Reductive bromination of *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine

V. A. Golubev[a]* *and Yu. D. Kim*[b]

[a]*Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 prosp. Akad. Semenova, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 (496) 515 5420. E-mail: vgolubev@icp.ac.ru*
[b]*M. V. Lomonosov Moscow State University, 1 Leninskie Gory, 119991 Moscow, Russian Federation. E-mail: yula.me.kim@gmail.com*

Unlike most arenes, *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine reacts with Br_2 *via* the reductive bromination mechanism. Here, two hydrogens in *ortho* positions of benzene rings are substituted by Br_2 and provide two-electron reduction of hydroxylamine to amine.

Key words: diarylhydroxylamines, halogenation, electrophilic substitution, reductive halogenation.

Most arenes react with halogens *via* the electrophilic substitution mechanism.[1,2] A known exception comprises diarylnitroxyl radicals reacting with halogens *via* reductive halogenation.[3—5] This process involves three-electron reduction of the nitroxyl group and formation of corresponding diarylamines. We found that the reductive halogenation reaction involves not only radicals but diamagnetic diarylhydroxylamines as well. So, the reaction of *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine (**1**) with Br_2 in the equimolar amounts produces dibromoamine **3** (yield 94±2%, Scheme 1) rather than bromohydroxylamine **2** and HBr.

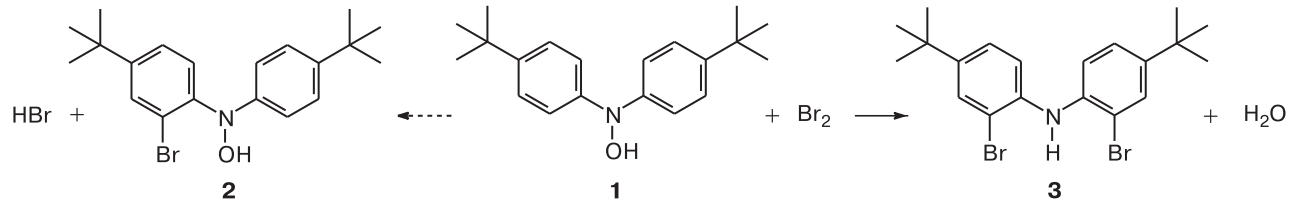
The reductive halogenation mechanism of arenes has not been fully revealed yet. So, the authors of study,[3] which describes the synthesis and properties of diphenylnitroxyl radical, suppose that bromine reduces this radical to tribromodiphenylamine, whose reaction with Br_2 excess yields final tetrabromodiphenylamine. The authors of monograph[6] suggest an alternative reductive bromination mechanism for this radical. According to their hypothesis, diphenylnitroxyl initially disproportionates into *N*-phenylquinone imine-*N*-oxide and diphenylamine. The latter reacts with Br_2 to yield tetrabromodiphenylamine. However, such mechanism is not evidenced by releasing *N*-phenylquinone imine-*N*-oxide or derivatives thereof. The reaction of bis(4-*tert*-butylphenyl)amineoxyl with Br_2 yields dibromoamine **3** and corresponding tribromoamine in comparable amounts.[4] The authors of study[4] supposed that the reductive bromination of this radical involves formation of intermediate bromohydroxylamine **2** and dibromodiphenylaminyl radical.

Being stoichiometrically simple, the reaction of hydroxylamine **1** with Br_2 is a convenient model reaction to study the reductive bromination of arenes. The major goal of our work is to reveal the mechanism of this unusual reaction.

