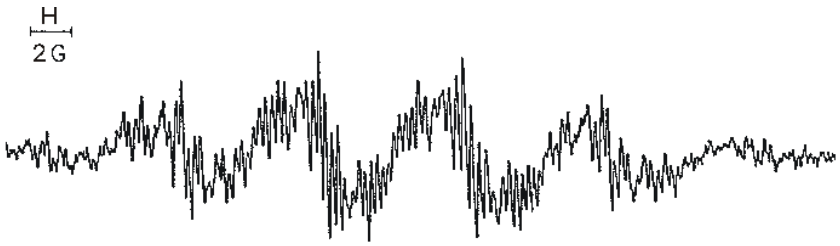


Fig. 1. The ESR spectrum of the radical-cation of N-methylphenothiazine perchlorate in *o*-xylene at 293 K.

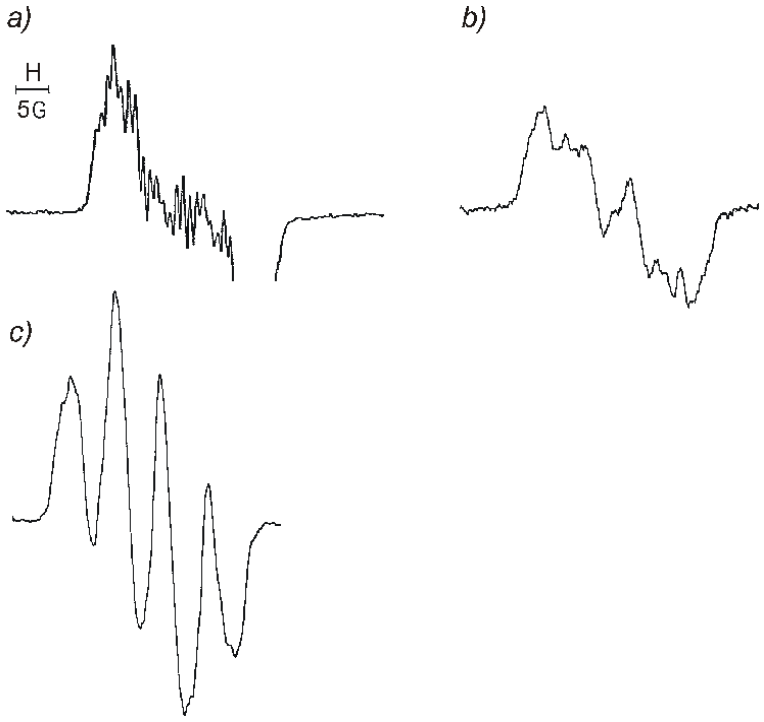


Fig. 2. The ESR spectra of the radical-cation of N-propargylphenothiazine perchlorate at temperatures: a) 293 K; b) 323 K; c) 393 K.

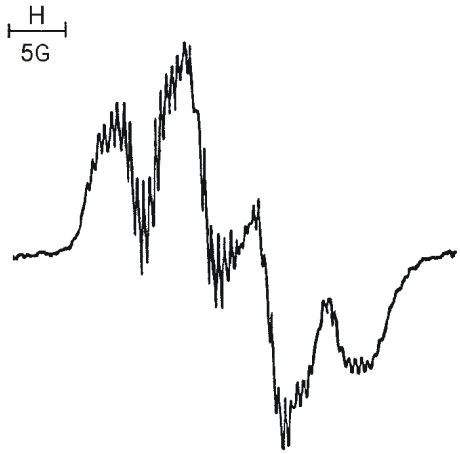
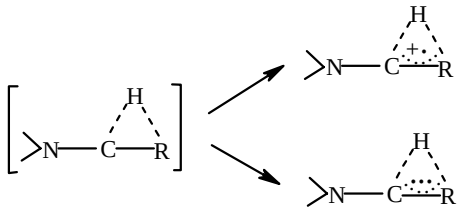


Fig. 3. The ESR spectrum of the radical-cation of N-benzylphenothiazine at 293 K.

