ELECTROPHILIC SUBSTITUTION OF 5- AND 6-SUBSTITUTED BENZO-1,4-DIOXANES

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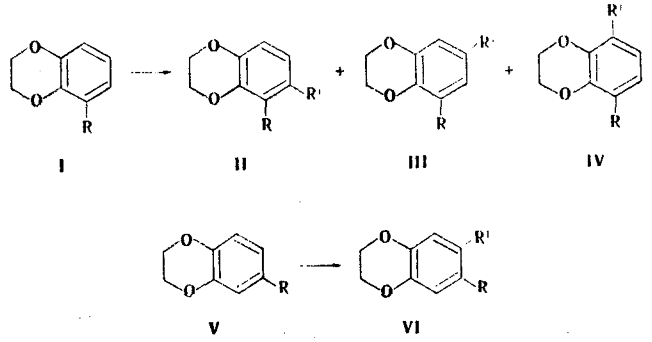
The compositions of the products of bromination, nitration, and acetylation of 5- and 6-fluoro(chloro, nitro, methoxy, methyl, formyl, and carboxy)benzo-1,4-dioxanes were established. The reactivity indexes and the characteristics of the UV spectra of the starting compounds were calculated by the self-consistent-field (SCF) MO LCAO method within the Pariser–Parr–Pople (PPP) and CNDO/2 CI (complete neglect of differential overlap with configuration interaction) approximations, and the results were compared with the experimental data.

In a continuation of our research on electrophilic substitution in the benzo-1,4-dioxane series [1] we studied the compositions of the products of bromination, nitration, and acetylation of 5- and 6-substituted benzo-1,4-dioxanes (I and V) [2-4]:



a R = Cl, OCH_3, CH_3; R' – Br, NO_2, $COCH_3$; b R = F, NO_2, CHO, COOH; R' = Br, NO_2

The reaction conditions for I and the ratios of products II-IV are presented in Table 1. The reactions of isomers V carried out under the same conditions gave only VI (in 80-95% yields).

The structure of III is confirmed by the presence in their PMR spectra of signals of aromatic protons in the form of two doublets (J = 2-3 Hz); the spectra of isomers VI contain two singlets. Two doublets (J = 8-10 Hz) are observed in the case of isomers II and IV, whereas characteristic doublets of doublets and, respectively, doublets are observed in the spectra of fluoro derivatives II, III, and VI (R = F) (Table 2).

Compounds V (R = Br or NO_2) were obtained by oxidation of II (R = CH_3, R^1 = Br) and II (R = CHO, R^1 = NO_2) with subsequent decarboxylation of resulting acids II (R = COOH, R^1 = Br or NO_2) [2]. We were unable to isolate II (R = F, R^1 = NO_2) and III (R = COOH, R^1 = NO_2) in individual form; however, the PMR spectrum of the mixture of isomers II and III (R = F, R^1 = NO_2) in deuteroacetone contains a doublet of doublets (J = 2 and 11 Hz) of the proton in the 8 position of the ring of isomer II (δ 6.86 ppm) and a multiplet (7.55 ppm) of the remaining aromatic protons. Compound V (R = NO_2) free of isomer I is formed in the decarboxylation of a mixture of acids II and III (R = COOH, R^1 = NO_2). The structures of II (R = CH_3, R^1 = NO_2, $COCH_3$) were established from the similarity between their UV spectra and the spectra of V (R = NO_2, $COCH_3$) and the difference from the spectra of isomer I [3]; the structures of II (R = Cl, R^1 = Br, NO_2, $COCH_3$) were established from the presence in their PMR spectra of the

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TABLE 1. Data from the Electrophilic Substitution Reactions of I