Results and Discussion

The structure of dibromoamine **3** was identified by IR, UV, and NMR spectra. The spectra of the synthesized compound are identical to those of dibromoamine **3**, which we obtained *via* bromination of bis(4-*tert*-butylphenyl)amine (**4**) and corresponding nitroxyl radical.[4] In relation to hydroxylamine **1**, bromine acts simultaneously as a brominating and two-electron reducing agent. The reductive bromination rate of hydroxylamine **1** is much higher than that of its electrophilic bromination to bromo-

Scheme 1



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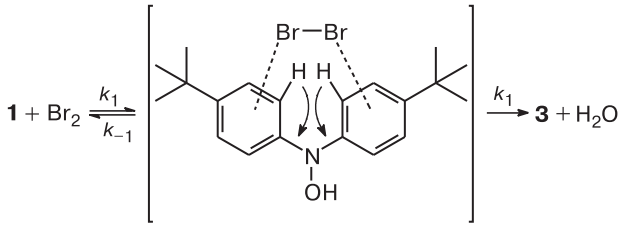
hydroxylamine **2**. We did not detect the latter among the reaction products. The conversion of hydroxylamine **1** to dibromoamine **3** involves the intermediate complex **A** forming *via* Scheme 2 immediately upon mixing the reagents.

Scheme 2



A

The UV spectrum of complex **A** shows two absorption bands in the range from 250 to 700 nm. The first band with λ_{max} = 406 nm (Fig. 1) accounts for the brown reddish color of the reaction solution. The peak of this absorption band is close to that of Br_2 (422 nm). However, the extinction coefficient (ε ~ 3600 L mol^{-1} cm^{-1}) of this band of the complex is 16 times higher than that of Br_2. The absorption of complex **A** almost completely masks that of Br_2. The band intensity of the complex rapidly decreases upon its conversion to dibromoamine **3**. The half-life of this conversion is ~3.5 min at $[\mathbf{1}]_0 = [Br_2]_0 = 2 \cdot 10^{-3}$ mol L^{-1} and 25 °C.

The second band of complex **A** with λ_{max} = 308 nm is red-shifted by 26 nm in relation to the absorption band of

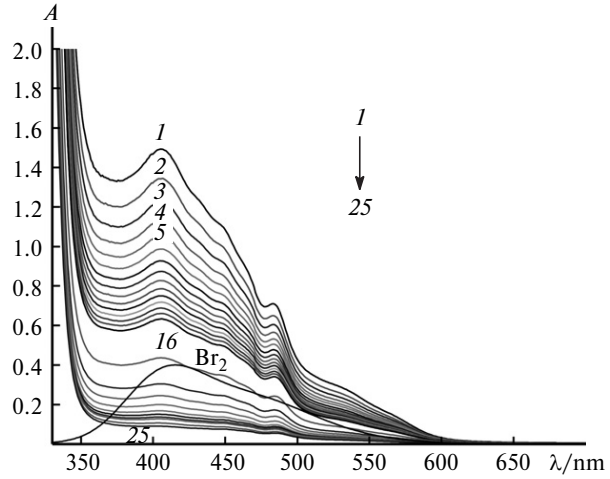


Fig. 1. Absorption spectra of Br_2 and products of its reaction with *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine (**1**) in CCl_4 at 25 °C. $[Br_2]_0 = [\mathbf{1}]_0 = 2 \cdot 10^{-3}$ mol L^{-1}, 1.00 cm cuvette, reaction time, min: 0.7 (*1*), 1.06 (*2*), 1.41 (*3*), 1.77 (*4*), 2.12 (*5*), 2.47 (*6*), 2.82 (*7*), 3.17 (*8*), 3.52 (*9*), 3.87 (*10*), 4.22 (*11*), 4.57 (*12*), 4.92 (*13*), 5.27 (*14*), 5.62 (*15*), 10.8 (*16*), 16.7 (*17*), 22.7 (*18*), 30.7 (*19*), 40.7 (*20*), 50.7 (*21*), 62 (*22*), 73 (*23*), 121 (*24*), and 251 (*25*).

