STUDY OF THE ELECTRONIC STRUCTURE AND REACTIVITY OF 4-HYDROXYISOQUINOLINE BY THE MOLECULAR ORBITAL METHOD

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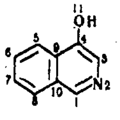
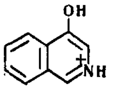
UDC 547.833.6:541.67

The reactivity indexes of the neutral, cationic, anionic, and dipolar forms of 4-hydroxyisoquinoline, calculated by the molecular orbital method using dynamic and static approximations, were compared with the experimental data on electrophilic substitution reactions in various media. Good agreement between the experimentally found orientations (3 > 1 > 8, 7, 6, 5) and the localization energies and boundary densities was obtained. The reactivity indexes of the neutral form of 4-hydroxyisoquinoline were calculated by the Pariser–Parr–Pople method.

A characteristic feature of 4-hydroxyisoquinoline (I) is its ability to exist in neutral (A), cationic (B), anionic (C), and dipolar (D) forms [1], depending on the pH of the medium.



A



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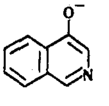

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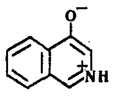

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Despite the rather large volume of experimental material [2, 3], there have as yet been no theoretical investigations of the electronic structures and reactivities of these forms of I. The goal of this study was a calculation, by means of the Hückel method, of the energy and structure indexes and correlation of them with the properties and reactivities of the four forms of 4-hydroxyisoquinoline. The neutral form was also calculated by the Pariser–Parr–Pople (PPP) method.

The Hückel program was kindly placed at our disposal by D. A. Bochvar and A. Tutkevich, while the PPP program was furnished by G. I. Kagan [4]. The coulombic integrals are presented in Table 1. The resonance integrals were taken from Pullman [5].

TABLE 1. Calculated Parameters

Element	Compound	Coulombic integral $\alpha_2 = \alpha_0 + h_2\beta_0$	Compound	Coulombic integral $\alpha_2 = \alpha_0 + h_2\beta_0$
Carbon Nitrogen Oxygen	A	$h_{c4}=0{,}25$; $h_{c3,\,c1}=-0{,}119$ $h_N=0{,}340$ $h_O=1{,}43$	C	$h_{c4}=0{,}105$ $h_{c3,\,c1}=-0{,}119$ $h_N=0{,}340$; $h_O=0{,}60$
Carbon Nitrogen Oxygen	B	$h_{c4}=0{,}25$; $h_{c3,\,c1}=-0{,}26$ $h_N=0{,}765$ $h_O=1{,}43$	D	$h_{c4}=0{,}105$ $h_{c3,\,c1}=-0{,}26$; $h_N=0{,}765$ $h_O=0{,}60$

Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Scientific-Research Institute of Organic Intermediates and Dyes, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 197-201, February, 1972. Original article submitted September 24, 1970.

TABLE 2. Energy Characteristics of 4-Hydroxyisoquinoline in Beta Units

Compound form	DE_π	$\frac{DE_\pi}{n}$	E_{HOMO}	E_{LFMO}	ΔE $(E_{HOMO} - (E_{LFMO})$	λ_{max},nm
A	4,08	0,34	0,4464	0,6546	1,1010	322
B	3,81	0,32	0,4091	0,6439	1,0530	348
C	4,09	0,34	0,2092	0,7121	0,9213	360
D	3,80	0,32	0,1584	0,6898	0,8482	390

TABLE 3. Bond Orders (ρ_{ij}), Bond Lengths (r_{ij}), and Charges (Q_i) of Forms A, B, C, and D of 4-Hydroxyisoquinoline

