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Molecular Orbital Studies of the Radicals of Hydroxybenzenes and Epinephrine

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Abstract: When calculations of proton hyperfine coupling constants of free radicals from hydroxybenzenes (phenol, 1,2- and 1,4-dihydroxybenzene, 1,2,3- and 1,2,4-trihydroxybenzene) and epinephrine were done using the INDO (intermediate neglect of differential overlap) method, experimental data for 1,2-dihydroxybenzene, 1,4-dihydroxybenzene, and 1,2,4-trihydroxybenzene were exactly reproduced. Calculations for the remaining hydroxybenzenes served to explain the experimental data qualitatively. The hyperfine coupling constants of the radical from epinephrine could be assigned from the present calculations. Although past calculations were done to determine structures of a quinol type, we found in the INDO calculations that semiquinone radicals have a quinoidlike structure. In these radicals, the C-O bond lengths are fairly short, the adjacent C-C bond lengths relatively long, and the next C-C bond lengths in the rings relatively short. The proton hyperfine coupling constants of the radical formed by the oxidation of epinephrine in alkaline ethanol media were measured by electron spin resonance absorption spectroscopy and the magnitudes were 1.28, 2.61, and 0.59 G. The splitting constants calculated by means of the INDO method were consistent with the observed values.

Introduction

Most radicals from hydroxybenzenes can be easily produced in alkaline ethanol solution and there are numerous reports¹⁻¹¹ concerning experimental proton hyperfine coupling constants. Geometries which reproduce the experimental data exactly have apparently not been documented. As stated by Pople,¹² the calculated results in the INDO method for the semiquinones were not supported. The ab initio calculations do not reproduce the observed data. In all these calculations or others,¹³⁻¹⁷ the geometries of the semiquinone radicals were considered to be hexagons or a close resemblance and the C-O bond lengths were estimated to be those of a quinol type. The calculated results by Pople also can be reproduced in the geometries of a quinol type.

In the present INDO calculations, we found that these semiquinone anion radicals have a quinoidlike structure, with the rings which are fairly distorted from regular hexagons and the short C-O bond lengths. Lack of success with past calculations may be due to lack of adequate consideration that the molecular geometries of these radicals are distorted as compared to a regular hexagon; i.e., they are of quinoidlike structures. The INDO method has been widely used in studies of radicals and the sigmatropic shifts.¹⁸⁻²⁵ The INDO calculations in studies of proton hyperfine splitting constants of

semiquinones have not been successful; however, this method may still be used providing that the geometries of quinone type are reinvestigated.

Pyrocatechol, epinephrine, and related compounds are substrates for the COMT (catechol-O-methyltransferase) and the relationship between their biological activities and chemical structures has not been well determined.

The authors have reported that the diuretic actions of triazine derivatives²⁶ principally depend upon the force of the charge transfer at their active centers, and that the carbonic anhydrase inhibitory actions of sulfonamide derivatives²⁷ parallel the formal charge of the sulfonamide groups.

Information on molecular geometries of the radicals from hydroxybenzenes and epinephrine is required to determine the structure selectivity by the COMT or the meta/para ratios of the O-methylated products. In the present work, calculations of the proton hyperfine coupling constants of semiquinone anion radicals and epinephrine anion radical were made using the INDO method as well as the HMO and the McLachlan methods. We measured the ESR spectra of epinephrine radical, calculated its proton hyperfine coupling constants, and made assignments. Molecular geometry which well explains the observed proton hyperfine splitting constants of epinephrine radical was obtained.

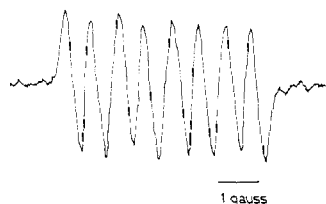


Figure 1. ESR spectrum of the radical from epinephrine in 0.02 mol of NaOH per liter of ethanol.

