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### Influence of N-Substitution on Electron Spin Resonance (ESR) Behavior of 2-(2-Nitrophenyl)-1H-benzimidazole Derivatives

Jorge Valenzuela<sup>a</sup>; Hernan Pessoa-Mahana; Ana María Atria<sup>b</sup>; Martín Contreras<sup>a</sup>; Jacqueline Pezoa<sup>a</sup>

<sup>a</sup> Departamento de Química Orgánica y Fisicoquímica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile <sup>b</sup> Departamento de Química Inorgánica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile

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## **Influence of N-Substitution on Electron Spin Resonance (ESR) Behavior of 2-(2-Nitrophenyl)-1*H*-benzimidazole Derivatives**

**Jorge Valenzuela and Hernan Pessoa-Mahana**

Departamento de Química Orgánica y Fisicoquímica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile

**Ana María Atria**

Departamento de Química Inorgánica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile

**Martín Contreras and Jacqueline Pezoa**

Departamento de Química Orgánica y Fisicoquímica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile

**Abstract:** The synthesis of 2-(2-nitrophenyl)-1*H*-benzimidazole (**1**), 1-benzoyl-2-(2-nitrophenyl)-1*H*-benzimidazole (**2**), and 1-acetyl-2-(2-nitrophenyl)-1*H*-benzimidazole (**3**) is reported. Stable radical anions (**1**<sup>•−</sup>, **2**<sup>•−</sup>, and **3**<sup>•−</sup>) were generated by chemical reduction in DMSO and studied by ESR spectroscopy. The interpretation of the ESR spectra was done by means of computational simulation process. Hyperfine coupling constants were assigned by comparison with related compounds, and on the basis of calculation based on SCF INDO MO method in the unrestricted Hartree–Fock scheme.

**Keywords:** Anion radicals, ESR, 2-(2-nitrophenyl)-1*H*-benzimidazoles

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Address correspondence to J. Valenzuela or H. Pessoa-Mahana, Departamento de Química Orgánica y Fisicoquímica, Universidad de Chile, Casilla 233, Santiago 1, Chile. E-mail: jvalenzu@uchile.cl; hpessoa@ciq.uchile.cl

## INTRODUCTION

Nitroaromatic compounds have been extensively studied and reviewed, mainly because of their interesting biological activities, as well as because of their extended use in the chemical industry.<sup>[1,2]</sup> However, it is well-known that the pharmacological treatment with some nitroarenes offers the disadvantage of generating nitroanion radicals and aminoreduced species, which are finally responsible for DNA-binding and mutagenesis in mammals.<sup>[3,4]</sup>

In this field, the ESR technique has represented an efficient tool either for detection or characterization of such species. In this respect, Ciminale<sup>[5]</sup> has recently reported an interesting ESR characterization for a series of nitro-benzothiazole isomers, correlating the electron-withdrawing effects of the molecules with the coupling constants obtained.

To get further information about the ESR characterization of nitroanion radical derivatives of biological interest, we decided to study the ESR behavior of some 2-nitrophenyl benzimidazole derivatives. It is interesting to point out that the 2-phenylbenzimidazole skeleton has been incorporated as partial structural component in the antitumorals suramine<sup>[6]</sup> and pibenmizol.<sup>[7]</sup>

In the current paper, we report an ESR study for the nitroanion radicals 2-(2-nitrophenyl)-benzimidazole derivatives **1**, **2**, and **3**. The aim of this work is to obtain ESR information on hindered *o*-nitrobenzene systems, bonded to a benzimidazolic heterocyclic portion. The spectroscopic characterization was supported by theoretical calculations and structural feature of the molecules.