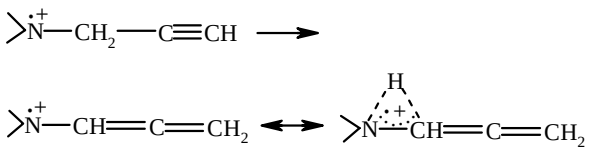
The four-component spectrum remained after the subsequent cooling of sample to room temperature. Such a change of the hfs with temperature makes it possible to suppose the existence of two radical forms, one of which (Fig. 2a) changes irreversibly into the other at high temperatures (Fig. 2b, c). A similar pattern of variation in the ESR spectrum is observed for the radical-cations of N-ethylphenothiazine. For the radical-cation of the N-benzyl derivative, obtained by the action of $SnCl_4$ on the initial N-benzylphenothiazine, the four-component spectrum is observed even at room temperature and does not change with increase in temperature (Fig. 3).

The similar variation of the ESR spectra at high temperatures for the CH_2R substituents with various groups R in the series of radical-cations of N-substituted phenothiazines presupposes a similar resultant localization of the unpaired electron, independent on R. It can be supposed that a molecular fragment in the form of a bridging radical, which contains odd number of electrons (one or three) and can be both electrically neutral and carry charge, acts as localization region.



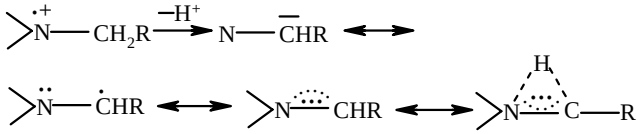
(1)

The generation of the presented resultant localization of the unpaired electron can be achieved in various ways depending on the type of group R. Thus, acetylene–allene rearrangement at the radical-ion center is possible for N-propargylphenothiazine.



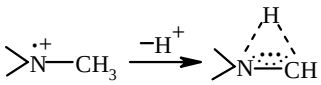
(2)

For the radical-cations of N-ethyl- and N-benzylphenothiazine the formation of a bridging radical can be proposed on the basis of the ability of such radical-cations to act as H acids.



(3)

The proposed hypothesis about the existence of a bridging radical makes it possible to construct formally such a structure also for the radical-cation of N-methylphenothiazine, which has a different HFS in the ESR spectrum from the radicals examined above.



(4)

However, the different character of the localization of the unshared electron pair in the radical-cation of N-methylphenothiazine shows conclusively that the realization of the bridging radical is brought about by specific conditions of the bond between the three-membered fragment and the heterocyclic ring and, in particular, by the agreement of the structural parameters.

For the purposes of experimental investigation of the conformational features of the structure of N-alkyl derivatives of phenothiazine the vibrational spectra of compounds **1**, **2**, **3**, **4**, **5** and 3,7-dinitrophenothiazine (**6**) and their radical-cations were studied. The counterion in the radical-cations was the perchlorate ion. Certain information about the conformational structure of the investigated molecular systems can be obtained by analysis of the frequencies of the stretching vibrations of the C–N bonds of the heterocyclic ring.

As known, the absorption bands of the C–N bond for aromatic amines lie in the region of 1350-1280 cm^{-1} for secondary and 1360-1310 cm^{-1} for tertiary amines. As mentioned in [7], the presence of absorption bands in approximately the same spectral region for the secondary and tertiary aromatic amines indicates that the frequencies of the stretching vibrations of the C–N bond are determined to a greater degree by the electronic structure of the heterocyclic ring. This is confirmed by the variation of the frequencies of the stretching vibrations of the C–N bond for phenothiazine (1313 cm^{-1}) and 3,7-dinitrophenothiazine (1289 cm^{-1}), which can be regarded as the result of transfer of the electronic effects of the strongly accepting substituents. However, for the given molecular structure the effect of the substituents at the nitrogen atom also makes a no less significant contribution to the shift of the frequencies of the stretching vibrations of the C–N bond. Thus, in the series of N-substituted phenothiazines the frequencies of the stretching vibrations of the C–N bond have the following values: (**2**) 1331 cm^{-1}, (**3**) 1322 cm^{-1}, (**4**) 1363 cm^{-1}. The changes in the frequencies of the stretching vibrations of the C–N bonds can be compared with the increase in the inductive effect of the substituent in the series Bn < Me < Et.

