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Oxidative Cross-Coupling of Some 2,6- and N,N-Disubstituted Aniline Derivatives with 4-Aminophenol Mediated by Cerium(IV) Ions in Aqueous Perchloric Acid

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Summary. The mechanism of the oxidation of mixtures of 2,6-dimethylaniline (**1**), N,N-dimethylaniline (**2**), 2,6-diethylaniline (**3**), N,N-diethylaniline (**4**), N-methylaniline (**5**), 2,6-difluoroaniline (**6**), and 2,3,5,6-tetrafluoroaniline (**7**) with 4-aminophenol (**8**) by cerium(IV) ions in aqueous perchloric acid has been investigated. The indoaniline salts $[O{=}C_6H_4{=}N\text{-}C_6H_2(R^1)_2NH(R^2)_2]^+ClO_4^-$ ($R^1 = H$, $R^2 = CH_3$, C_2H_5 or *vice versa*) are formed as intermediates in the cross-coupling reaction; they undergo oxidation to imino-4-benzoquinone (**9**) and its corresponding derivatives by cerium(IV) ions in high yields. The mechanism of this process is discussed.

Keywords. 4-Aminophenol; Aniline derivatives; Cerium(IV); Indoaniline derivatives; Oxidative cross-coupling.

Durch Cer(IV)-Ionen induzierte oxidative Kreuzkupplung einiger 2,6- und N,N-disubstituierter Anilinderivate mit 4-Aminophenol in wässriger Perchlorsäure

Zusammenfassung. Die Oxidation von Mischungen von 2,6-Dimethylanilin (**1**), N,N-Dimethylanilin (**2**), 2,6-Diethylanilin (**3**), N,N-Diethylanilin (**4**), N-Methylanilin (**5**), 2,6-Difluoranolin (**6**) und 2,3,5,6-Tetrafluoranilin (**7**) mit 4-Aminophenol (**8**) durch Cer(IV)-Ionen in wässriger Perchlorsäure wurde untersucht. Als Zwischenprodukte der Kreuzkupplungsreaktion treten die Indoanilinsalze $[O{=}C_6H_4{=}N\text{-}C_6H_2(R^1)_2NH(R^2)_2]^+ClO_4^-$ ($R^1 = H$, $R^2 = CH_3$, C_2H_5 oder umgekehrt) auf. Diese werden durch Cer(IV)-Ionen in hohen Ausbeuten zu Imino-4-benzochinon (**9**) und seinen entsprechenden Derivaten oxidiert. Der Mechanismus dieses Vorgangs wird diskutiert.

Introduction

Certain 2,6-disubstituted 1,4-benzoquinones, which are versatile substrates for the synthesis of many important compounds, can be obtained from the corresponding phenols as main products in high yields [1–8]. However, these methods are not practical owing to high costs and toxicity of some oxidants (e.g. thallium(III) nitrate [1], *Fremy*'s salt [7], or *Jones* reagent [8]).

A comparison of experiments and quantum-mechanical calculations shows that the corresponding 1,4-benzoquinones cannot be obtained if carbon atoms C4 of the cation radicals are negatively charged (2,6-difluorophenol, 2,6-diphenylphenol, and 2,3,5,6-tetrafluorophenol) [9]. In such cases, the oxidation results in the corresponding 4,4′-diphenoquinone derivatives and/or 4-phenoxyphenol. The corresponding derivatives of 4,4′-diiminodiphenoquinone and/or N-phenyl-4-phenylenediimine are the products of electrochemical or chemical oxidation of N,N-and 2,6-disubstituted anilines depending on the acidity of the reaction medium, the basicity of the nitrogen atom, and the steric hindrance [10, 11]. Dimeric intermediate products formed as a result of oxidation of the aniline and phenol derivatives undergo further oxidation by cerium(IV) ions to the corresponding derivatives of 1,4-benzoquinone in yields of max. 50% with respect to the parent substrate and only several percent based on the oxidizing agent.

