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Synthesis, Structure, and Antioxidant Activity of Hybrid N-Substituted Salicylic Acid Amides

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Abstract—Sterically hindered phenols, 3-*tert*-butyl-*N*-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-ethyl-2-hydroxybenzamide and *N*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl]-2-hydroxybenzamide, were synthesized as potential antioxidants, and the formation of hydrogen bonds by their molecules was shown by UV and IR spectroscopy.

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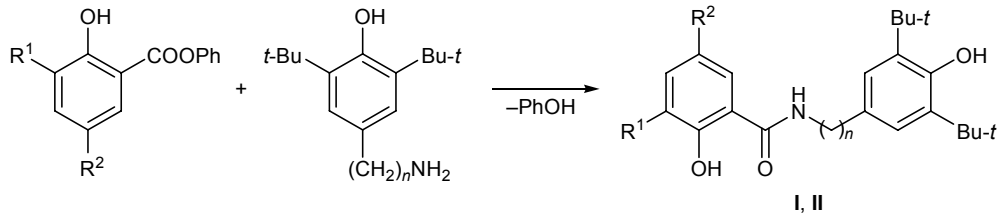
Hybrid antioxidants based on sterically hindered phenols containing a sulfanyl, sulfide, disulfide [1, 2], ester, or amide group [3] have been reported. Salicylic acid and its derivatives absorb UV light, in particular in the region λ 300–305 nm which is the most hazardous from the viewpoint of development of melanoma [4, 5]. In this connection it seems reasonable to synthesize antioxidants capable of inhibiting the oxidation process under UV initiation due to the presence of salicylic acid residue and via direct interaction of phenol with peroxide radicals and exhibiting peroxidase activity due to the presence of amino or amide groups. Taking into account the above stated, we have synthesized amides **I** and **II** (Scheme 1).

Both benzene rings and functional groups in molecule **I** constitute a common conjugation system, whereas the salicylic acid amide and phenol fragments in structure **II** are separated by three methylene groups. The degrees of steric shielding of the phenolic hydroxy groups in **I** and **II** are also different. Amide **I** containing *tert*-butyl groups in the *ortho* positions with respect to the hydroxy groups may be regarded as sterically hindered, and amide **II**, as partly shielded dihydric phenol.

The UV spectra of amides **I** and **II** displayed long-wave absorption bands with their maxima at λ 325, 225 and 311, 220 nm, which correspond to n–π* and π–π* transitions, respectively [6, 7]. The IR spectra of **I** and **II** contained absorption bands due to stretching vibrations of free phenolic hydroxy group (νOH 3644 cm^{-1}) and νNH band which usually appears at about 3450 cm^{-1} [8]. The νNH band maxima were located at 3454 (**I**) and 3442 cm^{-1} (**II**). The high-frequency shift of the νNH band is determined by weaker electron density delocalization in amide **II** as compared to **I**. In addition, absorption bands at 3529

Scheme 1.

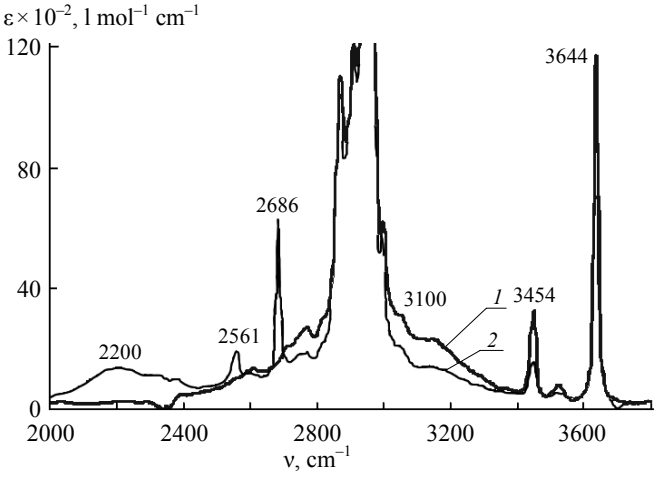


I, **II**

I, n = 0, R^1 = *t*-Bu, R^2 = Et; **II**, n = 3, R^1 = R^2 = H.

(**I**) and 3469 cm^{-1} (**II**) were observed, which were assigned to composite vibrations of the benzene rings as π-bases involved in weak intermolecular hydrogen bonds. The position of these bands reflects π–π- and π–ρ-conjugation effects. Therefore, the corresponding band in the spectrum of **I** (which is characterized by a higher degree of conjugation) is more intense and is located at higher frequencies ($\Delta\nu = 60$ cm^{-1}).