## EXPERIMENTAL

### Synthesis

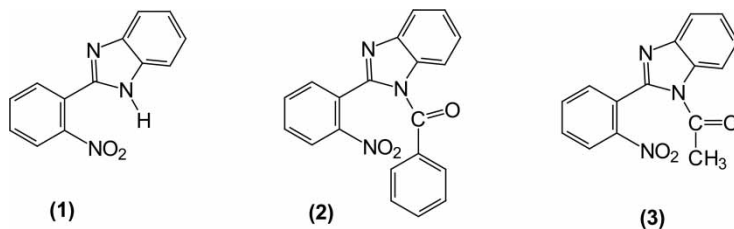
The benzimidazoles object of our studies are displayed in Scheme 1 and were obtained as follows.<sup>[8,9]</sup>

#### 2-(2-Nitrophenyl)-1*H*-benzimidazole (**1**)<sup>[8]</sup>

To a solution of 2-nitrobenzaldehyde (200 mg, 1.32 mmol) in ethanol (50 ml) was added *o*-phenyldiamine (143 mg, 1.32 mmol); the resulting solution was refluxed for 8 hr. After this time, the solution was evaporated to reduce volume and stood at room temperature to give 2-(2-nitrophenyl)-1*H*-benzimidazole **1** as pale yellow crystals (259 mg, 82%), mp: 276.5–277°C

#### 1-Benzoyl-2-(2-nitrophenyl)-1*H*-benzimidazole (**2**)<sup>[9]</sup>

To a stirred solution of 2-(2-nitrophenyl)-benzimidazole **1** (228 mg, 0.953 mmol) and dry *N,N*-triethylamine (96.43 mg, 0.953 mmol) in anhydrous THF (70 mL) was added benzoyl chloride (134 mg, 0.953 mmol) under inert



Scheme 1.

atmosphere at 0°C. The mixture was maintained at r.t. with stirring for 4 hr, and then poured into water (100 mL). The mixture was extracted with EtOAc (3 × 50 mL) and dried with MgSO<sub>4</sub>. Removal of the solvent afforded 1-benzoyl-2-(2-nitrophenyl)-1*H*-benzimidazole **2** (252 mg, 77%) mp: 154.5–155.5°C.

#### 1-Acetyl-2-(2-nitrophenyl)-1*H*-benzimidazole (**3**)<sup>[8]</sup>

To a stirred solution of 2-(2-nitrophenyl)-benzimidazole **1** (178 mg, 0.745 mmol) and dry *N,N*-triethylamine (75.3 mg, 0.745 mmol) in anhydrous THF (60 mL) was added acetyl chloride (58.5 mg, 0.745 mmol) under inert atmosphere at 0°C. The mixture was maintained at r.t. with stirring for 3 hr, and then poured into water (100 mL). The mixture was extracted with EtOAc (3 × 50 mL) and dried with MgSO<sub>4</sub>. Removal of the solvent afforded **3** (172 mg, 82%), mp: 168–169°C.

### ESR Measurements

Anion radicals **1**<sup>•−</sup>, **2**<sup>•−</sup>, and **3**<sup>•−</sup> were chemically generated by reduction with potassium *tert*-butoxide in dimethylsulfoxide (DMSO) as described elsewhere.<sup>[10,11]</sup> Approximately 0.4 mg of the nitro compound in 1.0 mL of dry DMSO was placed in one leg of an H-cell, and potassium *tert*-butoxide (24 mg) dissolved in 1.0 mL of dry DMSO in the other leg. Both solutions were simultaneously deoxygenated with prepurified nitrogen for 20 min. The solutions were finally mixed by inverting the cell, affording estimated concentrations of 0.001 M in nitro compound and 0.1 M in potassium *tert*-butoxide. DMSO and potassium *tert*-butoxide utilized were obtained from Aldrich.

ESR measurements were performed at X-band frequencies (9.5 GHz) using a spectrometer Bruker ECS 106 equipped with a 9-in magnet with 50 kHz field modulation. ESR spectra were recorded at room-temperature (20°C). All computed spectra were simulated with a Lorentzian line shape. Reported coupling constants are averages of at least three individual measurements. Coupling constants are reported in gauss (G), with an estimated

accuracy of  $\pm 0.05$  G. The corresponding g-values of the radicals are included in Table 1. The linewidths are listed at the footnotes of Figures 1(b), 2(b), and 3(b).