We have found that in acidic solution an equimolar mixture of **4** and **8** was oxidized to 1,4-benzoquinone (**10**) by cerium(IV) ions in 94% yield based both on the organic substrates and the oxidizing agent. The aim of this paper is to present some less expensive and more efficient methods for the synthesis of 1,4-benzoquinone derivatives from the corresponding anilines (usually less expensive than the corresponding phenols) as well as to investigate the influence of the acidity of the reaction medium, the basicity of the nitrogen atom, and the steric hindrance on the reaction pathway.

Results and Discussion

It has been reported earlier that the type of products formed by chemical and electrochemical oxidation of aromatic amines depends on the basicity of the nitrogen atom of the amino group, on the acidity of the reaction medium, and on the steric hindrance [10, 11, 14–20]. The main products of the oxidation of N,N- and 2,6-dialkylsubstituted aniline derivatives are the corresponding diphenoquinone-4,4′-diimines (**11**). Under less acidic conditions ($HClO_4$, 0.5–1.0 *M*), in the case of 2,6-dialkyl substituted aniline derivatives the corresponding N-phenyl-4-phenylenediimine derivatives are formed as well. 1,4-Benzoquinone derivatives are formed in the process of hydrolysis of the corresponding N-phenyl-4-phenylenediimine derivatives or in the process of their further oxidation. The yield of the latter does not exceed 50%. **10** is the only product of the oxidation of **8** by cerium(IV) ions which proceeds *via* formation of **9**. This two-electron process occurs immediately.

On the other hand, it has been reported that the intermediate product of the oxidation of a mixture of **2** and **8** by cerium(IV) ions is an indoaniline derivative ($[OC_6H_4NC_6H_4NH(CH_3)_2]^+ClO_4^-$ (**12**); $\lambda_{max} = 620$ nm; [21]). Oxidation of the N,N-dialkyl derivatives of N-(4′-hydroxyphenyl)-4-phenylenediamine [22–32] results in compounds of the same type. It has been established that **12** hydrolyzes to N,N-dimethyl-1,4-benzoquinoneammonium chlorate (**13**) and to **8**, and it is easily oxidable by cerium(IV) ions to N,N-dimethyl-1,4-benzoquinoneammonium chlorate and to 1,4-benzoquinoneammonium chlorate in a two-electron process. The oxidation of an equimolar mixture of **2** and **8** by cerium(IV) to the above mentioned products involves the reduction of 3 mmoles of cerium(IV) ions per mmole of parent substrates.

Mixtures of 2,6-disubstituted aniline derivatives and **8** undergo oxidation according to a similar mechanism which would enable the transformation of 2,6-

dialkyl aniline derivatives to the corresponding 4-aminophenol derivatives. Taking into account the spectra of solutions with equimolar amounts of N,N- or 2,6-dialkyl aniline derivative and **8**, it could be established that after adding cerium(IV) chlorate the corresponding indoaniline derivatives ($\lambda_{max} = 620$ nm) as well as final products (i.e., 1,4-benzoquinoneammonium chlorate (**14**) and its derivatives) are formed. The fact that the oxidation of a mixture of the aniline derivative and **8** (equimolar quantities) to **9** and to its corresponding derivative is due to a three-electron process (per 1 mmol of reducing agent) shows that the oxidation rates of the substrates and of the intermediate are similar (Fig. 1a). All processes occur immediately except for the oxidation of the mixture of **7** and **8** (Table 1). It should