As known from published data [8], phenothiazine has a nonplanar structure, in which the conformational hindrances to rotation around the C–N bond of the molecular fragment N–CH_2R make little contribution to the change in the frequencies of the vibrations of the C–N bonds of the heterocyclic ring. Therefore, as shown above, the changes in the frequencies of the stretching vibrations of the C–N bond of the heterocyclic ring are mainly

TABLE 1. The Frequencies of the Stretching Vibrations of the C–N Bond of the Heterocyclic Ring in N-Substituted Phenothiazines and their Radical-cations

Compound	ν_{C-N}, cm^{-1} (initial substances)	ν_{C-N}, cm^{-1} (radical-cations)
1	1313	1327
2	1331	1331
3	1322	1315
4	1363	1360
6	1289	1289

determined by the electronic effects alone. Transition to the radical-cations leads to significant changes in the stereochemical structure of the molecular systems. In this case the phenothiazine fragment represents a predominantly planar system, and this is confirmed by the results obtained from calculation by the MNDO PM3 method for the radical-cations of the N-derivatives of phenothiazine [1] and also by the data from [8].

At the same time the calculations show the special features of the spatial arrangement of the substituents at the nitrogen atom. Whereas the angle between the N–CH_3 bond and the plane of the phenothiazine ring in the N-methylphenothiazine radical-cation amounts to 153.2°, the corresponding angles in the radical-cations of N-ethyl-, N-allyl-, and N-propargylphenothiazine are of 176.6°, 175.2°, and 175.0° respectively. As follows from Table 1, the order of variation in the frequencies of the stretching vibrations of the C–N bond in the series of radical-cations acquires a different form (for R = Me, Et, Bn, $\Delta\nu_{C-N}$ are 4, 12, and 33 cm^{-1} respectively). This is determined by the above-mentioned structural features, which secure the transfer of the electronic effects of the substituents to the heterocyclic ring.

Thus, an essential condition for the realization of a bridging radical is such a geometry for the N–CH_2R fragment that provides the most favorable conjugation of the unpaired electron of the nitrogen atom with the electrons of the carbon atoms of the methylene group, i.e., creates favorable conditions for expansion of the region of electron localization.

In summary it can also be mentioned that the discovered relationships in the behavior of the radical-cations of N-substituted phenothiazines provide a method of assessing the "rigidity" of localization of the unpaired electron at the atom representing the formal carrier.

EXPERIMENTAL

The Fourier IR spectra were recorded on a Perkin-Elmer FTFR-1725X spectrophotometer at resolution of 4 cm^{-1} (in tablets with potassium bromide). The ESR spectra were recorded on a Bruker 200D-SRC instrument in evacuated tubes; the concentration of the solutions was $2\cdot10^{-3}$-$5\cdot10^{-3}$ M (acetonitrile, *o*-xylene).

N-Methylphenothiazine (2). The compound was obtained by the well-known procedure [1].

N-Ethylphenothiazine (3). The compound was obtained by a similar procedure.

N-Benzylphenothiazine (4). A three-necked flask with a stirrer and a reflux condenser was filled with liquid ammonia (about 150 ml), and catalytic amount of $Fe(NO_3)_3\cdot9H_2O$ was added. After this, sodium (0.5 g, 0.022 mol) was added in small pieces. After 45 min, compound **1** (4 g, 0.022 mol) was added in small portions, and after stirring for 1 h benzyl chloride (5 g, 0.04 mol) was added drop by drop. Stirring was continued for further 2 h. After evaporation of ammonia the reaction mixture was extracted with benzene, the extract was concentrated, and the product was chromatographed on a column of alumina with petroleum ether as eluent. Colorless crystals melting at 90°C were obtained. Yield 58%.

N-Propargylphenothiazine (5). The compound was synthesized by the well-known procedure [9].

Perchlorate of the Phenothiazine Radical-cation. The compound was obtained according to the procedure described in [10]. To mixture of compound **1** (0.25 g, 1.3 mmol) and 57% perchloric acid (3 ml) while stirring for 10 min at 0°C we added solution of nitric acid in 57% perchloric acid (1 ml), containing 55% nitric acid (0.045 g, 0.4 mmol). After 10 min the dark-green precipitate was filtered off and washed with ether. Yield 78%.

Perchlorates of the radical-cations of **2**, **3**, **4**, **5**, **6** were obtained similarly.

In other cases the radical-cations were generated by mixing benzene solutions (C = 0.5 M) of the N-substituted phenothiazines with equivalent amount of the oxidizing agent (*o*-chloranil, *o*-bromanil, $SnCl_4$), dissolved in benzene (C = 0.5 M).

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