It is known that salicylic acid and its derivatives in organic aprotic solvents form complexes via intra- and intermolecular hydrogen bonding between the phenolic hydroxy group and the neighboring carbonyl group [8, 9]. It seemed important to examine specificities of supermolecular organization of amides **I** and **II** determined by the possibility for formation of different hydrogen bonds. Amides **I** and **II** showed in the IR spectra a broad composite band in the region 2300–3400 cm^{-1} (see figure). According to published data [10], this region corresponds to stretching vibrations of phenolic hydroxy group involved in intra- or intermolecular hydrogen bond. Comparison of the IR spectra of salicylic acid, acetylsalicylic acid, and salicylic acid methyl ester showed that the OH band involved in intramolecular hydrogen bond appears at 3230 cm^{-1} and that intermolecularly bound phenolic hydroxy group gives rise to a complex absorption pattern in the region 2500–3300 cm^{-1} [10]. Denisov et al. [11] studied the IR spectra of salicylaldehyde (–O–H···O=C) and *o*-nitrophenol (–O–H···O=N–) and found that intramolecular bonds therein are characterized by a strong maximum at 3200 cm^{-1} and appreciable low-frequency shift of the ν(OH) band. The ν(OH) band from the intermolecularly bound phenolic hydroxy group is usually located in the region



IR spectra of (*1*) amide **I** and (*2*) its partially deuterated analog at the OH and NH groups; CCl_4, $c = 10^{-2}$ M.

3400–3560 cm^{-1}, and it has a complex structure and a half-width of 400 cm^{-1} [9, 11].

Identification of hydrogen bonds formed by amides **I** and **II** is complicated by the presence of strong absorption bands belonging to =C–H and C–H stretching vibrations in the region 2800–3100 cm^{-1}. With a view to elucidate the nature of hydrogen bonds in amides **I** and **II**, we compared their IR spectra with those of partially deuterated analogs. Superposition of the IR spectra of amide **I** and its OD/ND analog (see figure) shows that the absorption bands belonging to unassociated OH and NH groups (3644 and 3454 cm^{-1}, respectively) do not change their position, but their intensity decreases. The spectrum of the deuterated analog contains new bands corresponding to stretching vibrations of the OD and ND bonds (2686 and 2561 cm^{-1}, respectively). In the low-frequency region we observed a new broad band with its maximum at 2200 cm^{-1}. This indicated formation of hydrogen bonds by the OD group and is determined by Fermi-resonance frequency interaction and cumulative difference transitions including low-frequency vibrations [12]. The corresponding ν(OH) band of H-complexes should be observed at about 3100 cm^{-1}: $\nu(OH) \approx 2^{0.5}\nu(OD)$. In fact, a maximum was observed on the shoulder on the composite band arising from =C–H and C–H stretching vibrations. Deuteration reduces the intensity of that fragment in the spectrum, which provides an additional support to the formation of hydrogen bonds.

We also compared a series of the IR spectra of amides **I** and **II** in solution with a concentration ranging from 1.0×10^{-2} to 25.0×10^{-4} M. The absorbance was normalized by unit concentration (*c*, M) and unit thickness of the absorbing layer *l*: $\varepsilon = \ln(I_0/I)/cl$. Insignificant reduction of the ν(=C–H, –C–H) and ν(–O–H) absorption intensity was observed in going to the H-complexes, which suggests their high strength. The absorption intensity almost does not change with variation of temperature in the range from 25 to 70°C, which also indicates formation of strong intramolecular hydrogen bonds.

Unlike hydroxy compounds, amides and secondary amines are weak proton donors [8] which do not form N–H···O=C hydrogen bonds. This is confirmed by the absence of a characteristic shift of the νNH frequency, which may reach 14 to 74 cm^{-1} for H-complexes.

Amides **I** and **II** were tested as potential antioxidants. We have found that these compounds efficiently inhibit radical oxidation regardless of the mode

Kinetic parameters of the oxidation of methyl oleate in the presence of amides **I** and **II** ($c = 2\times10^{-4}$ M) under different initiation conditions

Compound no.	$k_7\times10^4$, l mol^{-1} s^{-1}	f	τ_{ind}, min (333 K)		$W_{ROOH}\times10^{-4}$, g of I_2 per 100 g of lipid per second (293 K)
			AIBN[a]	UV[b]	
I	1.69	2.6	200	590	3.3
II	0.52	3.3	240	950	3.4
Dibunol	1.4	2	190	900	0

[a] $W_i = 4.2\times10^{-8}$ mol/s.
[b] $W_i = 0.6\times10^{-8}$ mol/s.

of its initiation (UV irradiation or thermal decomposition of azo compounds). At comparable concentrations, their antioxidant effect characterized by the induction period (τ_{ind}) exceeded the effect of the reference inhibitor Dibunol (2,6-di-*tert*-butyl-4-methylphenol; see table).

Compounds **I** and **II** also exhibited antiradical activity (see table). It is known that the rate constant of the reaction of an oxidation inhibitor with peroxy radicals (k_7) increases in parallel with the number and size of *ortho*- and *para*-substituent in its molecule [13]. The results obtained for amides **I** and **II** were consistent with that relation. The rate constants k_7 for sterically hindered phenols (Dibunol and amide **I**) were higher by a factor of 2.7–3.3 than that for partially shielded amide **II**. The stoichiometric coefficient of inhibition characterizing the number of radical chains terminated by one antioxidant molecule reflects the number of phenolic groups; this coefficient for **I** and **II** is higher than that of Dibunol by a factor of 1.5.