Form	Bond	ρ_{ij}	r_{ij}	Atom	Q_i
A	1—2	0,7068 (0,7833)*	1,322	1	0,0760
	1—10	0,5535 (0,5245)	1,415	2	−0,1688 (−0,2128)
	2—3	0,6068 (0,5717)	1,340	3	0,0321
	3—4	0,6766 (0,6996)	1,404	4	−0,0516
	4—9	0,5187 (0,5011)	1,421	5	−0,0016
	9—10	0,5204 (0,5626)	1,421	6	−0,0004
	9—5	0,5643 (0,5328)	1,424	7	−0,0056
	5—6	0,7205 (0,7544)	1,387	8	0,0055
	6—7	0,6045 (0,5684)	1,407	9	−0,1003
	7—8	0,7239 (0,7561)	1,386	10	−0,0182
	8—10	0,5542 (0,5279)	1,415	11	0,1363 (0,1215)
	4—11	0,3519 (0,3480)	1,357		
B	1—2	0,6701	1,329	1	0,2185
	1—10	0,5524	1,416	2	−0,3607
	2—3	0,5746	1,348	3	0,1374
	3—4	0,6824	1,393	4	−0,1013
	4—9	0,5212	1,421	5	−0,0109
	9—10	0,5183	1,421	6	0,0122
	9—5	0,5635	1,424	7	−0,0146
	5—6	0,7207	1,387	8	0,0221
	6—7	0,6040	1,407	9	0,0148
	7—8	0,7234	1,386	10	−0,0402
	8—10	0,5549	1,415	11	0,1224
	4—11	0,3247	1,370		
C	1—2	0,6921	1,325	1	0,0005
	1—10	0,5537	1,415	2	−0,1651
	2—3	0,6266	1,337	3	−0,0398
	3—4	0,6228	1,404	4	−0,0017
	4—9	0,4851	1,427	5	0,0045
	9—10	0,5219	1,421	6	−0,0196
	9—5	0,5789	1,411	7	−0,0035
	5—6	0,7120	1,388	8	−0,0111
	6—7	0,6078	1,411	9	−0,0291
	7—8	0,7219	1,387	10	−0,0178
	8—10	0,5532	1,418	11	0,2831
	4—11	0,5100	1,325		
D	1—2	0,6588	1,331	1	0,1411
	1—10	0,5592	1,414	2	−0,3561
	2—3	0,5924	1,343	3	0,0722
	3—4	0,6343	1,402	4	−0,0411
	4—9	0,4942	1,426	5	−0,0026
	9—10	0,5160	1,422	6	−0,0087
	9—5	0,5749	1,412	7	−0,0119
	5—6	0,7149	1,388	8	0,0052
	6—7	0,6042	1,407	9	−0,0153
	7—8	0,7241	1,386	10	−0,0405
	8—10	0,5507	1,419	11	0,2583
	4—11	0,4767	1,331		

*Data calculated by the PPP method is presented in parentheses.

In the calculation by the PPP method, the interatomic distances in the rings were assumed to be equal to 1.395 Å, the C−O bond was taken as 1.36 Å, and all of the angles were considered to be 120°.

The calculation indicates that the π electrons and the unshared pair of electrons of the exocyclic oxygen are in bonding orbitals. All four forms of I are consequently stable.

The delocalization energy per π electron [$(DE_\pi)/n$, where $n = 12$ for forms A, B, C, and D] is close to that in benzene (0.333 β) (Table 2). The calculated bond orders in the rings (Table 3) range from 0.48 to 0.75. This is evidence for the high level of aromatic character of the four forms of 4-hydroxyisoquinoline.

TABLE 4. Reactivity Indexes of 4-Hydroxyisoquinoline

Form	Position	L_E	L_N	L_R	Q_i	f_E	f_N	F_i
A	1	(11,63)* 2,0572	(11,67) 2,0026	(3,50) 2,0309	(+0,0853) +0,076	(0,3498) 0,1807	(0,3659 0,1867	0,4717
	3	(11,39) 2,0662	(12,12) 1,7800	(3,62) 1,9233	(+0,0028) +0,0321	(0,4159) 0,1652	(0,019) 0,0175	0,4486
	5	(11,65) 2,2882	(11,69) 2,2440	(3,49) 2,2661	(−0,0099) −0,0016	(0,2024) 0,0913	(0,3702) 0,1808	0,4472
	6	(12,09) 2,4400	(11,91) 2,4102	(3,81) 2,4251	(+0,0034) −0,0004	(0,0849) 0,0484	(0,2168) 0,0925	0,4070
	7	(12,03) 2,4494	(12,06) 2,3886	(3,83) 2,4190	(−0,0021) −0,0056	(0,1037) 0,0416	(0,096) 0,0512	0,4036
	8	(11,67) 2,2722	(11,56) 2,2502	(3,47) 2,2612	(+0,0093) +0,0055	(0,1964) 0,0936	(0,4066) 0,2044	0,4539
B	1	1,9588	1,8448	1,9018	+0,2195	0,1474	0,2259	0,5095
	3	1,5188	1,3876	1,4532	+0,1374	0,1898	0,0012	0,4750
	5	2,2546	2,1568	2,2057	−0,0109	0,0901	0,1539	0,4478
	6	2,4750	2,4244	2,4497	+0,0122	0,0341	0,1245	0,4073
	7	2,4252	2,2904	2,3578	−0,0146	0,0504	0,0273	0,4046
	8	2,2986	2,2594	2,2780	+0,0221	0,0765	0,2109	0,4537
C	1	1,7654	1,7562	1,7608	+0,0005	0,2003	0,00199	0,4862
	3	1,7424	1,0538	1,3981	−0,0398	0,1898	0,1409	0,4826
	5	2,3064	2,2600	2,2832	+0,0045	0,0217	0,2032	0,4411
	6	2,2820	2,0468	2,1644	−0,0196	0,0472	0,0871	0,4122
	7	2,4490	2,3844	2,4167	−0,0035	0,0104	0,0579	0,4023
	8	2,1516	1,9678	2,097	−0,0111	0,0569	0,2176	0,4569
D	1	1,5958	1,2440	1,4199	+0,1411	0,1658	0,1799	0,5140
	3	1,5344	0,9274	1,2309	+0,0722	0,2083	0,0031	0,5053
	5	2,2556	2,1464	2,2010	−0,0026	0,0241	0,1687	0,4422
	6	2,2736	2,0860	2,1748	−0,0087	0,0396	0,1190	0,4129
	7	2,3864	2,3512	2,3688	−0,0119	0,0153	0,0298	0,4037
	8	2,1422	1,7876	1,9649	+0,0051	0,0478	0,2155	0,4572