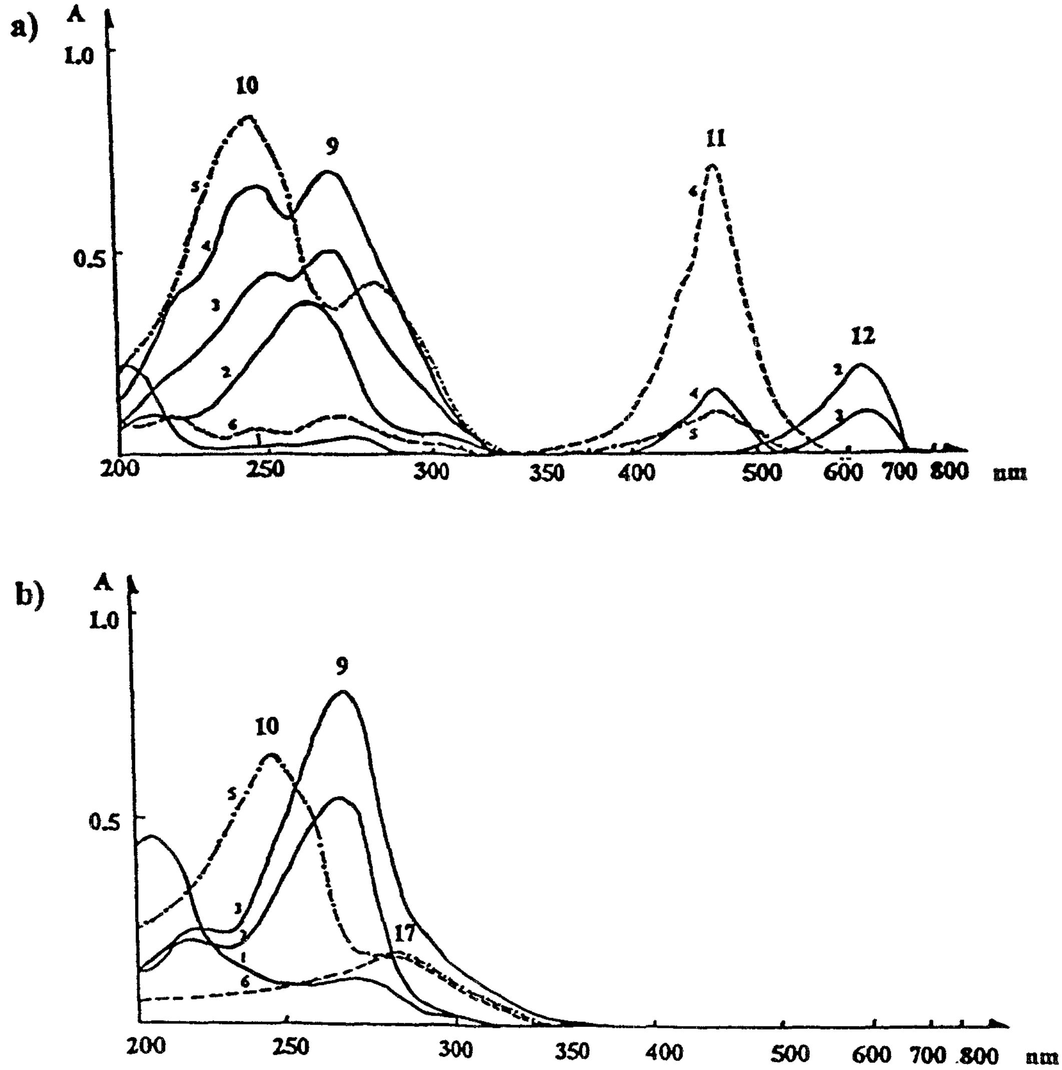


Fig. 1. UV/Vis spectra of solutions of **1** (6a) and **7** (6b) and their mixtures with **8** (1–4a, 1–3b); molar concentrations ratio (ox:Σred): 1 0:1; 2 1:1; 3 2:1; 4 3:1; 5 after hydrolysis of **9**; reducing agent concentrations (1–4a and 1–3b): **8** = **2** (a) = 7 (b) = 5×10^{-5} *M*, **2** (6a) = **7** (6b) = 5×10^{-5} *M*; perchloric acid concentration 0.5 *M* temperature: 293K; path length: 1 cm