Methods of Calculation

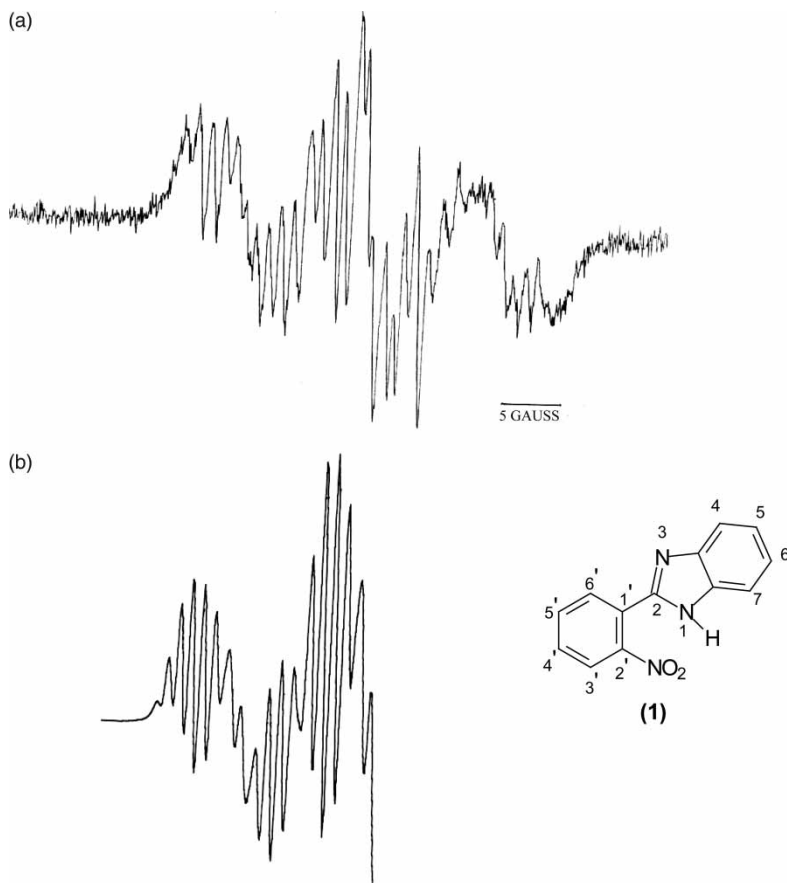
The spin densities were determined using SCF INDO MO method (HyperChem 6.0) employing the open shell UHF option. The theoretical hyperfine coupling constants were calculated using the expression proposed by Pople, Beveridge, and Dobosh:<sup>[12]</sup>

$$a_x = \{ (4\pi/3) g \beta \gamma_x \hbar \langle S_z \rangle^{-1} | \phi_{S_x} (R_x) |^2 \} \rho_{Sx \text{ } Sx}$$

Table 1. Experimental and calculated hyperfine coupling constants/G, and g-values

Radical Anion	Nucleus	Position	$a_{\text{exp}}^a$	INDO	
				$a_{\text{theor}}^b$	g-value <sup>c</sup>
<b>1<sup>•-</sup></b>	N(NO <sub>2</sub> )	2'	10.81	9.53	2.0050
	H	6'	0.90	2.01	
	H	5'	3.52	−3.00	
	H	4'	0.90	1.78	
	H	3'	3.17	−3.07	
	N	1	0.90	1.10	
	N	3	0.90	1.12	
	H	1	1.17	−0.21	
<b>2<sup>•-</sup></b>	N(NO <sub>2</sub> )	2'	9.90	9.33	2.0050
	H	6'	1.20	1.74	
	H	5'	3.90	−2.91	
	H	4'	1.00	1.58	
	H	3'	3.50	−3.20	
	N	1	1.10	0.77	
	N	3	1.10	0.78	
	H	1	1.17	−0.21	
<b>3<sup>•-</sup></b>	N(NO <sub>2</sub> )	2'	9.90	9.24	2.0049
	H	6'	1.30	1.80	
	H	5'	3.60	−2.95	
	H	4'	1.10	1.62	
	H	3'	3.20	−3.22	
	N	1	0.95	0.84	
	N	3	0.95	0.84	
	H	1	1.17	−0.21	

<sup>a</sup>Experimental coupling constants ( $\pm 0.05$ )  
<sup>b</sup>Theoretical coupling constants  
<sup>c</sup>g ( $\pm 0.0002$ )

