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Oxidative Coupling of Some 2,6-Disubstituted Phenol Derivatives in Perchloric Acid Mediated by Cerium(IV) Ions

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Summary. 2,6-Disubstituted phenol derivatives have been oxidized by cerium(IV) perchlorate in aqueous or aqueous-acetonitrile solutions of perchloric acid as well as in two-phase systems to the corresponding 1,4-benzoquinones, 4,4′-diphenoquinones, and oligomeric poly(1,4-phenylene) oxides in good yield. Nature and constitution of the oxidation products as a consequence of reaction conditions and physico-chemical properties of radicals and radical ions are reported. These properties are discussed in terms of stabilities, *pK* values, and electron densities at carbon C4 and oxygen.

Keywords. 2,6-Disubstituted phenols; Cerium(IV) perchlorate; Products of oxidation; Mechanism; Quantum mechanical calculations.

Oxidative Kupplung einiger 2,6-disubstituierter Phenolderivate in Perchlorsäure in Gegenwart von Cer(IV)-Ionen

Zusammenfassung. 2,6-Disubstituierte Phenolderivate wurden in wäßrigen oder wäßrig-acetonitrilischen Lösungen sowie in Zweiphasensystemen mittels Cer(IV)perchlorat zu den entsprechenden 1,4-Benzochinonen, 4,4′-Diphenochinonen und Poly(1,4-phenylen)oxiden oxidiert. Es wird über die Abhängigkeit der Art und Konstitution der Oxidationsprodukte von den Reaktionsbedingungen und den physikochemischen Eigenschaften der Radikale und Radikalionen berichtet. Die Ergebnisse werden im Zusammenhang mit Stabilitäten, *pK*-Werten und Elektronendichten an C4 und am Sauerstoff diskutiert.

Introduction

Most of the general methods of oxidation of 2,6-dialkylphenols with weak acidic properties ($pK_a > 4$), including oxidation by cerium(IV) ions, produce corresponding 1,4-benzoquinones in quite good yields [1–14]. These compounds are versatile substrates in the synthesis of many natural products, and they are often used as dienophils in *Diels-Alder* reactions. In the case of the reaction with cerium(IV) ions, the increase in acidic properties of oxidized phenol (2,6-difluorophenol [15],

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2,3,5,6-tetrafluorophenol [16]) or the stabilization of cation radicals and radicals (2,6-di-*tert*-butylphenol) causes a considerable decrease in the yield of 1,4-benzoquinones and an increase in the yield of the corresponding 4,4′-diphenoquinones (2,6-di-*tert*-butylphenol [14]) and/or polyphenylene oxides (2,6-difluorophenol, 2,3,5,6-tetrafluorophenol). The increase in yield can be lowered by an increase in the acidity of the reaction medium if cation radicals and radicals are not well-stabilized and if the protonation constant of the oxidized phenol derivative is lower than 4. This leads to the conclusion that the most probable reaction pathway will be determined by the acidic properties of the first intermediates (cation radicals) in the reaction of phenols with one-electron oxidizing reagents, by the electron densities on active atoms of these cation radicals (i.e. on the oxygen atom and carbon atom C4 with great spin density), and by the acidity of the reaction medium [17].

