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Investigation of intermolecular proton exchange of 3,6-di-tert-butyl-2-oxyphenoxyl with N-phenylanthranilic acid by ESR spectroscopy method

In this work we studied the intermolecular proton exchange (IPE) reaction between the spin probe of 3,6-di-tert-butyl-2-hydroxyphenoxyl (I) and the aromatic amino acid N-phenylanthranilic acid (N-PhAA). The experimental spectra of the 3,6-di-tert-butyl-2-hydroxyphenoxyl-N-phenylanthranilic acid system were recorded using dynamic EPR spectroscopy. The studies were carried out in a non-aqueous indifferent solvent toluene in a wide temperature range. The theoretical EPR spectra of the radical I — N-PhAA system corresponding to various process rates were successfully simulated using the ESR-EXHANGE program. This program is written in the modern version of the algorithmic language Fortran 90. The general line-form equation for the four-jump model have been derived from the modified Bloch equations. The second-order rate constants for the intermolecular proton exchange process between radical I and N-PhAA were determined by comparison of the experimental and simulated EPR spectra. The iterative least squares procedure was used for computer analysis of the kinetic data of intermolecular proton exchange and for obtaining activation parameters of the reaction. From kinetic data it follows that N-phenylanthranilic acid has the lowest value of protolytic ability in comparison with aminobenzoic acids.

Keywords: ESR-spectroscopy, spin probe, semiquinone radical, anthranilic acid, N-phenylanthranilic acid, 3,6-di-tert.butyl-2-hydroxyphenoxyl, OH-acids, proton exchange reactions, Bloch equation.

Introduction

It is well known that amino acids play an important role in chemical and biological processes [1]. Anthranilic acid (AA) is an indispensable participant in various biosynthesis processes. Currently, anthranilic acid and its derivatives including N-phenylanthranilic acid are actively studied by both experimental and quantum-chemical methods. Such interest is caused by the widespread use of these aromatic amino acids in both pharmaceutical and organic chemistry and serves as the starting material for the synthesis of various substances [2–4].

The stable semiquinone radical 3,6-di-tert.butyl-2-oxyphenoxyl (I) was used as acid spin probe for investigations of protolytic ability of different acids and bases such as carbonic acids, alcohols, tertiary amines, alkaloids, nitrogen heterocycles in organic solutions [5–8].

Thus the aim of this paper was to investigate the protolytic properties of N-phenylanthranilic acid with 3,6-di-tert.butyl-2-oxyphenoxyl spin probe by ESR spectroscopy method.

Experimental

N-phenylanthranilic acid ($C_{13}H_{11}NO_2$, T_m = 182–183 ℃) was purified by recrystallization of the acid from ethanol [9].

3,6-di-tert-butyl-o-benzoquinone ($C_{14}H_{20}O_2$) and 3,6-di-tert-butylpyrocatechol ($C_{14}H_{22}O_2$) were purified by recrystallization from tetrahydrofuran.

3,6-di-tert-butyl-2-hydroxyphenoxyl radicals was obtained by dissolving the mixture of 3,6-di-tert-butyl-o-benzoquinone and 3,6-di-tert-butylpyrocatechol in toluene in vacuum. Toluene was dried by standard procedures before use [9].

ESR spectra were recorded on a RE-1306 spectrometer (X-band) using a temperature block in the range of 200–400 K. The theoretical EPR spectra were calculated using the modified version ESR-EXHANGE program [10]. The program was written in Fortran language using the Visual Studio 2019 software package.
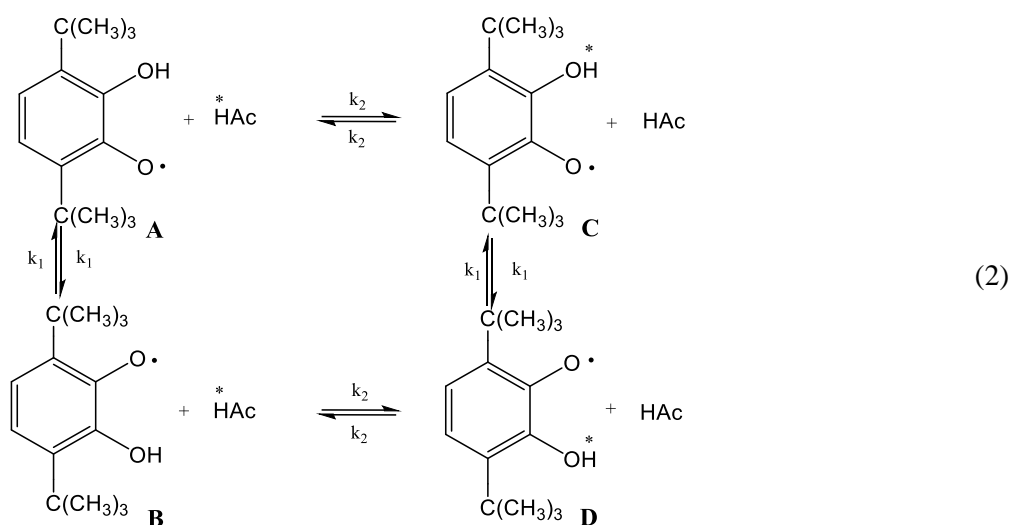
Intermolecular proton exchange can be represented for semiquinone radicals, taking into account the intramolecular processes by the following schemes:

$$
\begin{array}{ccc}
A & \underset{R_2}{\overset{R_2}{\rightleftarrows}} & C \\
R_1 \Updownarrow R_1 & & R_1 \Updownarrow R_1 \\
B & \underset{R_2}{\overset{R_2}{\rightleftarrows}} & D
\end{array}
\tag{1}
$$

Four-jump model and the modified Bloch equation is the basis of the developed program for the simulation of the ESR spectra of the radical and comparison with experimental data. ESR spectra are calculated from the coupling constants, the populations, the rate constants and the line widths of the all chemical configurations of radicals. The obtained kinetic data are subjected to statistical processing by the least squares method [10].

Results and Discussion

Intermolecular proton exchange for 3,6-di-tert.butyl-2-oxyphenoxyl with N-phenylanthranilic acid taking into account tautomeric transformations can be represented by the following scheme:
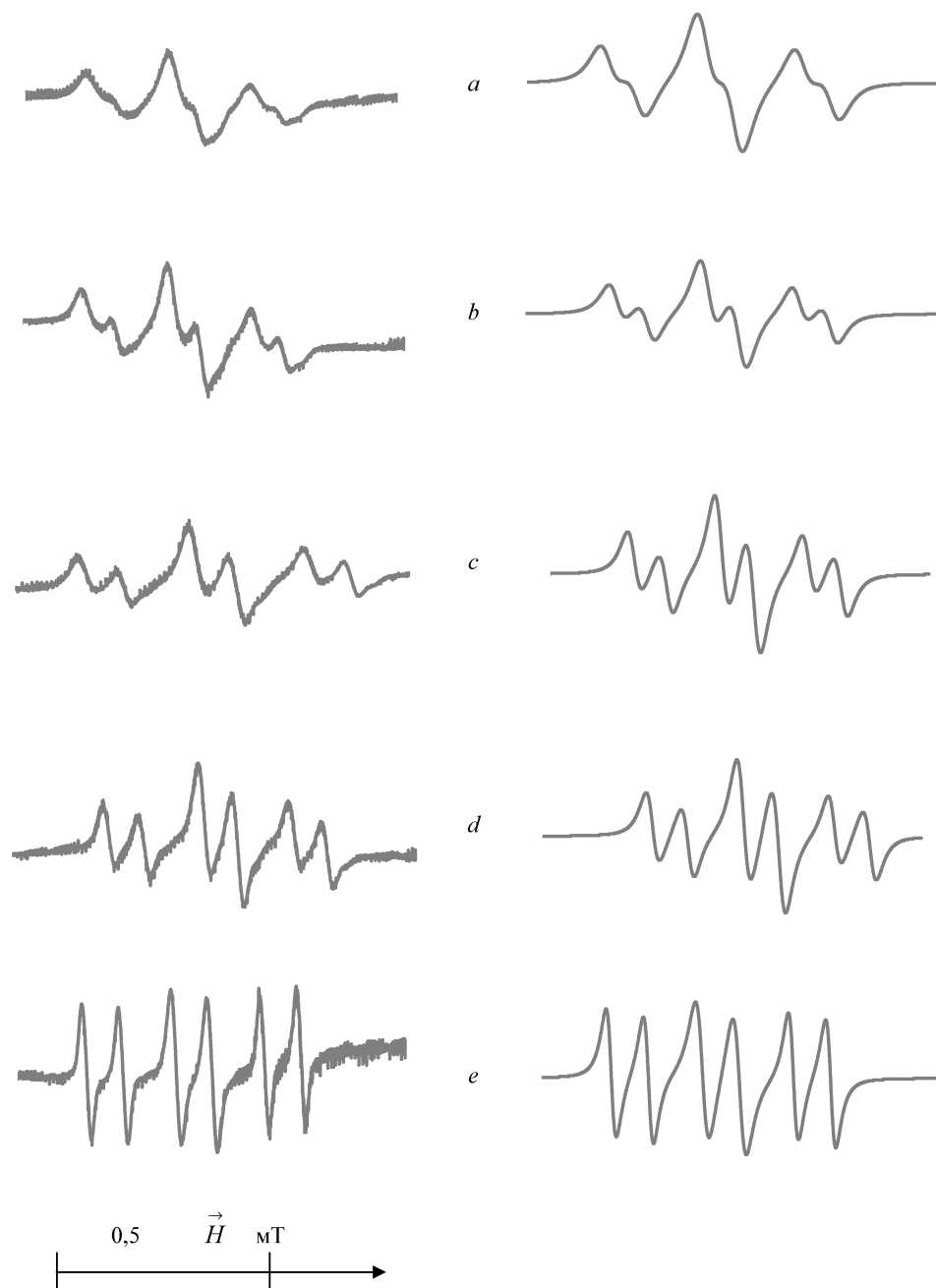