Experimental Section

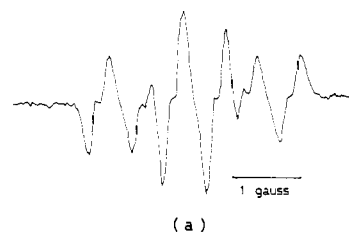
The ESR spectra of the free radical from epinephrine were obtained by autoxidation of L-epinephrine in alkaline ethanol solution. The ESR spectra of this compound have often been reported;^{6,28} however, no data are available on the quantitative proton hyperfine coupling constants. We reinvestigated this radical and determined the hyperfine coupling constants. L-Epinephrine (commercial) was dissolved in ethanol containing 0–1.6% sodium hydroxide. The spectra were recorded at a room temperature of 25 °C on a Japan Electron Optics Laboratory JEX-3BX spectrometer and a Hitachi MES-4001 spectrometer with a 100 kHz modulation.

Calculations of Spin Densities. The INDO method and its applications to the hyperfine coupling constants have been described by Pople and colleagues.^{12,15,29} Using this method we investigated the geometries of the radicals from phenol, 1,2- and 1,4-dihydroxybenzene, 1,2,3- and 1,2,4-trihydroxybenzene, and epinephrine. The INDO computer program was provided by the Quantum Chemistry Program Exchange, Indiana University, and translated into FACOM 230-75 FORTRAN of Kyoto University Data Processing Center. The Cartesian coordinates necessary for the calculations were obtained from the program termed XYZDR, which was coded by the authors and contains the drawing program with the XY plotter, CALCOMP 770-763. The digital computer FACOM 230-75 is based on binary inner memories and 72 bits in a double precision. The digital computer M 190 of Kyoto university Data Processing Center as well as FACOM 230-75 was used. The computer M 190 is 64 bits in a double precision. The convergence was judged at 10^{-6} .

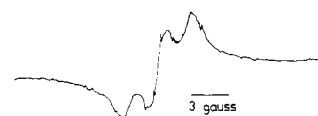
Results and Discussion

Hyperfine Coupling Constants of the Radical from Epinephrine. The ESR spectrum of the radical from epinephrine in 0.02 mol of NaOH per liter of ethanol is presented in Figure 1. These are eight spectral components ($2 \times 2 \times 2$). When measurements were carried out in 0.02–0.1 mol of NaOH per liter of ethanol, those eight lines of the spectrum were observed to be stable. In 0.4 mol of NaOH per liter of ethanol, the stable spectrum as shown in Figure 2a was observed. In 0.2 mol of NaOH per liter of ethanol, the spectrum gradually changed from the type in Figure 1 to the type of Figure 2a. In ethanol saturated with NaOH, the spectrum shown in Figure 2b was observed at about 10 min after the preparation. Figure 2a appears to be similar to the ESR spectrum of the radical from epinephrine in acid solution as reported by Borg²⁸ (1965), and Figure 2b to be similar to that from adrenochrome in 0.1 N NaOH also reported by this author.

The spectrum consisting of eight clear lines shown in Figure 1 was observed to be stable in alkaline ethanol solution containing NaOH in low concentration (e.g., 0.02 mol/L). Such spectrum was not stable or was not detected in alkaline ethanol solution with a high concentration (e.g., 0.4 mol/L) of NaOH (Figure 2a). Even in ethanol solution with a low concentration of NaOH, the spectrum of epinephrine radical varies from the pattern in Figure 1 to that in Figure 2b via that in Figure 2a with passage of time. These variations of the ESR spectra are considered to correspond to the stages of the autoxidation of epinephrine; the chemical structure of epinephrine radical is considered to vary with the stage of autoxidation. The measured values of splitting constants of the radical from epinephrine were 1.28 (A_3), 0.59 (A_5), and 2.61 (A_6) G. The as-



(a)



(b)

Figure 2. ESR spectra of the radical from epinephrine in 0.4 mol of NaOH per liter of ethanol and ethanol saturated with NaOH.

signment of splittings was done from the INDO calculations in this report.

The results of the present INDO calculations validate that the radical corresponding to the spectrum in Figure 1 is the epinephrine radical.