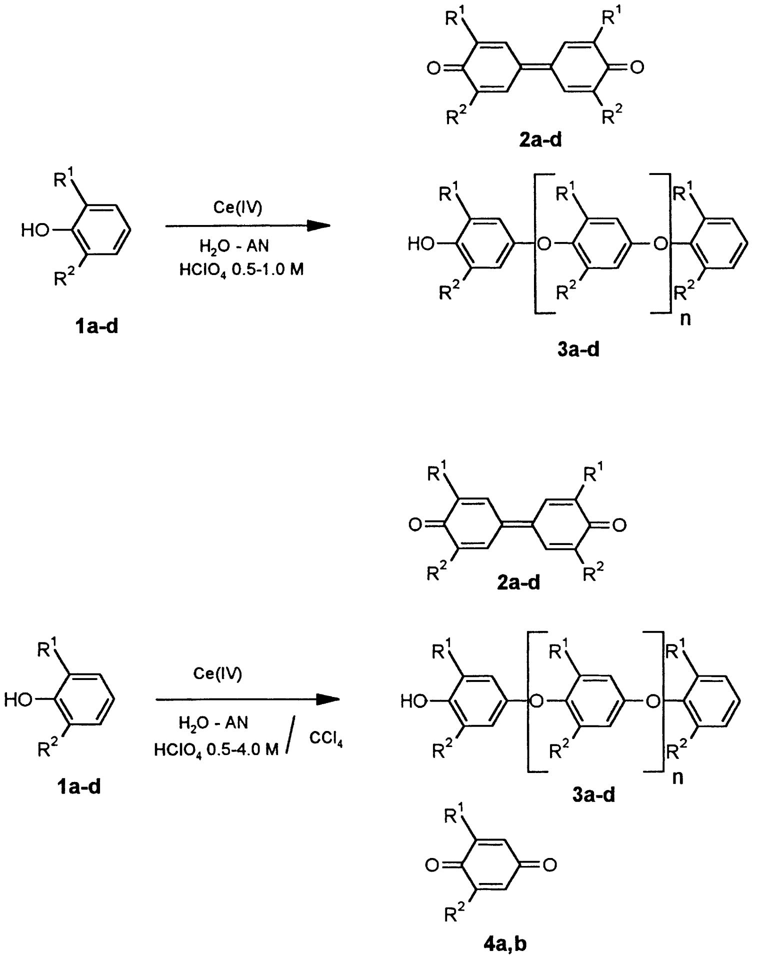
In this paper we describe simple methods of oxidation of some 2,6-disubstituted phenol derivatives by cerium(IV) ions as well as methods of synthesis of corresponding 1,4-benzoquinones and/or 4,4′-diphenoquinones and/or oligomeric poly(1,4-phenylene) oxides. We discuss the influence of the reaction conditions and the properties of cation radicals and radicals resulting from quantum mechanical calculations.

Results and Discussion

When 2,6-dimethylphenol is oxidized with cerium(IV) ions in aqueous or aqueous-acetonitrile solutions of perchloric acid (0.5–1.0 *M*) at room temperature, the corresponding 4,4′-diphenoquinone and 1,4-benzoquinone derivatives are obtained as the main products [14]. The oxidation of 2,6-diisopropylphenol (**1a**), 2-*tert*-butyl-6-methylphenol (**1b**), 2,6-diphenylphenol (**1c**), and 2,6-dichlorophenol (**1d**) performed under similar conditions results in the corresponding 4,4′-diphenoquinones (**2a**–**d**) and oligomeric poly(1,4-phenylene) oxides (**3a**–**d**). In the case of **1c**, the quantity of the resulting poly(1,4-phenylene) oxides (**3c**) is low due to the steric hindrance caused by the phenyl groups in the neighbourhood of the oxygen atom **1a** and **1b**, similarly to 2,6-dimethylphenol, are oxidized by cerium(IV) ions in a two-phase system (CCl_4/aqueous-acetonitrile solution of perchloric acid) and at high concentration of perchloric acid (4.0 *M*) in the reacting phase to give the corresponding 1,4-benzoquinones in good yields. This is not observed with 2,6-di-*tert*-butylphenol, **1c**, and **1d**. The results are summarized in Scheme 1 and Table 1.

Such different behaviour of the particular phenol derivatives in reactions with cerium(IV) ions requires some comment. The first intermediates of the oxidation of phenols, anisoles, and anilines by cerium(IV) ions are corresponding cation radicals, whose formation is a result of an electron transfer from the organic compound to the cerium(IV) ion in the donor-acceptor complex formed by the substrates. The following facts point to the crucial role of the oxygen and nitrogen donor atoms in the formation of the complexes:

1) Although in aqueous solution of 0.5 *M* perchloric acid N,N-diethylaniline reacts readily with cerium(IV) ions, in 4.0 *M* perchloric acid the reaction proceeds very slowly, and when the aniline derivative is added, neither a change of the