Table 1. Products and yields of aniline derivative and 4-aminophenol mixtures oxidation by cerium(IV) ions in perchloric acid (2*M*); reducers concentration: 0.02 *M*; the yield is given per mmol sum of substrates

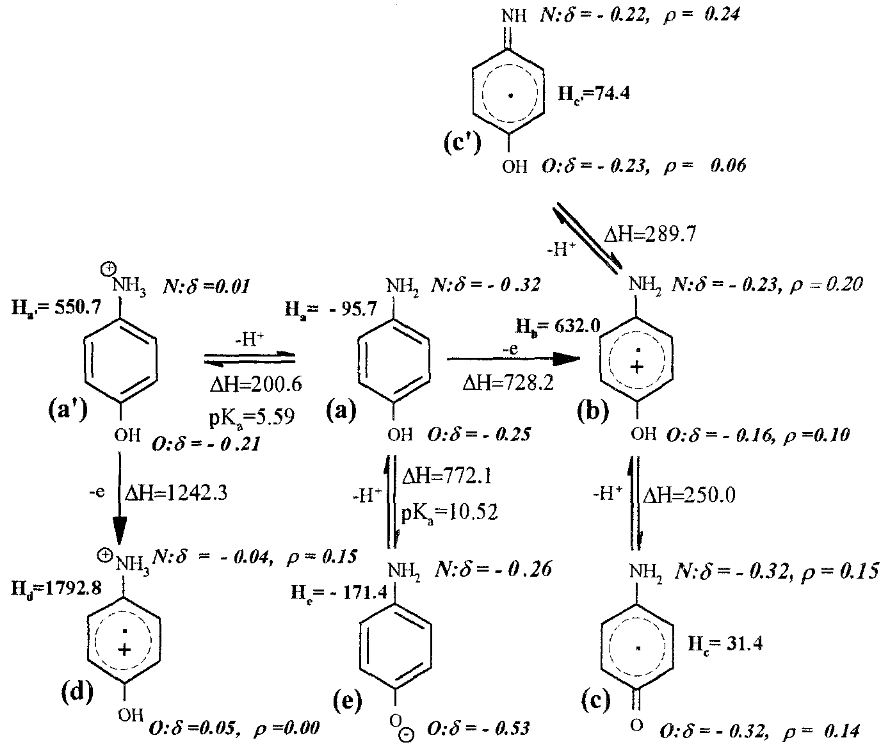
Reducers	$n_{\mathrm{ox}}/\Sigma n_{\mathrm{red}}$	Hydrolysis time (min)	Products	Melting point (°C)	Yield (%)
5, 8	3.05	10	1,4-benzoquinone	113–115	93
2, 8	3.05	10	1,4-benzoquinone	113–115	94
4, 8	3.05	50	1,4-benzoquinone	113–115	94
1, 8	3.05	0	1,4-benzoquinone	113–115	47
			2,6-dimethyl-1, 4-benzoquinone	71–73	45
3, 8	3.05	0	1,4-benzoquinone	113–115	47
			2,6-diethyl-1, 4-benzoquinone	81–83	44
6, 8	3.05	0	1,4-benzoquinone	113–115	48
			2,6-difluoro-1, 4-benzoquinone	121–123	44
7, 8	2.05	0	1,4-benzoquinone	113–115	45
			2,2′,3,3′,5,5′,6,6′-octafluoro-N-Phenyl-4-phenylenediimine	>300	43

be noted that the oxidation of **4** and **8** by cerium(IV) ions does not take place immediately and that different final products are obtained. The mixture of **4** and **8** (equimolar quantities) is easily oxidized to 1,4-benzoquinoneammonium (**15**) and N,N-diethyl-1,4-benzoquinoneammonium cations (**16**) by cerium(IV) ions in a three-electron process. The mixture of **7** and **8** (equimolar quantities) is oxidized in a two-electron process mainly to the N-phenyl-4-phenylenediimine derivative (which precipitates) and to **15**. In this case, we can observe the oxidation of **8** to **15** as a first step (Fig. 1b) and then of **7** to 2,3,5,6,2′,3′,5′,6′-octafluoro-N-phenyl-4-phenylenediimine (**17**). Indoaniline derivatives are also obtained during the electrochemical oxidation of the mixtures of **8** and aniline derivatives (except for **7**) in aqueous perchloric acid on a Pt electrode at potentials lower than the potentials of the electro-oxidation of aniline derivatives but higher than those of the oxidation of **8**. This indicates that in the cross-coupling stage of the reaction between the cation radical or the radical of **8** and a molecule or a protonated molecule of the aniline derivative the above mentioned mechanism should be taken into account.