Calculation of Splitting Constants by Hückel Molecular Orbital Method (HMO) and McLachlan Method. Electronic structures of hydroxybenzenes (phenol, 1,4- and 1,2-dihydroxybenzene, 1,2,3-, 1,3,5-, and 1,2,4-trihydroxybenzene) and epinephrine were calculated by means of the ω technique of the HMO method. The slightly modified ω technique reported by Ettinger³⁰ was used. The Coulomb integrals α_0 's were in the proximity of $\alpha + 2\beta$ at convergence in the iteration of ω technique. The resonance integrals β_{c-o} 's were calculated by the iterative method using the relationship between bond order and bond length, and these values were in the proximity of 0.6β when the iterative calculations converged. The electronic structure of epinephrine was calculated containing OH of the β position in the form of the hyperconjugated structure. The values of parameters α_{OH} 's and β_{C-OH} 's for this structure were $\alpha + 0.6\beta$ and 0.6β , respectively.

The splitting constants by the HMO method as well as by the McLachlan method were calculated (Table I). The relation proposed by McConnell was used in the calculations of the splitting constants. The magnitude of Q was 22.5 G. The calculated splitting constants qualitatively agree with those observed. According to the assignment by the INDO calculations, the calculated splitting constants of the radical from epinephrine as determined by the HMO method were not in agreement with the observed values. These HMO calculations were unsuccessful as estimation of the values of parameters of the β -hydroxyl group was difficult. The calculated splitting constants of *p*-semiquinone anion radical by the McLachlan method and of pyrogallol semiquinone anion radical by the HMO method are quantitatively in good agreement with the observed values while the values of semiquinone anion radical from 1,2,4-trihydroxybenzene appear to favor the assignment by Lott and co-workers.¹¹ The calculated values of pyrogallol semiquinone anion radical were in good agreement with the observed values, reported herein for the first time. The calculated splitting constants of *o*-semiquinone anion radical by the HMO method did not fit the experimental constants. These results suggest that conformations of the aromatic rings of these radicals are not the regular hexagon type, and that par- ametrization corresponding with the geometries is difficult.

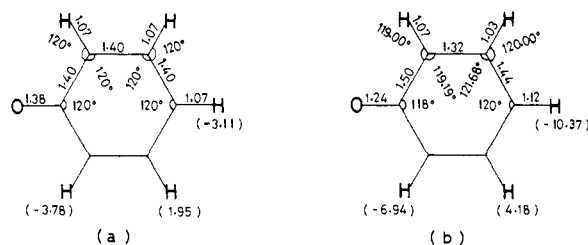
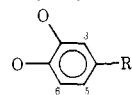


Figure 3. Calculated splitting constants of phenoxy radical (parenthesized) and its geometries.

Table I. Calculated Splitting Constants of Radicals from Hydroxybenzenes and Epinephrine by HMO and McLachlan Methods

Radicals	Position	Splitting constants, G		
		Obsd	ω technique	McLachlan method
Phenoxy radical	2	6.6	2.43	2.7675
	3	1.96	1.305	2.61
	4	10.4	6.615	4.635
<i>p</i> -Semiquinone anion radical	2	2.37	1.845	2.565
<i>o</i> -Semiquinone anion radical	3	3.65	0.135	1.8
Pyragallol semiquinone anion radical	4	0.95	4.1625	3.5775
Semiquinone anion radical from 1,2,4-trihydroxybenzene	4	9.96	0.9	2.115
	5	5.41	5.3775	3.96
Anion radical from epinephrine	3	1.3	0.65	0.27
	5	4.8	4.80	3.1725
	6	0.6	1.35	0.6525
epinephrine	3	1.28	0.18	1.35
	5	0.59	2.0925	2.1375
	6	2.61	0.405	1.26



Because the ESR spectrum of *m*-semiquinone anion radical in alkaline ethanol solution in our experiments consisted of 15–17 lines and was unresolved, the spin densities of this radical could not be calculated. The proton hyperfine splitting constants of this radical have been reported,²⁵ and its spin densities have not been calculated. The calculations of its spin densities will be reported by our group after the spectrum has been confirmed.