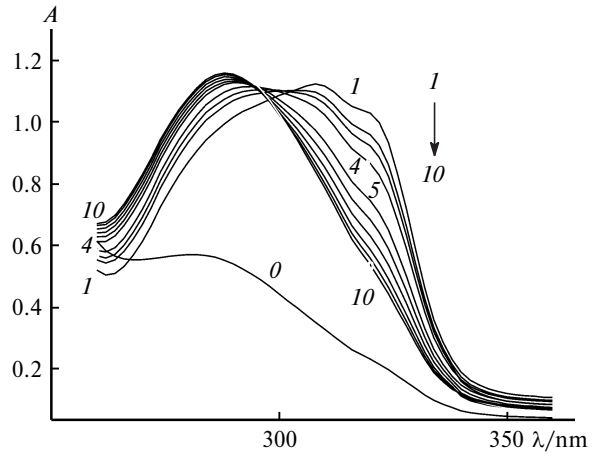


Fig. 2. Absorption spectra of *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine (**1**) and products of its reaction with Br_2 (*1*—*10*) in CCl_4. $[Br_2]_0 = [\mathbf{1}]_0 = 7 \cdot 10^{-4}$ mol L^{-1}, 0.10 cm cuvette, reaction time, min: 0 (*0*), 0.8 (*1*), 1.8 (*2*), 2.6 (*3*), 4.3 (*4*), 11.3 (*5*), 18.7 (*6*), 23.7 (*7*), 31.8 (*8*), 39.5 (*9*), and 47 (*10*).

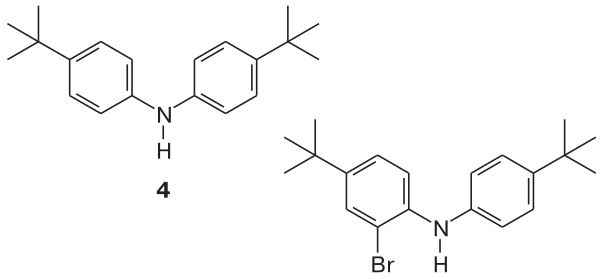
hydroxylamine **1** at λ_{max} = 282 nm (Fig. 2). During the reaction time (50 s), the absorption intensity of hydroxylamine **1** at λ = 260 nm decreases by *ca.* 16% upon its conversion to complex **A**. The extinction coefficient of complex **A** in the absorption band at 308 nm was calculated by the Lambert—Beer formula as ~81000 L mol^{-1} cm^{-1} that was 11 times higher than that of hydroxylamine **1**. Note that all the absorption curves of the reaction mixture, aside from those corresponding to the starting period, pass through the isosbestic point at λ_{iso} = 294 nm.

The reductive bromination mechanism of hydroxylamine **1** principally differs from the known electrophilic bromination mechanism of arenes *via* intermediate π- and σ-complexes.[1,2] The structures of these complexes are unambiguously determined by the X-ray structural data.[7,8] In π-complexes, Br_2 molecules are arranged almost perpendicularly to the aromatic ring plane and coordinated by C—C bonds with the highest electron density. At the reaction rate determining step, π-complexes turn into σ-complexes, which are brominated carbocations. The latter react with Br^- anion to yield bromoarenes and HBr. So bromination of arenes *via* electrophilic mechanism consumes only a half of bromine amount for the synthesis of bromoarenes. The electrophilic bromination is not selective as it always yields a mixture of isomers.

Unlike common π-complexes, Br_2 molecule in complex **A** is apparently coordinated by two benzene rings of hydroxylamine **1**. In the reaction rate determining step, two benzene hydrogens in *ortho* positions of the complex are substituted by bromine atoms and transferred to NOH group to reduce it to an amino group. Simultaneously, formed dibromoamine **3** releases water. This mechanism is evidenced with a high selectivity of reductive bromination yielding sole *ortho*-isomer of dibromoamine **3**. More-

over, the presence of an isosbestic point in the absorption curves evidences the direct conversion of complex **A** to the final product. Unlike the electrophilic mechanism, both bromine atoms are consumed for the synthesis of bromoarenes *via* the reductive bromination.

The reaction of hydroxylamine **1** with Br_2 yields, along with dibromoamine **3**, five by-products, which are HPLC detectable. Three chromatographic peaks at V_{ret} 355, 630, and 755 μL are attributed to amine **4**, bromoamine **5**, and tribromoamine **6**, whose yield is 0.8, 0.3, and 0.8 mol.%, respectively.