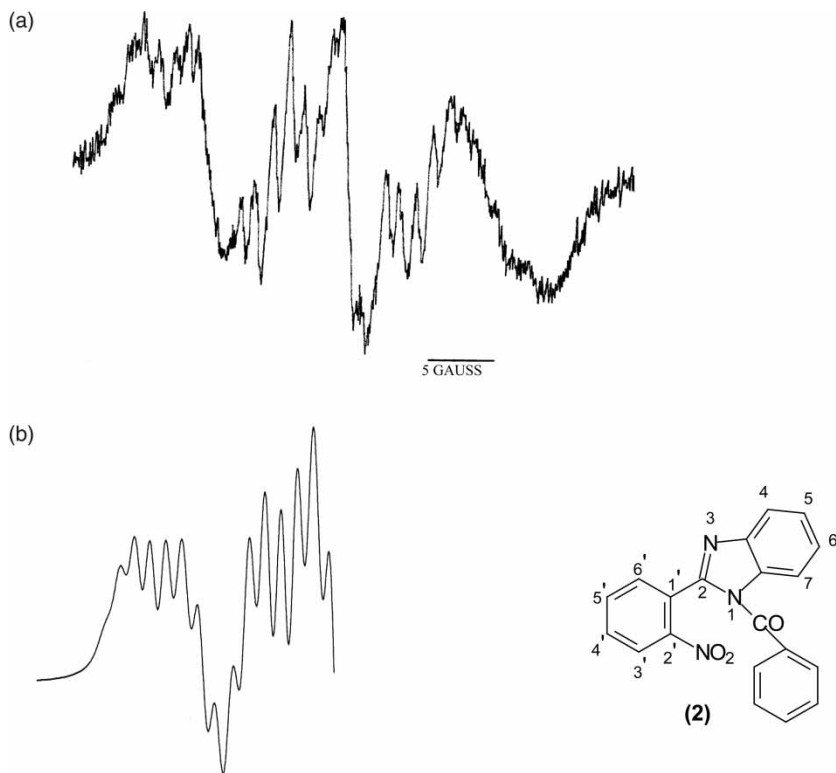


**Figure 1.** (a) ESR spectrum of 2-(2-nitrophenyl)-1H-benzimidazole ( $1^{\bullet-}$ ) (b) Calculated spectrum using coupling constants in Table 1 and linewidth of 0.5 G.

where  $a_X$  is the isotropic hyperfine coupling constant due to nucleus X,  $g$  is the electron  $g$  factor,  $\beta$  is the Bohr magneton,  $\gamma_X$  is the gyromagnetic ratio of the nucleus X,  $|\phi_{s_X}(R_X)|^2$  is the density of the valence  $s$  orbital of the atom X evaluated at the nucleus, and  $\rho_{s_X}$  is the unpaired electronic population of the valence  $s$  orbital of atom X. The quantity in brackets on the right-hand side of the expression is a constant for each type of magnetic nucleus. The values for  $^1\text{H}$  and  $^{14}\text{N}$  are 539.86 and 379.34, respectively.<sup>[12]</sup>

## RESULTS AND DISCUSSION

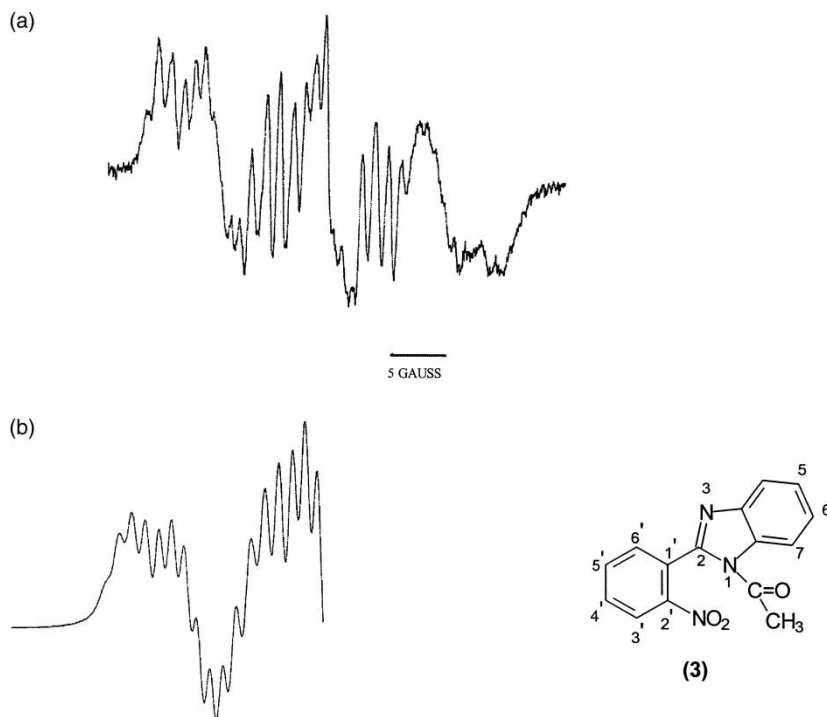
At first, it is important to point out that the lines in ESR spectra for nitro-group nitrogen nucleus may be broader on the high field side of the spectrum than