INDO Calculations. Phenoxy Radical. The observed splitting constants^{1–4} have been reported to be 6.6 (A_2), 1.96 (A_3), and 10.4 (A_4) G. In spite of many calculations^{13,14} including *ab initio*, there are apparently no reports which explain the observed splitting constants even qualitatively. The calculated values reported by Pople and his co-workers¹⁵ were -4.1 (A_2), 2.2 (A_3), and -3.4 (A_4), and were similar to the values (3.78, -1.95 , 3.11) calculated for the geometry of the hexagonal ring in Figure 3a. Both calculated values show the reverse trend to the observed ones. The values obtained from the geometry in Figure 3b, however, show a similar trend to the observed ones, that is, A_2 , A_3 , and A_4 are -6.94 , 4.18 , and -10.37 G, respectively. The fairly good agreement between the calculated values and the observed ones is due to the calculations for a quinoidlike structure. The molecular geometry of phenoxy radical is considered to be of a quinoidlike structure. The relationship between some bond lengths and the total energies, meta/ortho or para/ortho ratios of the calculated splitting constants of phenoxy radical are shown in Figure 4. The bond lengths C₂–C₃, O₁–C₁, and C₃–C₄ varied from 1.30 Å to 1.42 Å, from 1.10 Å to 1.22 Å, and from 1.40 Å to 1.50 Å, respec-

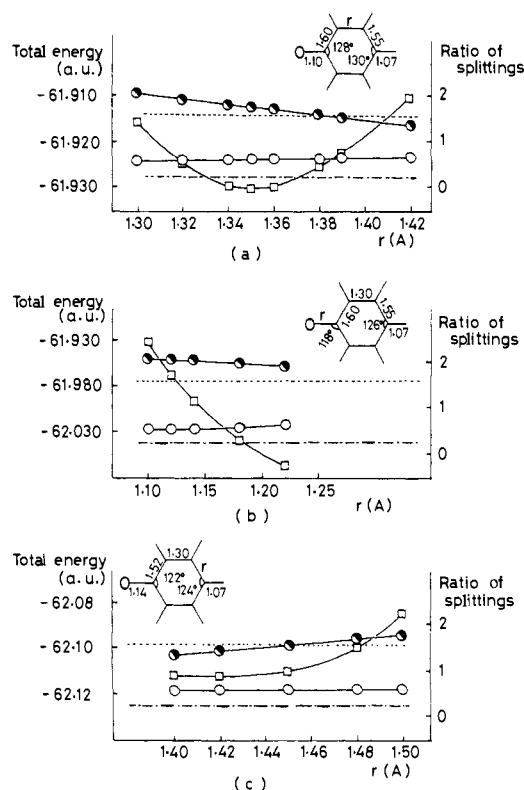


Figure 4. Total energies, meta/ortho and para/ortho ratios of calculated splitting constants of phenoxy radical as functions of bond lengths. Total energy, meta/ortho and para/ortho ratios of calculated splitting constants as a function of (a) C₂–C₃ bond length (in the range from 1.30 Å to 1.42 Å), (b) O₁–C₁ bond length (in the range from 1.10 Å to 1.22 Å), (c) C₃–C₄ bond length (in the range from 1.40 Å to 1.50 Å). ○—○, calculated meta/ortho ratio; ●—●, calculated para/ortho ratio; — — — —, observed meta/ortho ratio; — — — —, observed para/ortho ratio; □—□, total energy.

tively. The calculated splitting constants for the geometry in Figure 3b were the closest to the observed values among the 60 or so geometries we calculated.

***p*-Semiquinone Anion Radical.** Some of the calculated splitting constants by the empirical⁵ or semiempirical methods using some sets of parameters were reported to agree with the observed values of 2.37 G for *p*-semiquinone anion radical. These parameters in the empirical method, however, were not applicable to the splitting constants of other semiquinone radicals. The necessity of different parameters for different semiquinones reflects the variety of the molecular geometries of semiquinones. The calculated value by the INDO method was reported by Pople and his co-workers to be 0.9 G and we found the splitting constant calculated for the geometry of regular hexagon to have a similar value to that reported by Pople et al.¹⁵ In the present calculations, relationships as shown in Figure 5 were found between bond lengths (or bond angles) and the total energies (or the splitting constants) of *p*-semiquinone anion radical. Figure 6 shows five geometries which are likely for the *p*-semiquinone anion radical. The calculated splitting constants for these five geometries are in good agreement with the observed ones. The total energy of the radical shown in Figure 6 differs and the radical of Figure 6a gives a minimum energy among the five geometries. Therefore, the geometry in Figure 6a is the most likely for the *p*-semiquinone anion radical.