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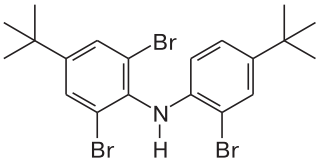

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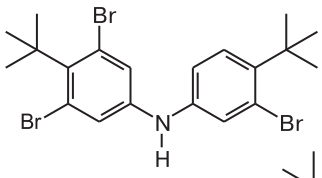
The structures of these substances were established on the basis of the identity of their UV and NMR spectra and those of the available samples.[4,8] Amine **4** exists as an impurity in the starting hydroxylamine **1**. Apparently, bromoamine **5** is formed *via* bromination of amine **4**, while tribromoamine **6** is formed by bromination of dibromoamine **3**. The bromination mechanism of amines **3** and **4** is likely electrophilic substitution as it releases the equivalent amount of HBr.

Aside of these impurities, the reaction yields tribromoamine **7** and quinone imine **9** (0.2 and 1 mol.%, respectively).

Tribromoamine **7** was detected chromatographically at V_{ret} = 720 μL and identified by ^{1}H NMR. The spectrum of the obtained compound shows a singlet signal of two *tert*-butyl groups (δ 1.24) and a singlet signal of NH (δ 5.46). The benzene ring with one bromine atom shows the signals of three protons. The doublet-doublet signal at δ 6.77 (J = 1.8 and 8.2 Hz) is attributed to H(6′), the doublet signal at δ 6.42 (J = 8.2 Hz) is attributed to H(5′), and the doublet signal at δ 6.73 (J = 1.8 Hz) is attributed to H(2′). The benzene rings with two bromine atoms shows two doublet signals of H(2) and H(6) at δ 6.66 and 6.93 (J = 2.0 Hz). Due to the steric hindrances caused by *tert*-butyl groups, C—N bond twisting is complicated, H(2) and H(6) atoms appear in different spatial environments and have different chemical shifts. Tribromoamine **7** is



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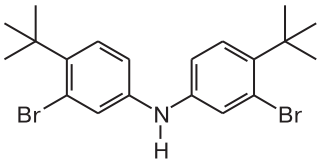

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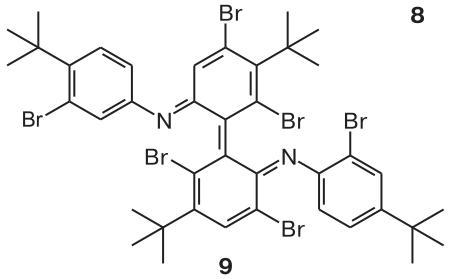

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probably formed by bromination of dibromoamine **8**, which is a *meta* isomer of dibromoamine **3**. As follows from the yield ratio of dibromoamine **3** and tribromoamine **7**, the rate of Br_2 addition in *ortho* position of benzene rings of hydroxylamine **1** is by ~500 times higher than that in *meta* position.