It follows from Scheme 1 that the predominant processes that **8** and its intermediates can undergo are the following:

$$\mathbf{a}' \overset{-\mathrm{H}^+}{\rightleftharpoons} \mathbf{a} \xrightarrow{-e} \mathbf{b} \overset{-\mathrm{H}+}{\rightleftharpoons} \mathbf{c} \qquad (2)$$

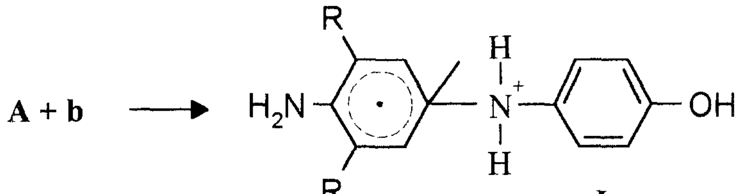
Among the investigated aniline derivatives, only **7** occurs in a non-protonated form (the addition of **7** to the perchloric acid solution does not change the concentration of hydrogen ions); **6** is almost completely protonated, and the dialkyl aniline derivatives are completely protonated (*pK*: Table 2). Considering the intermediate structures which form in the coupling process of cation radical **b** or of radical **c** with protonated ($\mathbf{A}^+$) or non-protonated (**A**) molecules of the aniline deriv-



Scheme 1. H_X: formation enthalpy (kJ/mol); ΔH: reaction enthalpy (kJ/mol); δ: Charge; p: electron spin density

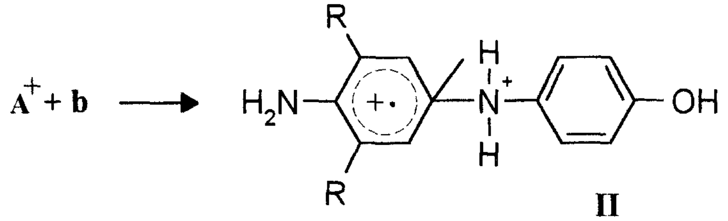
atives, one can suggest that the cross-coupling reactions (which lead to formation of C–N–C bonds between the rings) might be as follows ($R = CH_3$ or C_2H_5):

Considering the electron and spin densities on the N atom in cation radical **b** and in radical **c** of **8** (Scheme 1) and the electron densities at C4 in protonated and non-protonated aniline derivatives (Table 2), one can put forward the hypothesis that the reaction **A** + **c** → **III** (5) is the most unlikely one. The largest electron densities on the atoms under consideration to form the C–N–C bonds between the rings (minimum of electrostatic repulsion) can be found in reaction (4). The enthalpies of reactions (3)–(5) indicate that reaction (3) is preferred (Table 3). The formation enthalpies of dimers **II** and **III** are higher than those of dimer **I**. When the mixture of **7** and **8** is oxidized, no cross-coupling products are observed (*i.e.*, reaction **A** + **b** → **I** takes place). In this case, the electron density on the nitrogen atom of the cation radical and on the carbon atom C4 of **7** (which represent the coupling centre) is the smallest. The reaction enthalpy for this stage is the highest one. In the case of **1** and **8**, the reaction **A** + **b** → **I** takes place in spite of the high value of the energetical effect because of the favourable distribution of the electron density on the atoms under consideration. It has been observed that the oxidation of the mixtures of **8** and aniline derivatives by cerium(IV) chlorate is a 3.03–3.05-electron process per mmol of organic substrate (irrespective of the perchloric acid concentration in the reaction solution). The diphenoquinone-4,4′-diammonium or N-phenyl-*p*-phenylenediammonium derivatives (except for **7**) were not observed