The calculated value of ¹⁷O hyperfine coupling constant in this work is 7.6 and those of ¹³C are -2.85 (A_1) and 3.1 (A_2) G.

***o*-Semiquinone Anion Radical.** Calculations^{13,15} were made

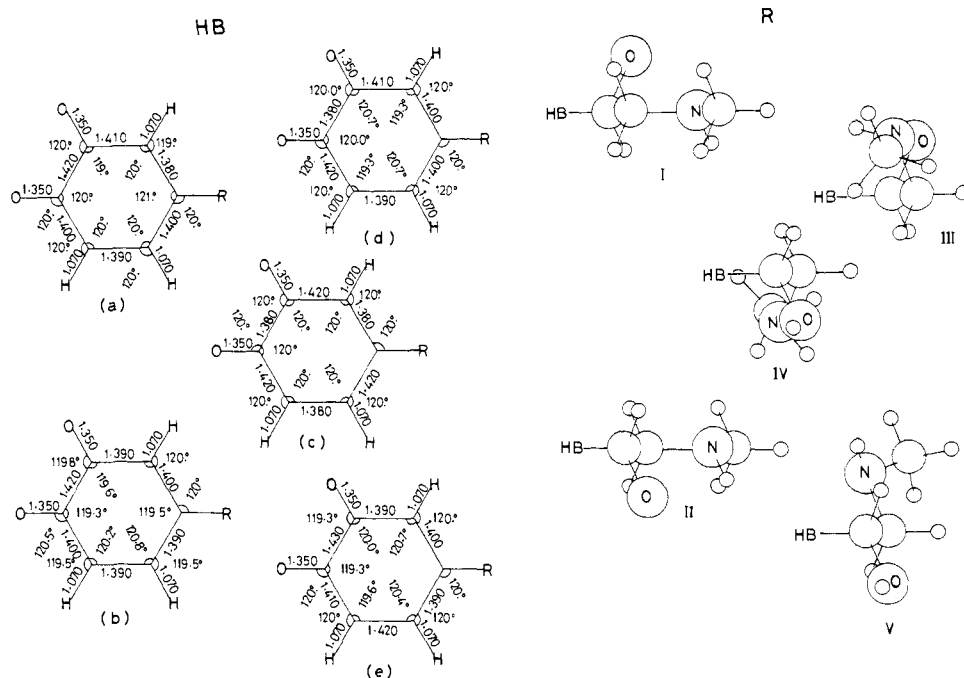


Figure 11. Resulting geometries of the hydroxybenzene ring (HB) and conformations of the side chain (R) of epinephrine anion radical.

constants, 2.37 G. The INDO calculations for the molecular geometries of a quinoid type reproduced exactly the experimental splitting constants of *o*-semiquinone anion radical and the semiquinone anion radical of 1,2,4-trihydroxybenzene which as well as pyrogallol semiquinone radical was suggested to be of the dianion type.

In the semiquinone anion radical of 1,2,4-trihydroxybenzene, the C₁-O₁ bond length was equivalent to the C₂-O₂ bond length, and the C₄-O₄ bond was longer than the other two C-O bonds. In the pyrogallol semiquinone radical, the C₁-O₁ bond length was equivalent to the C₃-O₃ bond length, and the C₂-O₂ bond was shorter than the other two C-O bonds. The INDO calculations reproduced the experimental splitting constants of phenoxy radical except for the value of the position of the third hydrogen atom. Some C-O bonds of the radicals of these hydroxybenzenes were a quinoidlike type, that is, shorter than those of regular hydroxybenzenes.

In conclusion, the molecular geometries of the radicals from hydroxybenzenes proved to be not of a quinol type but of a quinoid type. The present INDO calculations showed that the C-O bond lengths of these radicals are, in general, fairly short, the adjacent C-C bond lengths in the rings relatively long, and the next C-C bond lengths in the rings relatively short. The proton hyperfine splitting constants of *o*-semiquinone, *p*-semiquinone anion radical, and the anion radical of 1,2,4-trihydroxybenzene were explained quantitatively with the aid of the INDO calculations. The splitting constants of the phenoxy radical and pyrogallol semiquinone anion radical were explained qualitatively. The ESR spectrum of semiquinone anion radical of epinephrine was studied and the observed splitting constants and their assignments were determined.

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