Under UV irradiation at comparable initiation rates the examined N-substituted salicylic acid derivatives showed an appreciably higher efficiency; this may be rationalized by the fact that these compounds strongly absorb ultraviolet irradiation used to initiate oxidation (λ 313–365 nm); therefore, that can act as UV stabilizers.

Unlike Dibunol, amides **I** and **II** during autooxidation are capable of inhibiting peroxide accumulation and reducing their concentration in preliminarily oxidized lipids. The peroxidase activities of amides **I** and **II** are comparable to each other (see table), which is likely to be determined by the presence of an amide fragment in their molecules.

Thus, sterically hindered phenols 3-*tert*-butyl-*N*-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-ethyl-2-hydroxybenzamide and *N*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl]-2-hydroxybenzamide are efficient antioxidants acting at different steps of the complex radical oxidation process. The mechanism of inhibitory effect of amides **I** and **II** is determined by radical termination on antioxidant molecules, nonradical degradation of peroxides, and reduction of the oxidation initiation rate under UV irradiation.

EXPERIMENTAL

The IR spectra were recorded on Shimadzu IR Prestige-21 and Specord 75IR spectrometers from solutions in carbon tetrachloride. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer. The mass spectra were obtained using an HP 5971 mass-selective detector coupled with an HP 5890 Series II gas chromatograph. Amide **I** was deuterated by dissolution in CD_3OD, followed by evaporation of the solvent at 40–50°C.

3-*tert*-Butyl-*N*-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-ethyl-2-hydroxybenzamide (I). A mixture of 2.21 g (0.01 mol) of 4-amino-2,6-di-*tert*-butylphenol, 2.44 g of 3-*tert*-butyl-5-ethyl-2-hydroxybenzoyl chloride, 3 ml of DMF, and 1 ml of triethylamine was heated for 2 h at 90°C. The mixture was then dissolved in 30 ml of hot petroleum ether, the solution was washed with warm (40°C) water (2×25 ml), partially evaporated, and left to stand for 14 h in a refrigerator, and the precipitate was filtered off and washed with petroleum ether (20°C). Yield 1.8 g (42%), white crystals, mp 200–202°C. UV spectrum (EtOH): λ_{max} 318 nm (log ε 3.80). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3, J = 7 Hz), 1.40 s (9H, *t*-Bu), 1.43 s (18H, *t*-Bu), 2.56 q (2H, C**H**$_2$CH$_3$), 4.92 s (1H, OH), 7.10 d (2H, H_{arom}), 7.28 s (2H, H_{arom}), 12.55 s (1H, OH). Found: m/z 425.29384 $[M]^+$. $C_{27}H_{39}NO_3$. Calculated: M 425.29298.

***N*-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-2-hydroxybenzamide (II).** A mixture of 2.6 g of 85% phenyl 2-hydroxybenzoate and 2.69 g (0.01 mol) of

4-(3-aminopropyl)-2,6-di-*tert*-butylphenol was heated to 180°C, helium was passed therethrough, and the mixture was kept for 40 min under reduced pressure (water-jet pump) to distill off 0.83 g of phenol. The hot residue was transferred into a mortar and ground. The light yellow powder, 4.64 g, was washed with warm petroleum ether (40°C), and the residue was recrystallized from ethanol–petroleum ether. Yield 1.15 g, white powder, mp 115–117°C. UV spectrum (EtOH), λ_{max} (logε): 208 (4.44), 285 (3.61), 302 (3.68). ^{1}H NMR spectrum, δ, ppm: 1.90 m (2H, CH_2), 2.62 t (2H, Ar$C\mathbf{H}_2$, J = 6 Hz), 3.45 m (2H, $C\mathbf{H}_2$NH), 5.00 s (1H, OH), 6.00 t (1H, NH), 6.50–7.24 m (4H, H_{arom}), 6.90 s (2H, H_{arom}), 12.26 s (1H, OH). Found: m/z 383.24665 $[M]^+$. $C_{24}H_{33}NO_3$. Calculated: M 383.24603.

The rate constants of the reactions of peroxy radicals with oxidation inhibitors (k_7) and stoichiometric coefficients of inhibition (f) were determined by the chemiluminescence method [14]. The kinetics of oxygen absorption in the oxidation of methyl oleate with atmospheric oxygen under initiation by azobis(isobutyronitrile) or UV irradiation (DRSh-250-3 mercury lamp, λ 313–365 nm) were studied in an inert solvent (chlorobenzene, 1 : 1) at 60 ± 0.2°C using a Warburg manometer. The induction period was determined from the kinetic curves for the oxygen absorption [15]. The rate of initiation was estimated by the inhibitor method using Dibunol as reference antioxidant [16]. The kinetics of accumulation and degradation of hydroperoxides in a model substrate were studied under autooxidation conditions by reverse iodometric titration in nonaqueous medium. Amides **I** and **II** were used without additional purification; the solvents were of chemically pure grade.

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