Scheme 1

Table 1. Oxidation of substituted phenol derivatives (**1a–d**) by cerium(IV) ions in homogeneous (A) and heterogeneous (B) systems; temperature: 25°C; the yields of isolated products are based on the amounts of added phenols

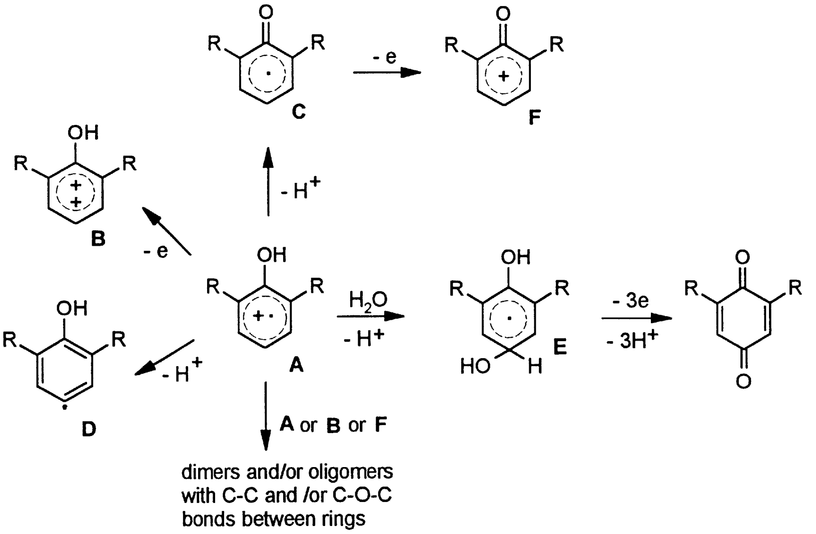
Phenol	Procedure	Molar ratio	Concentration of $HClO_4$ (*M*)	Time (min)	Conversion (%)	Products and yield (%)
1a	A	1:2.15	0.5	0	100	**2a** (85), **3a** (4), **4a** (8)
	B	1:4.00	4.0	30	100	**2b** (3), **4b** (90)
1b	B	1:2.25	0.5	180	100	**2b** (54), **3b** (37)
	B	1:3.75	4.0	90	100	**2b** (12), **3b** (21), **4b** (56)
1c	A	1:2.25	0.5	0	100	**2c** (70), **3c** (23)
1d	A	1:1.75	0.5	0	100	**2d** (30), **3d** (65)

solution colour nor a change of the formal potential of the Ce(IV)/Ce(III) system is observed.

2) Anisole and 2,3,5,6-tetrafluorophenol react readily with cerium(IV) ions, irrespective of the hydrogen ion concentration in the reaction medium, whereas

2,3,5,6-tetrafluoroanisole does not. When 2,3,5,6-tetrafluoroanisole is added to a solution containing cerium(IV) ions, neither a change of the solution colour nor a change of the formal potential of the Ce(IV)/Ce(III) system is observed [16].

If we consider the fact that the total π-electron densities of 2,3,5,6-tetrafluorophenol and 2,3,5,6-tetrafluoroanisole are identical, the only difference between these compounds is that the oxygen donor atom of 2,3,5,6-tetrafluoroanisole is sterically hindered, thus preventing participation of the oxygen atom in the formation of the complex with cerium(IV) ions. The resulting cation radical (**A**) can undergo the following reactions:

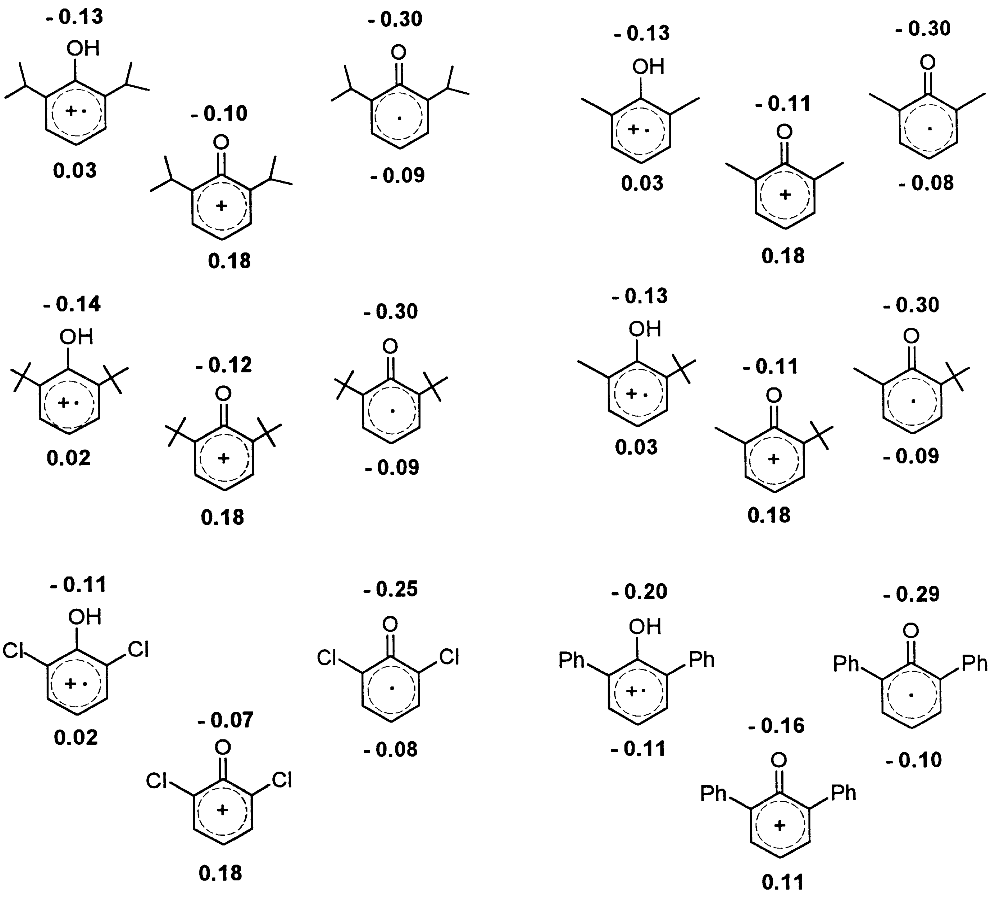


Scheme 2. Possible reactions of the cation radical of 2,6-disubstituted phenol derivatives

Owing to thermodynamical aspects, the reactions **A**→**B** and **A**→**D** should not be taken into consideration. A comparison of the experimental results (Table 1) and the quantum mechanical calculations (AM1) shows that the reaction **A**→**E** occurs only when C4 is positively charged and **A** is not well-stabilized (*i.e.* 2,6-methylphenol).

In the case of positively charged carbon atoms C4 of **A** and of considerably strong acidic properties of the oxidized phenol derivatives (2,6-difluorophenol, 2,6-dichlorophenol) the corresponding 1,4-benzoquinone derivatives are obtained in very low yield. It seems that the predominant process then is the reaction **A**→**C**, and a mixture of derivatives of 4,4′-diphenoquinone and poly(1,4-phenylene) oxides is obtained.

However, if we consider the fact that the charges at C4 of the radicals (**C**) shown in Scheme 3 are negative and those of the cations (**F**) are positive, the lack of the corresponding 1,4-benzoquinone derivatives among the oxidation products of the phenol derivatives with strong acidic properties (2,6-difluoro- [15], 2,6-