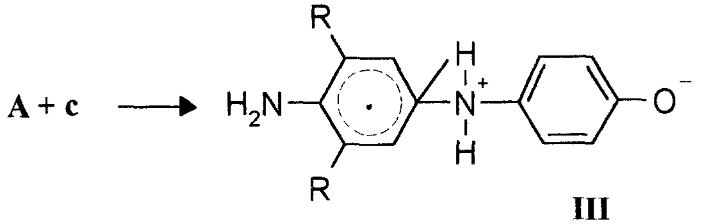
I

(3)



II

(4)



III

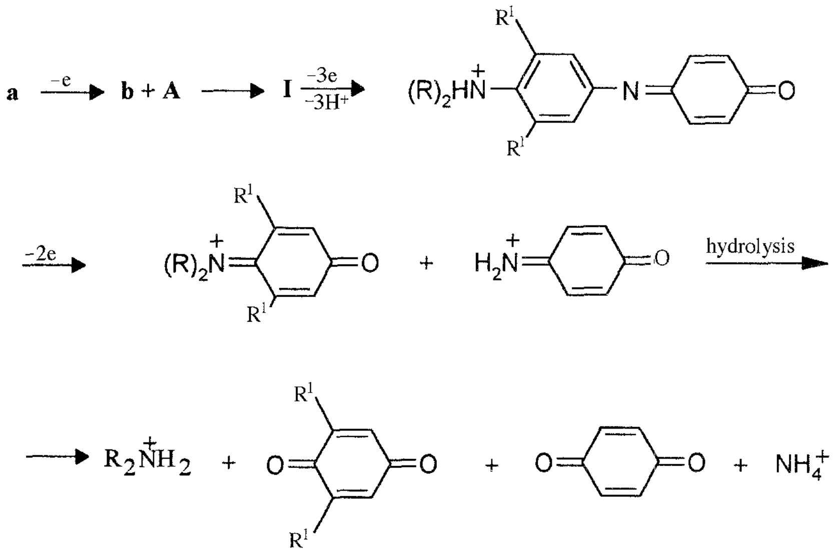
(5)

Table 2. Electron densities on the nitrogen and carbon atoms in the aromatic ring; formation and reaction enthalpies are calculated employing the AM1 method

	pK_a	H_A (kcal/mol)	H_A^+ $\Delta H_{A \to A^+}$ (kcal/mol)	electron densities in **A**		electron densities in **A**$^+$	
				N C2	C4 C6	N C2	C4 C6
2	5.03	31.1	182.9	−0.26	−0.17	0.06	−0.07
			50.9	−0.19	−0.19	−0.10	−0.11
4	6.53	19.7	172.2	−0.26	−0.17	0.05	−0.07
			50.2	−0.19	−0.18	−0.10	−0.12
5	4.70	24.2	178.4	−0.29	−0.17	0.03	−0.07
			48.5	−0.19	−0.19	−0.10	−0.10
1	3.70	6.0	159.1	−0.32	−0.17	0.00	−0.06
			49.6				
3	3.80	−3.6	148.6	−0.33	−0.17	0.00	−0.06
			50.5				
6	1.17	−69.6	91.7	−0.32	−0.13	0.01	−0.02
			41.4				
7	<1	−154.5	16.4	−0.33	−0.22	0.01	−0.11
			31.8				

Table 3. Dimers formation enthalpies (AM1)