$$\tag{2}$$

where A, B, C, D denote same forms of radical I differing spin of the hydrogen atom [8].

Studies were performed in a degassed, saturated solution of N-PhAA in toluene [11]. Figure 1 illustrates the ESR spectra of the radical I with N-phenylanthranilic acid to the solution of toluene (N-PhAA concentration 0.09 mol/l) as a function of the temperature.

The ESR spectra of the 3,6-di-tert.butyl-2-hydroxyphenoxyl radical presented triplet of doublets with the hyperfine interaction constants (hfc) of aromatic protons equal to $a_H = 0.392$ mT and with the hfc the proton of the hydroxyl group equal to $a_H^{OH} = 0.162$ mT respectively. The broadening of the lines leading to a decrease in the hydroxyl proton constant indicates the presence of intermolecular proton exchange and the transformation of the radical spectrum from a triplet of doublets to a triplet. An analogous dependence is observed in the ESR spectra of the investigated radical and in the presence of others acids. In accord with the theory, such broadening of the lines in the ESR spectra is accompanied by a decrease in the hyperfine interaction. As can

be seen from Figure 1 the ESR spectrum of the radical undergoes a characteristic broadening of the lines corresponding to the intermolecular proton exchange, broadening increases with rising temperature.

The resulting complex due to the hydrogen bond between N-PhAA and the radical is quite strong. This effect slows down the rate of intramolecular tautomerism in the radical. This is evidenced by a decrease in the intensity of the central components of the triplet (Fig. 1 e).

a — k_{exch} =3.56×10^8 mol^{-1}s^{-1} at 397 K; b — k_{exch}=2.76×10^8 mol^{-1}s^{-1} at 382 K; c — k_{exch} =2.44×10^8 mol^{-1}s^{-1} at 374 K; d — k_{exch} =1.33×10^8 mol^{-1}s^{-1} at 351 K; e — k_{exch} =3.11×10^7 mol^{-1}s^{-1} at 295 K. Linewidth = 0.035 mT. Concentration of N-PhAA is 0.09 mol/l

Figure 1. Left: Temperature-dependent ESR spectra of 3,6-di-tert-butyl-2-oxyphenoxyl + N-phenylanthranilic acid in toluene, 290–400 K; Right: the simulated spectra