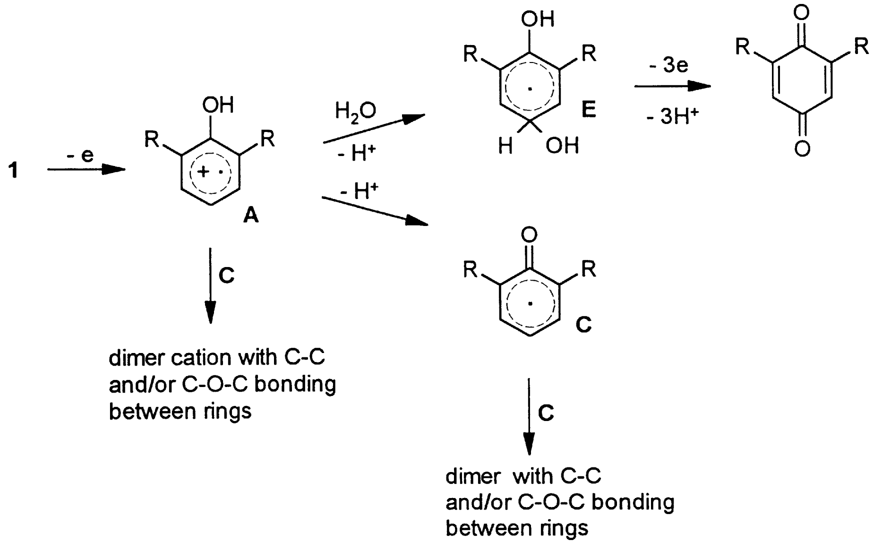


Scheme 3. Electron densities on the oxygen and carbon C4 atoms in **A**, **C**, and **F**

dichloro-, 2,6-diphenyl-, or 2,3,5,6-tetrafluorophenol [16]) suggests that reaction **C**→**F** does not take place. This leads to the conclusion that in the case of phenol derivatives with weak acidic properties the concentrations and the acidic properties of 2,6-disubstituted phenols and their corresponding cation radicals **A** and radicals **C** (*i.e.* the charges at C4 and oxygen) as well as the concentration of the hydrogen ions in the reacting mixture have a crucial influence on the type and constitution of the obtained products.

Although the quantum mechanical calculations were performed for particular species in the gas phase, they show that from the thermodynamical point of view the most favourable reactions for the formation of bonds between the rings are **A**+**C**→dimer cation and **C**+**C**→dimer. The calculations also show that in the case of 2,6-dimethylphenol the more convenient stages are those involving C–C bond formation between rings, and in the case of 2,6-difluorophenol or 2,3,5,6-tetrafluorophenol, the more convenient stages are those with formation of C–O–C bonds; this is in agreement with the experimental results.

Taking all the results into consideration, the general mechanism of the oxidation of 2,6-disubstituted phenols by cerium(IV) ions might be as follows:



Scheme 4

When the dimer is formed with a C–C bond between the rings, the final products is a 4,4′-diphenoquinone derivative. In the case of a dimer with a C–O–C bond between the rings, the reaction proceeds further, and the final products are mixtures of corresponding oligomeric poly(1,4-phenylene) oxides. It should be pointed out that in the reaction medium with a higher concentration of hydrogen ions ($>2.0\,M$) those compounds undergo multielectron oxidation.

The experimental results show that in this case only one of the rings is oxidized to the corresponding 1,4-benzoquinone derivative, and the remaining rings undergo fragmentation. The yields of the 1,4-benzoquinone derivatives are not greater than 45–50%.

Assuming that there is a possibility of electrochemical regeneration of the utilized oxidizing agent in purified (filtration through active carbon) post-reaction solutions [18], the presented experimental results show that cerium(IV) ions can be used both in the synthesis of 2,6-dialkyl-1,4-benzoquinones and as a mediator of oxidative coupling of 2,6-disubstituted phenols.

Experimental

Melting points were determined with a melting point apparatus (Veb Nagema). UV/Vis spectra of the reaction mixtures and IR spectra of obtained compounds were recorded on a Philips PU 8630 spectrometer and a Specord IR M 80 spectrometer. NMR spectra were recorded on a Tesla BS 467 (60 MHz) spectrometer. The quantum mechanical calculations for particular molecules in the gas phase (*i.e.* enthalpy of formation and electron and spin densities) were carried out on an IBM PC 486DX/50 computer with 16 MB RAM by means of semiempirical methods from the MOPAC 6 packet at the AM1 level [19]. 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.