	ΔH_{I} ($\mathbf{A}+\mathbf{b}\rightarrow\mathbf{I}$) (kcal/mol)	ΔH_{II} ($\mathbf{A}^{+}+\mathbf{b}\rightarrow\mathbf{II}$) (kcal/mol)	ΔH_{III} ($\mathbf{A}+\mathbf{c}\rightarrow\mathbf{III}$) (kcal/mol)
2	−2.5	72.3	40.7
4	−2.5	70.7	41.7
5	−1.6	73.7	41.0
1	−1.7	74.1	40.6
3	−2.6	72.1	40.0
6	7.7	84.1	47.8
7	8.9	81.6	47.4



Scheme 2. If R = H then R^1 = alkyl or F; if R^1 = H then R = alkyl

among the intermediates of those reactions. Taking into account these two facts, one can suggest the mechanism outlined in Scheme 2.

The presented data seem to indicate that it is possible to develop simple and efficient methods for the preparation of 2,6-disubstituted 1,4-benzoquinone derivatives from the corresponding aniline derivatives. It should be pointed out that the manufacturing process can be made almost wasteless since it is possible to re-use the same solutions of cerium salts by purifying the reaction solutions and electrooxidizing cerium(III) [33].

Experimental

Melting points were determined with a melting points apparatus (Veb Nagema). UV/Vis spectra of the reaction mixtures with various molar concentration ratios of the reagents were recorded on a

Specord UV/Vis double-beam spectrophotometer with 1.00 cm quartz cuvettes in the range of 200–800 nm. The type and ratio of the reaction and the yield of the products were determined on the basis of the UV/Vis spectra. The presence of cerium(IV) ions in the reaction mixture was detected potentiometrically. The qualitative and quantitative constitution of the products was established on the basis of UV/Vis, IR (Specord M-80), and NMR (Varian 200 MHz) spectra as well as of TLC (Kieselgel 60 F_{254} plates (Merck), eluent: 35% acetone, 65% *n*-hexane) and of column chromatography (SiO_2 eluent: 35% acetone, 65% *n*-hexane). The quantum mechanical calculations (AM1 [12], Mopac 6 packet) were carried out on PC 486DX/50 computer with 16 MB RAM. Geometries of all analyzed structures were calculated using the PRECISE option. All internal coordinates were taken into account and no assumptions as to the symmetry were made during the geometry optimization.

Cerium(IV) chlorate (1.03 *M*) in an aqueous solution of perchloric acid (1.54 *M*) was prepared from cerium(III) chloride following the procedure proposed by *Smith* and *Getz* [31]. The concentration of the solution was determined by potentiometric titration with sodium oxalate (0.05 *M*). Compounds **1–6** (Aldrich) were distilled under normal or reduced pressure; the respective fractions were collected at the following boiling points: **1**, 214°C/739 mm Hg; **2** 193–194°C; **3** 114°C/10 mm Hg; **4** 217°C; **5** 196°C; **6** 51–52°C/15 mm Hg. The respective refractive indices n_D^{20} were: **1**, 1.560; **2**, 1.558; **3**, 1.542; **4**, 1.542; **5**, 1.571; **6**, 1.508. Compounds **7** and **8** (Aldrich) were recrystallized from ethanol (m.p.: **7**, 31–32°C; **8**, 188–190°C).

General procedure for the oxidation of mixtures of aniline derivatives and 4-aminophenol on the example of **1** *and* **8**

To 50 cm^3 of aqueous perchloric acid (0.50, 2.50, and 4.00 *M*) containing 1 mmole of **1** and 1 mmole of **8** was added dropwise a solution of cerium(IV) chlorate (6.1 mmol) in perchloric acid of a corresponding concentration until an excess of the oxidizng agent could be detected potentiometrically. After 2 hours of hydrolysis, the reaction mixture was extracted with CCl_4 (6 × 25 cm^3). The organic layer was dried over Na_2SO_4 and $CaCO_3$ and concentrated *in vacuo*. After chromatographic separation and drying, 98 mg of **10** (90%) and 129 mg of 2,6-dimethyl-1,4-benzoquinone (88%) were obtained. The isolated products were identified by their melting points and by comparison of their IR and NMR spectra with those of original samples.

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