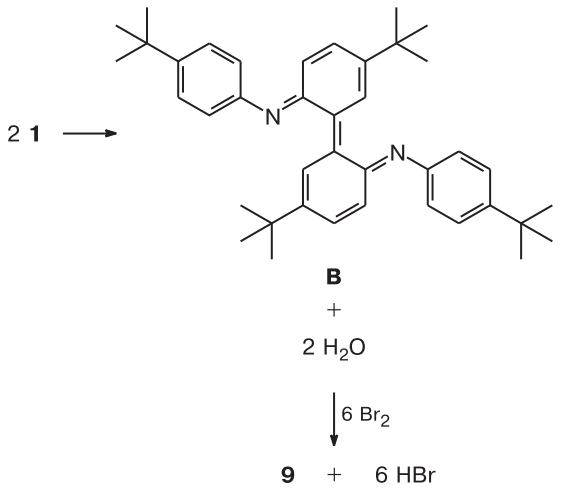
The structure of quinone imine **9** is evidenced by the mass, UV, and NMR spectra. The mass spectrum of this compound shows a peak of protonated molecular ion at m/z = 1027 and thirteen isotope peaks whose intensity ratio is closed to the theoretical ratio of isotope peaks for a molecule with six Br atoms. The UV spectrum of compound **9** shows a band at λ_{max} = 494 nm, which accounts for its red color, as well as an intense band at λ_{max} = 276 nm, which is characteristic for phenylamines. The ^{1}H NMR spectrum of quinone imine **9** shows three overlapping singlet signals at δ 1.25, 1.27, and 1.32 from four *tert*-butyl groups and two singlet signals at δ 5.52 and 5.78 from two protons of the quinone imine moiety. Quinone imine **9** comprises two different benzene moieties each having three protons. See an assumable attribution of six signals from benzene protons in the Experimental section.

Apparently, dye **9** results from dimerization of hydroxylamine **1** to intermediate quinone imine **B**, which is brominated to final quinone imine **9** according to Scheme 3.

A probable catalyst for dimerization of hydroxylamine **1** is HBr. As was noted in study,[9] when affected by acids, hydroxylamine **1** does not only disproportionates but also yields quinone imine dyes.

Therefore, the reaction of arenes with Br_2 may occur not only *via* the electrophilic substitution mechanism but also *via* the reductive halogenation mechanism. To realize the latter, arenes should comprise readily reducible substituents such as hydroxylamine or nitroxyl groups.

Scheme 3



Experimental

N,*N*-Bis(4-*tert*-butylphenyl)hydroxylamine (**1**) synthesized according to the known technique[9] and recrystallized from hexane decomposed at 113—115 °C. According to ^{1}H NMR, it comprised 3% bis(4-*tert*-butylphenyl)amine (**4**). Bromine (pure grade) was distilled under ambient pressure at b.p. 58 °C. Carbon tetrachloride was distilled on a 50-cm column with glass spirals at b.p. 76.5 °C.

IR reflection spectra were recorded with a Spectrum 100 instrument. NMR spectra were recorded in chloroform-d_1 with a Bruker AIII spectrometer (500 MHz). UV spectra were recorded with a Specord UV—VIS and a Specord 210 instruments. ES mass spectra were recorded in a methanol solution with a Shimadzu LCMS 2020 instrument at the ionizing voltage of 5 kV and temperature of 65 °C. The melting points were determined on a PHMK warm table. The chromatographic tests were carried out with a Millikhrom chromatograph, a UV detector at 290 nm (column 2×64 mm, Separon C18, 5 μm), and aqueous 90% MeCN eluent. The substance retention volumes (V_{ret}/μL) were as follows: 1080 (**3**), 355 (**4**), 630 (**5**), 755 (**6**), 720 (**7**), and 395 (**9**). The quantitative HPLC test was carried out by the peak intensities of these substances. The calibration used the knowingly impurity-free substances. Further, the reaction product was quantitatively tested by the amino group signal peak area ratio in ^{1}H NMR at δ 6.26 (**3**), 5.59 (**4**), 5.93 (**5**), 5.96 (**6**), 5.46 (**7**), and 6.04 (unidentifiable substance). The thin-layer chromatography used TLC Al Fluka plates with a 254 nm indicator. The substances were preparatively separated on a 10×105-mm column (Merck 9385 silica gel; 37—63 μm). The preparative TLC used 200×200-mm plates coated with silica gel (1.5-mm layer) comprising a fluorescent indicator.