General procedure for the conversion of phenols to quinones; procedure A on the example of 2-tert-butyl-6-methylphenol (**1b**)

50 ml of CCl_4 containing **1b** (0.328 g, 2.0 mmol) were added dropwise within 5 min under stirring to 100 ml of the aqueous acetonitrile solution (10% v/v of acetonitrile) of perchloric acid (4.0 *M*) containing 7.5 mmol of cerium(IV) perchlorate and 6.0 mmol of cerium(III) perchlorate (which does not take part in the reaction). The mixture was then stirred vigorously for 90 min. After the reaction has been completed, the two-phase mixture was separated, and the aqueous-acetonitrile phase was extracted with CCl_4 (2×25 ml). The organic phase and the combined extracts, after being dried over Na_2SO_4, were distilled to yield ~0.310 g of a red-brown oil. After the crystallization was initiated by addition of a few crystals of 3,3′-di-*tert*-butyl-5,5′-dimethyl-4,4′-diphenoquinone, the corresponding isomers of 4,4′-diphenoquinone crystallized quantitatively. The remaining oil was washed off the residue with 1.5 ml of acetonitrile, and the solvent was evaporated. After distillation (2.0 mm Hg), 0.195 g of a yellow oil of **4b** (56% yield) were obtained. ^{1}H NMR: δ (CCl_4) = 1.29 (9H, *tert*-butyl), 2.23 (3H, methyl), 6.86 (2H, =CH) ppm; IR: ν (Nujol) = 1659 cm^{-1} (C=O). After distillation the residue contains **3b** (~0.07 g, 21% yield); m.p.: 328–338 K; one hydroxyl group per 8–10 mers (*pH*-metrically determined in aqueous-acetonitrile solution); IR: ν (KBr) = 3500 (OH), 1275 and 1020 (C–O–C), 1430 and 1375 (CH), 1395 and 1370 (*tert*-butyl) cm^{-1}. Recrystallization of the crude remaining after washing from acetonitrile gives **3b** as a mixture of isomers (0.04 g, 12% yield; m.p.: 477–480 K).

The procedure for the synthesis of **4a** was similar employing 25% (v/v) acetonitrile, an amount of 4.0 mmol oxidizing agent per 1.0 mmol of reducing agent, and 2.0 mmoles (0.356 g) of **1a** in a solution of 100 ml of CCl_4.

General procedure for the conversion of phenols to 4,4′-diphenoquinones (**2b**, **2c**, **2d**); *procedure B on the example of* **1d**

1d (0.163 g; 1.0 mmol) was dissolved in 100 ml of aqueos acetonitrile solution (50% v/v of acetonitrile) of the perchloric acid (0.5 *M*) containing cerium(III) perchlorate (0.3 *M*) (which does not take part in the reaction). Under stirring a water-acetonitrile solution of perchloric acid (0.5 *M*) containing cerium(IV) perchlorate (0.24 *M*) was added (~7.3 ml, 1.75 mmol) dropwise within 5 minutes until an excess of cerium(IV) ions could be detected potentiometrically. After filtering, the resulting solid was washed first with an aqueous solution of perchloric acid (5%), then with water, and dried at 80 °C. This gave 0.155 g of the solid. After washing and recrystallization from CH_2Cl_2, ~0.046 g of **2d** (30% yield; m.p. >600 K; characteristic band in acetonitrile at λ = 427 nm) and 0.103 g of **3c** (64% yield; m.p.: 373–388 K; IR: ν (KBr) = 3580, 1212, 1075, 960 cm^{-1}) were obtained.

A similar procedure was followed for **1a** and **1c**. In the case of **1a**, 2.0 mmol (0.356 g) of the compound were dissolved, and 4.3 mmol of cerium(IV) perchlorate were used. In the case of **1c**, the amounts were 0.3 mmol and 0.6 mmol, respectively. Owing to the fact that under homogeneous conditions (procedure B) the mixtures of products coated the reaction vessel, the oxidation process of **1b** was conducted following procedure A. The concentration of perchloric acid in the aqueous-acetonitrile phase was 0.5 *M* (10% v/v of acetonitrile), the concentration of cerium(IV) perchlorate was 0.045 *M* (2.25 mmol of oxidizing agent per 1.0 mmol of reductor), and the reaction time was about 3 h.

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