**Figure 2.** (a) ESR spectrum of 1-benzoyl-2-(2-nitrophenyl)-1*H*-benzimidazole ( $2^{\bullet-}$ ) (b) Calculated spectrum using coupling constants in Table 1 and linewidth of 1.0 G.

on the low field side.<sup>[13,14]</sup> This linewidth effect might be due to asymmetric variations resulting from electron spin relaxation,<sup>[15]</sup> which can be clearly observed in this study, making difficult the coupling constants assignments to specific nuclei, especially due to the high number of nonequivalent nuclei involved.

Figure 1a shows the ESR spectrum of the anion radical  $1^{\bullet-}$ . The spectrum of the anion radical  $1^{\bullet-}$  would be expected to give a triplet attributed to a nitrogen nucleus, four doublets due to four nonequivalent protons belonging to the phenyl ring, a quintet due to the two nitrogens from the benzimidazole ring, and a doublet originated by the benzimidazolic NH proton. The experimental spectrum is in good agreement with the simulated spectrum shown in Fig. 1b. The largest coupling constant of 10.81 G was assigned to the nitrogen nucleus of the nitroaromatic group. The other coupling constants were assigned by comparison with other nitroaromatic anion radicals.<sup>[16–19]</sup> The experimental and theoretical hyperfine coupling constants of radical  $1^{\bullet-}$  are summarized in Table 1.

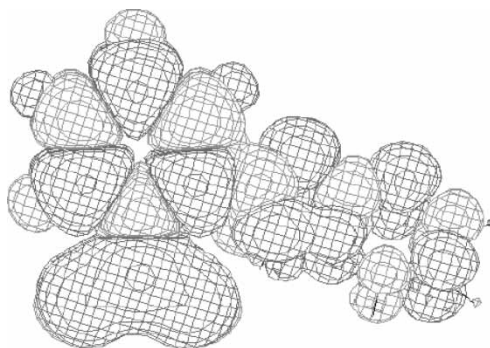


**Figure 3.** (a) ESR spectrum of 1-acetyl-2-(2-nitrophenyl)-1H-benzimidazole ( $3^{\bullet-}$ ) (b) Calculated spectrum using coupling constants in Table 1 and linewidth of 0.85 G.

The assignments were supported by INDO calculations; however, in contrast with numerous reported examples, this method predicts a longer  $a_H(3')$  than  $a_H(5')$  in nitroaromatic anion radicals. This assignment is not trustworthy, specifically when the coupling constants are of comparable size as it occurs in our study.<sup>[20]</sup> For this reason we have assigned the largest coupling constant to position  $5'$ . The same explanation is also applicable to radical  $2^{\bullet-}$  and  $3^{\bullet-}$ .

The ESR spectrum of the anion radical  $2^{\bullet-}$  is displayed in Fig. 2a. The theoretical multiplicity for this spectrum would expect to give a triplet due to the nitro-group nitrogen nucleus, four doublets attributed to four non-equivalent protons, and a quintet due to the nitrogens from the benzimidazole ring. The experimental spectrum exhibited the expected multiplicity as it is visualized in the simulated spectrum (Fig. 2b). The largest coupling constant of 9.90 G is straightforward and corresponds to the nitrogen of the nitroaromatic group.<sup>[16–19]</sup> The other coupling constants were assigned by analogy to other nitroaromatic anion radicals and supported by INDO calculations. Both experimental and theoretical coupling constant assignments are given in Table 1.