Reaction of *N*,*N*-bis(4-*tert*-butylphenyl)hydroxylamine (1) with Br_2. Bromine (53.4 mg, 0.334 mmol) solution in CCl_4 (1 mL) was added to diarylhydroxylamine **1** (93.6 mg, 0.315 mmol) solution in CCl_4 (1 mL) at 22 °C. The reaction mixture immediately became brown-red. The color weakened in time and became pink in 20—30 min. The reaction solution was extracted with water (2 mL), which potentiometric titration detected HBr (0.011 mmol, 3.3 mol.% of Br_2). The solvent (CCl_4) was evaporated under reduced pressure to yield the solid reaction product (137 mg). HPLC, V_{ret}/μL (I_{rel} (%)): 355 (10) **4**, 395 (2.1) **9**, 630 (5.6) **5**, 720 (0.8) **7**, 755 (2.4) **6**, 1080 (100) **3**. According to the quantitative HPLC test, the product comprised dibromoamine **3** (130±3 mg, 0.296 mmol, 94±2%). The reaction product composition was also determined by the ^{1}H NMR signal area ratio in the range of 5.4 to 6.4 ppm. According to NMR data, the product comprised dibromoamine **3** (96.5%, amine **4** (0.8%), bromoamine **5** (0.3%), tribromoamine **6** (0.8%), tribromoamine **7** (0.2%), and quinone imine **9** (1%). The reaction product was recrystallized from Pr^iOH to obtain dibromoamine **3** (106 mg, 77%). The mother liquor was evaporated to dry, the residue was dissolved in hexane, then the solution was put on a column with silica gel and eluated with hexane. The first zone (V_{ret} 10—20 mL) comprised primarily dibromoamine **3**. The second zone (V_{ret} 20—40 mL) was evaporated to yield a colorless product (5 mg) whose ^{1}H NMR spectrum detected dibromide **3** (10%), monobromide **5** (47%), tribromide **6** (37%), and tribromide **7** (5%). The second zone TLC (silica gel, hexane eluent) yielded monobromide **5** (m.p. 90 °C, 2 mg) and tribromide **6** (m.p. 182 °C, 1.5 mg). The third chromatographic zone (V_{ret} 40—60 mL) comprised primarily amine **4**. The fourth (red) zone was eluated with a benzene—hexane (1 : 1) mixture, which evaporation yielded quinone imine dye **9** (0.9 mg).

Bis(2-bromo-4-*tert*-butylphenyl)amine (3). Colorless prismatic crystals, m.p. 163 °C (from Pr^iOH); *cf.* Ref. 4: m.p. 163 °C. UV (EtOH), λ_{max}/nm (ε): 287 (22700), 236 sh (9300), 208 (39900). IR (reflection), ν/cm^{-1}: 3389 (NH); 3038 (Ar); 2961, 2900, 2866 (CH_3); 1601, 1519 (Ar), 1331, 1262, 1116, 1036, 882, 814, 712. ^{1}H NMR, δ: 1.30 (s, 18 H, $C(CH_3)_3$); 6.26 (s, 1 H, NH); 7.21 (m, 4 H, H(5), H(6)); 7.56 (br. dd, 2 H, H(3), J = 1.8 Hz, J = 0.7 Hz).

***N*-(2-Bromo-4-*tert*-butylphenyl)-*N*-(4′-*tert*-butylphenyl)amine (5).** Colorless crystals, m.p. 90 °C (from MeCN); *cf.* Ref. 4: m.p. 90 °C. UV (EtOH), λ_{max}/nm (ε): 286 (21800), 238 sh (7530), 202 (40140). ^{1}H NMR, δ: 1.28 (s, 9 H, C(4)$(CH_3)_3$); 1.32 (s, 9 H, C(4′)$(CH_3)_3$); 5.93 (c, 1 H, NH); 7.07 (dm, 2 H, H(2′), H(6′), J = 8.6 Hz); 7.17 (m, 2 H, H(5), H(6)); 7.32 (dm, 2 H, H(3′), H(5′), J = 8.6 Hz); 7.51 (br. dd, 1 H, H(3), J = 1.5 Hz, J = 0.9 Hz).