*The localization energies (in electron volts) calculated by the PPP method are given in parentheses.

TABLE 5. Predicted (on the basis of localization energies) and Experimental Orders of Orientation of Electrophilic Substituents in 4-Hydroxyisoquinoline

Molecule	Hückel MO method	Exptl. data
A	3>1>8>5>6>7	
B	3>1>5>8>7>6	$3(NO_2^+, Br^+)$, benzene ring (SO_3H)
C	3>1>8>6≥5>7	
D	3>1>8>5>6>7	$3(Br^+, I^+, ArN_2^+)$

The calculated differences ($\Delta E = E_{HOMO} - E_{LFMO}$) correlate linearly with the absorption maxima of the long-wave bands of the corresponding forms of I (Table 2).

It follows from the charges on oxygen and the C−O bond orders obtained that oxygen interacts strongly with the ring. According to the calculations, ionization of the hydroxyl group leads to a sharp increase in the charge and bond order (Table 3), which is in agreement with existing concepts [6]. The data obtained by the Hückel method are in good agreement with the results of the more accurate PPP method (Table 3). This makes it possible to consider the data obtained by the Hückel method to be sufficiently reliable.

The interatomic distances from the bond orders calculated from the formula in [7] are in agreement with experimental data for 8-hydroxyisoquinoline [8] (Table 3), and the interatomic distance for the $C-O^-$ bond is ~ 0.035 Å less than for the C−OH bond.

The reactions that have been the subject of the greatest study are electrophilic substitutions occurring at pH 4-9, i.e., in acidic, neutral, and weakly alkaline media [2, 3].

A comparison of the localization energies (L_E) for the various reaction centers of forms B, C, and D in electrophilic substitution reactions indicates that the most reactive positions are found at C_3, C_1, and C8. The L_E values calculated by the Hückel method for form A in these reactions are arranged in the order $C_1 \leq C_3 < C_8 < C_5 < C_6 < C_7$, while the values calculated by the PPP method are arranged in the order $C_3 < C_1 < C_5 \leq C_8 < C_7$, C_6 (Table 4).

The calculated orders of entry of the substituents during electrophilic substitution are in good agreement with the experimental data (Table 5). In fact, the nitration in sulfuric acid [2] and bromination in acetic acid [9] of 4-hydroxyisoquinoline, which exists in form B, proceed in the order $3 > 1$. On the other hand, the bromination and iodination in alkaline solution of I, which exists in form C, proceed readily at room temperature in the order of substitution $3 > 1 > 8$, 7, 6, 5 [9]. Finally, aminomethylation and azo coupling of 4-hydroxyisoquinoline, which proceed in weakly alkaline media, are characterized by the order of substitution $3 > 1 > 8$, 7, 6, 5 [10].

An examination of the boundary densities (f_E) demonstrates that the order of entry of electrophilic substituents for forms B and D ($C_3 > C_1 > C_8$) coincides with the order of L_E and the experimental data (Tables 4 and 5). Complete agreement of the boundary densities calculated by the PPP method with the L_E values and the experimental data on electrophilic substitution ($3 > 1 > 8$) was obtained for the neutral form. In this case, the boundary densities and L_E values calculated by the Hückel method give a different order ($1 > 3 > 8$) than the PPP method. According to the f_E values, the most reactive position for form C is C_1 rather than C_3, although the f_E values do not differ markedly in this case.

An examination of the f_N and Q values demonstrates that the order of nucleophilic substitution does not agree with the order of substitution according to L_N. In all four forms of 4-hydroxyisoquinoline, the free valence indexes (F_i) indicate that the C_1 position is more reactive, although, according to the L_E data for radical reactions, the primary site of attack should be C_3. The differences between F_1 and F_3, however, are small.

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