Kinetic parameters of 3,6-di-tert.butyl-2-hydroxyphenoxyl with N-phenylanthranilic acids intermolecular proton exchange were calculated using the program in the algorithmic language Fortran. The data obtained

are presented in Table 1. The kinetic parameters of some acids are also presented in Table 1 [12–13]. The Eyring plot gave a clear linear relationship between ln k_{exch} and 1/T with correlation coefficient r = 0.98 (Fig. 2).
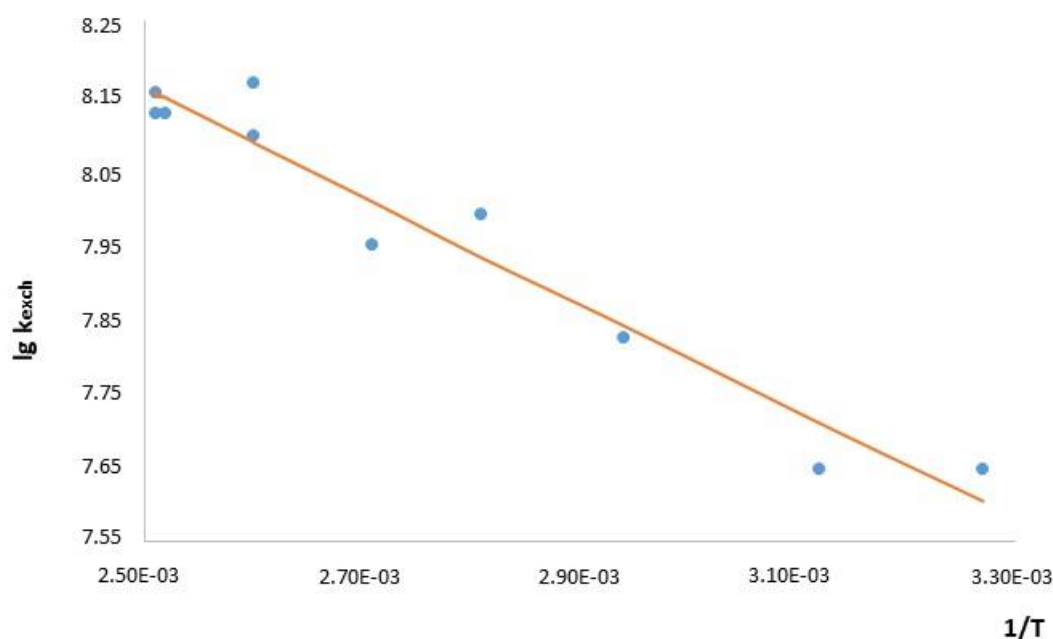

Figure 2. Eyring plot of the intermolecular rate constant (k_{exch}) for 3,6-di-tert-butyl-2-oxyphenoxyl + + N-phenylanthranilic acid obtained from simulations of the ESR spectrum

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Kinetic parameters of the fast intermolecular proton exchange reactions between radical I and various OH-acids in toluene

Acid	k_{exch} (293K), l/mol·s	k^o_{exch}, l/mol·s	E_a, kJ/mol	pK_a
Benzoic	$(1.32\pm0.11)\cdot10^8$	$6.01\cdot10^9$	9.3 ± 0.9	4.18
Salicylic	$(1.48\pm0.09)\cdot10^7$	$8.57\cdot10^9$	15.5 ± 0.5	3.00
Anthranilic 2-Aminobenzoic	$(1.76\pm0.21)\cdot10^8$	$9.34\cdot10^9$	9.7 ± 0.2	4.95
3-Aminobenzoic	$(2.55\pm0.19)\cdot10^8$	$7.22\cdot10^9$	8.2 ± 0.9	4.73
4-Aminobenzoic	$(2.93\pm0.15)\cdot10^8$	$1.52\cdot10^{10}$	9.6 ± 0.9	4.64
N-Phenylanthranilic 2-(Phenylamino)benzoic	$(3.15\pm0.20)\cdot10^7$	$9.25\cdot10^9$	13.8 ± 1.1	5.28

A comparison of the kinetic parameters of the proton exchange of N-phenylanthranilyc acid with similar parameters anthranilyc acid shows that the exchange rate is slightly lower, and the activation barrier is higher by 3 kJ / mol, as shown in Table 1. The decrease in the reaction rate is possibly associated with the formation of a stronger intramolecular complex between the carboxyl group and amino group acid. A second benzene ring conjugated to the nitrogen atom of the amino group acts on the complex being formed.

Conclusions

Comparison of the protolithic properties of N-phenylanthranilyc acid showed that the acid was the weakest acid submitted. The molecular structure of N-phenylanthranilyc acid presents coplanarity between the carboxylic group and the nitrogen atom of the aromatic ring. In turn the lone pair on the nitrogen atom is in resonance with the aromatic rings. Perhaps that the molecular coplanarity is a consequence of the formation of a hydrogen bond between the oxygen of the carboxyl group and the hydrogen of the amino group. The

difference in the protolytic properties of anthranilic acid and N-phenylanthranilic acid is due to the influence of the second aromatic ring bound to the nitrogen atom.