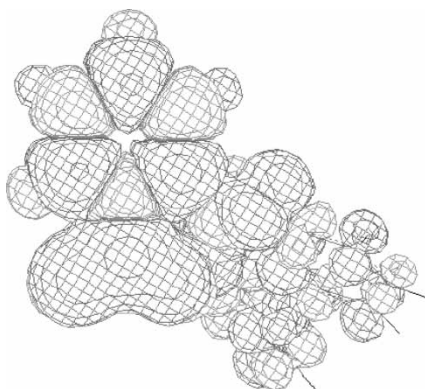




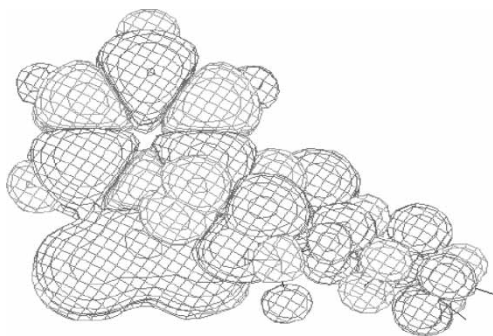
**Figure 4.** Optimized molecular structure and spin density distribution of  $1^{\bullet-}$ .

The ESR spectrum of the anion radical  $3^{\bullet-}$  is displayed in Fig. 3a. The spectrum of  $3^{\bullet-}$  could be theoretically interpreted in terms of a triplet due to the nitro-group nitrogen nucleus, four doublets attributed to four nonequivalent protons, and a quintet due to the nitrogens from the benzimidazole ring. The experimental spectrum exhibited the expected multiplicity, as it is visualized in the simulated spectrum shown in Fig. 3b. The coupling constant of 9.90 G was assigned to the nitrogen of the nitro aromatic group. The assignments of the other coupling constants were also done by comparison with anion radicals of similar structure<sup>[16–19]</sup> and INDO calculations. The experimental and theoretical coupling constants are given in Table 1.

As it is known, the nitrogen coupling constants in nitrobenzene derivatives are affected by steric effects and electronic properties of the substituent,<sup>[5,18]</sup> in such a way that bulky groups in the *ortho* position increase the nitro coupling constant. A similar effect is observed for nitrobenzene ring, bearing groups electron-donating at *para* position. On the contrary,



**Figure 5.** Optimized molecular structure and spin density distribution of  $2^{\bullet-}$ .



**Figure 6.** Optimized molecular structure and spin density distribution of  $3^{\bullet-}$ .

the nitrogen coupling constant decreases with electron-withdrawing groups substitution at this position.

Based on the observed experimental values of the nitrogen and proton splitting constants, we optimized the molecular structure of the radicals, by using INDO method. In all cases we obtained the best results, keeping the nitro group coplanar to the phenyl group, meanwhile the benzimidazole framework was rotated. Figures 4, 5, and 6 show the optimized molecular structure, and the spin density distributions of the anion radicals.

For radical  $1^{\bullet-}$ , a good correlation between experimental and theoretical coupling constant values was obtained, when the distortion of the bond angle between the benzimidazolic substituent and the nitrobenzene ring was  $45^\circ$ . In regard to radicals  $2^{\bullet-}$  and  $3^{\bullet-}$ , the best correlation involved a rotation of  $63^\circ$  of the benzimidazole moiety with respect to the nitrobenzene group. On the other hand, the finding that the nitro-group nitrogen coupling constants of  $2^{\bullet-}$  and  $3^{\bullet-}$  are smaller than  $1^{\bullet-}$  may be attributed to an increased  $\pi$ -deficient character of the heterocyclic portion, due to the extra electron-attracting power exerted by the benzoyl and acetyl N-substitution. Thus the nitro group becomes more deficient of unpaired electron density, promoting lowering hyperfine coupling constants. In all cases, the steric effect apparently would play a secondary role.

In conclusion, a series of nitrobenzene anion radical derivatives **1**, **2**, **3** were characterized by ESR. The experimental coupling constants measured were in agreement with the theoretical predictions and are consistent with the stereoelectronic effects expected for this substitution pattern. On the basis of these results, further efforts on ESR research are currently underway in our laboratory.

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