***N*-(2,6-Dibromo-4-*tert*-butylphenyl)-*N*-(2′-bromo-4′-*tert*-butylphenyl)amine (6).** Colorless plate crystals, m.p. 182 °C (from heptane); *cf.* Ref. 4: m.p. 182 °C. UV (EtOH), λ_{max}/nm (ε): 286 (9380), 234 sh (18400), 208 (69300). ^{1}H NMR, δ: 1.27 (s, 9 H, C(4′)$(CH_3)_3$); 1.32 (s, 9 H, C(4)$(CH_3)_3$); 5.96 (s, 1 H, NH); 6.29 (d, 1 H, H(6′), J = 8.5 Hz); 7.10 (dd, 1 H, H(5′), J = 8.5 Hz, J =2.2 Hz); 7.52 (d, 1 H, H(3′), J = 2.2 Hz); 7.60 (s, 2 H, H(3), H(5)).

***N*-(3,5-Dibromo-4-*tert*-butylphenyl)-*N*-(3′-bromo-4′-*tert*-butylphenyl)amine (7).** ^{1}H NMR, δ: 1.24 (s, 18 H, $C(CH_3)_3$); 5.46 (s, 1 H, NH); 6.42 (d, 1 H, H(5′), J = 8.2 Hz); 6.66 (d, 1 H, H(2), J = 2.0 Hz); 6.73 (d, 1 H, H(2′), J = 1.8 Hz); 6.77 (dd, 1 H, H(6′), J = 8.2 Hz, J = 1.8 Hz); 6.93 (d, 1 H, H(6), J = 2.0 Hz).

***N*-(3′-Bromo-4′-*tert*-butylphenyl)-*N*′-(2″-bromo-4″-*tert*-butylphenyl)-3,5,7,10-tetrabromo-4,9-di-*tert*-butyl-1,6-dipheno-quinone diimine (9).** Red deliquescing crystals. UV (MeCN), nm (A_{rel} (%)): 494 (3.4), 298 (65), 276 (100), 253 (75), 241 (82), 206 (321). ^{1}H NMR, δ: 1.25, 1.27 and 1.32 (all s, 36 H, $C(CH_3)_3$); 5.52 (s, 1 H, H(8)); 5.78 (s, 1 H, H(2)); 6.50 (d, 1 H, H(6″), J = 8.4 Hz); 6.93 (dd, 1 H, H(6′), J = 8.2 Hz, J = 2.1 Hz); 7.06 (d, 1 H, H(5′)), J = 8.2 Hz); 7.07 (br.s, 1 H, H(2′)); 7.13 (dd,

1 H, H(5″), J = 8.4 Hz, J = 1.7 Hz); 7.50 (d, 1 H, H(3″), J = 1.7 Hz). Mass spectrum, m/z (I_{rel} (%)): 1027 $[M + H]^+$ (12), 1028 $[M + 2]^+$ (7), 1029 $[M + 3]^+$ (16), 1030 $[M + 4]^+$ (22), 1031 $[M + 5]^+$ (45), 1032 $[M + 6]^+$ (28), 1033 $[M + 7]^+$ (100), 1034 $[M + 8]^+$ (72), 1035 $[M + 9]^+$ (94), 1036 $[M + 10]^+$ (54), 1037 $[M + 11]^+$ (46), 1038 $[M + 12]^+$ (17), 1039 $[M + 13]^+$ (15), 1040 $[M + 14]^+$ (9). $C_{40}H_{44}Br_6N_2$. Calculated, m/z (I_{rel} (%)): 1026 $[M]^+$ (5), 1027 $[M + 1]^+$ (2), 1028 $[M + 2]^+$ (30), 1029 $[M + 3]^+$ (13), 1030 $[M + 4]^+$ (75), 1031 $[M + 5]^+$ (32), 1032 $[M + 6]^+$ (100), 1033 $[M + 7]^+$ (42), 1034 $[M + 8]^+$ (77), 1035 $[M + 9]^+$ (32), 1036 $[M + 10]^+$ (33), 1037 $[M + 11]^+$ (13), 1038 $[M + 12]^+$ (7), 1039 $[M + 13]^+$ (2).

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