In addition, interpretation of the obtained experimental data requires the use of corresponding quantum chemical calculations.

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3,6-ди-трет-бутил-2-оксифеноксилдің N-фенилантранил қышқылымен молекулааралық протон алмасуын ЭПР-спектроскопия әдісімен зерттеу

Мақалада 3,6-ди-трет-бутил-2-гидроксифеноксил (I) мен N-фенилантранил қышқылының спиндік зонд арасындағы молекулааралық протон алмасуының (МПА) реакциясы зерттелген. Динамикалық ЭПР спектроскопиясының көмегімен 3,6-ди-трет-бутил-2-гидроксилфеноксил – N-фенилантранил қышқылы (N-ФАҚ) жүйесінің тәжірибелік спектрлері тіркелген. Зерттеу жұмыстары кең температуралық диапазондағы сусыз индифферентті толуол еріткішінде жүргізілген. ESR-EXCHANGE бағдарламасын қолдана отырып, әртүрлі технологиялық жылдамдықтарға сәйкес келетін I — N-ФАҚ радикалды жүйесінің теориялық ЭПР спектрлері сәтті түрде модельденді. Бағдарлама Fortran 90 алгоритмдік тілінің заманауи нұсқасында жазылған. Төрт секірмелі модельге арналған сызық формасының жалпы теңдеуі модифицирленген Блох теңдеулерінен алынған. Радикал I және N-ФАҚ арасындағы молекулааралық протон алмасу процесінің екінші ретті жылдамдық тұрақтылықтары тәжірибелік және модельденген ЭПР спектрлерін салыстыру арқылы анықталған. Ең аз квадраттардың итерациялық процедурасы молекулааралық протон алмасуының кинетикалық мәліметтерін компьютерлік талдау және реакцияның активтену параметрлерін алу үшін қолданылған. Кинетикалық мәліметтерден N-фенилантранил

қышқылы аминобензой қышқылдарымен салыстырғанда төмен протолиттік қабілеттілікке ие екендігі анықталған.

Кілт сөздер: ЭПР спектроскопиясы, спиндік зонд, семихинонды радикал, антранил қышқылы, N-фени-лантранил қышқылы, 3,6-ди-трет-бутил-2-оксифеноксил, ОН-қышқылдар, протон алмасу реакциясы, Блох теңдеуі.

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Исследование межмолекулярного протонного обмена 3,6-ди-трет-бутил-2-оксифеноксила с N-фенилантраниловой кислотой методом ЭПР-спектроскопии

В статье исследована реакция межмолекулярного протонного обмена (МПО) между спиновым зондом 3,6-ди-трет-бутил-2-гидроксифеноксилом (I) и ароматической аминокислотой N-фенилантраниловой кислотой (N-ФАК). Экспериментальные спектры системы 3,6-ди-трет-бутил-2-гидроксифеноксил – N-фенилантраниловая кислота регистрировали с помощью динамической ЭПР-спектроскопии. Исследования проводились в неводном индифферентном растворителе — толуоле в широком температурном диапазоне. Теоретические спектры ЭПР системы радикал I — N-ФАК, соответствующие различным скоростям процесса, были успешно смоделированы с использованием программы ESR-EXHANGE. Программа была написана на современной версии алгоритмического языка Фортран 90. Общее уравнение формы линии для четырехпрыжковой модели было получено из модифицированных уравнений Блоха. Константы скорости второго порядка для процесса межмолекулярного протонного обмена между радикалом I и N-ФАК были определены путем сравнения экспериментального и модельного спектров ЭПР. Итеративная процедура наименьших квадратов была использована для компьютерного анализа кинетических данных межмолекулярного протонного обмена и получения активационных параметров реакции. Из кинетических данных следует, что N-фенилантраниловая кислота обладает наименьшим значением протолитической способности по сравнению с аминобензойными кислотами.

Ключевые слова: ЭПР-спектроскопия, спиновый зонд, семихиноновый радикал, антраниловая кислота, N-фенилантраниловая кислота, 3,6-ди-трет-бутил-2-оксифеноксил, ОН-кислоты, реакции протонного обмена, уравнение Блоха.

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