R	R¹	Reaction conditions			Overall yield, %	Product ratio		
		reagent amounts (moles per mole of I)	temp, °C	time, h		II	III	IV
F	Br	Br_2, Fe, CH_3COOH (1,1; 0,02; 15)	55	35	71	1	0	0
	NO_2	HNO_3 (56%), CH_3COOH (1; 9)	60	3	66	1	1,1	0
Cl	Br	Br_2, Fe, CH_3COOH (1,1; 0,02; 30)	55	8	80	1	0	0
	NO_2	HNO_3, H_2SO_4, CH_3COOH (1; 6; 30)	15	2	95	1,3	1	0
	$COCH_3$	CH_3COCl, $AlCl_3$, CS_2 (1; 1; 17)	45	20	88	4,6	1	0
		CH_3COCl, $AlCl_3$, $C_6H_5NO_2$ (1; 1; 7)	60	12	96	1	1,7	0
NO_2	Br	Br_2, Fe (1,2; 0,03)	55	3	90	0	1	0
	NO_2	HNO_3, H_2SO_4, CH_3COOH (1,1; 1; 9)	35	2	91	5,5	1	0
OCH_3	Br	Br_2, CCl_4 (1; 20)	−5	0,1	94	1	0	5
		Br_2, Fe, CH_3COOH, H_2O (1; 0,02; 70; 20)	0	0,1	90	1	0	5
	NO_2	CH_3COONO_2, $(CH_3CO)_2O$ (2; 5)	−10	0,5	88	1	6	4
		HNO_3 (56%), CH_3COOH (1,2; 10)	5	2	84	1	8	2,7
		HNO_3 (56%) (8)	0	1	85	1	4,3	2,5
	$COCH_3$	CH_3COCl, $AlCl_3$, CS_2 (1; 1; 15)	15	20	86	0	0	1
		CH_3COCl, $AlCl_3$, $C_6H_5NO_2$ (1; 1; 12)	20	48	90	0	0	1
CH_3	Br	Br_2, CCl_4 (1; 15)	55	3	90	1	0	0
		Br_2, Fe, CH_3COOH (1,05; 0,02; 25)	55	5	95	1	0	0
	NO_2	CH_3COONO_2, $(CH_3CO)_2O$ (1,5; 25)	20	3	94	1	1,4	0
		HNO_3 (56%), CH_3COOH (1; 20)	5	10	89	1	1,1	0
	$COCH_3$	CH_3COCl, $AlCl_3$, CS_2 (1; 1; 12)	−5	2	87	1	1,7	0
		CH_3COCl, $AlCl_3$, $C_6H_5NO_2$ (1; 1; 7)	0	3	90	1	1,7	0
CHO	Br	Br_2, CCl_4 (1; 25)	20	12	80	0	1	0
		Br_2, Fe, CH_3COOH (1,05; 0,02; 120)	55	6	82	0	1	0
	NO_2	HNO_3 (72%), CH_3COOH (3; 12)	50	0,5	95	2,5	1	0
COOH	Br	Br_2, Fe, CH_3COOH (1,05; 0,02; 70)	55	20	70	0	1	0
	NO_2	HNO_3, H_2SO_4, CH_3COOH (1,2; 1; 70)	20	5	81	6	1	0

signal of the proton in the 8 position of the ring at stronger field than the signals (Ar—H) of isomers III and VI. Isomers II and III (R = OCH_3, R^1 = NO_2) are known compounds [5], and structure IV was therefore assigned to the third of them. The remaining synthesized II-IV and VI have been previously described [4-7].

The directions of substitution of I and V do not correlate with the charges on the carbon atoms of their aromatic rings (Tables 1 and 3). The directions of nitration and acetylation (attack by more active electrophiles) correlate with the electron populations of the atomic orbitals of the carbon atoms of the aromatic ring that are due to the boundary occupied molecular orbitals [8] and also with the stabilization energies (ε_r^+) [9] of the same atoms, i.e., with the reactivity indexes for electrophilic substitution reactions with a transition state that is structurally intermediate ("early") between the starting molecule and the σ complex.

Compound I (R = OCH_3) is nitrated exceptionally readily, and the ratio of its nitro derivatives II-IV (R = OCH_3, R^1 = NO_2) is probably determined by steric effects. The dependence of the ratio of the products of acetylation of I (R = Cl) on the solvent is also evidently due to steric effects [10], since II and III (R = Cl, R^1 = $COCH_3$) do not undergo isomerization under the conditions of their formation.

The direction of bromination (attack by a less active electrophile) is possibly due to the stability of the intermediate σ complex [11], stabilized primarily by the ethylenedioxy group, which orients the substituent to the 6 and 7 positions of the ring [1, 2]. Compounds V therefore form 7-substituted derivatives (VI), whereas I gives 6-substituted derivatives (II, R = an electron donor) or 7-substituted derivatives (III, R = an electron acceptor), since the 5-substituent (R) plays an auxiliary role in orientation. The preponderance of product IV (R = OCH_3, R^1 = Br) over isomer II in the bromination of I (R = OCH_3) is probably due to steric effects [1].

TABLE 2. Characteristics of the Synthesized Compounds

Compound	R	R'	mp, °C (solvent)	UV spectrum		PMR spectrum,[a] δ, ppm	Found, %				Empirical formula	Calc., %			
				λ_{max}, nm	lg ε		C	H	Hal	N		C	H	Hal	N
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
II	F	Br	44—45 (hexane)	209 227 281	4,45 3,96 3,00	6,45 (dd, J=2 and 9 Hz, 8-H)[b] 6,86 (dd, J=7 and 9 Hz, 7-H)	41,4	2,8	—	—	$C_8H_6BrFO_2$	41,2	2,6	—	—
VI	F	Br	70—71 (ethanol)	205 224 294	4,39 3,84 3,62	6,57 (d, J=9 Hz, 5-H)[b] 6,93 (d, J=7 Hz, 8-H)	41,5	2,8	—	—	$C_8H_6BrFO_2$	41,2	2,6	—	—
III	F	NO_2	159—160 (ethanol)	219 236 312	3,74 3,50 3,57	7,54 (m, 8-H)[c] 7,60 (dd, J=2 and 10 Hz, 6-H)	48,7	3,2	—	7,1	$C_8H_6FNO_4$	48,3	3,0	—	7,0
II	Cl	Br	44—44,5 (hexane)	210 228 293	4,69 4,00 3,36	6,56 (d, 8-H)[b] 6,98 (d, 7-H)	38,3	2,4	46,4	—	$C_8H_6BrClO_2$	38,5	2,4	46,2	—
VI	Cl	Br	140—141 (ethanol)	210 227 296 330	4,68 3,95 3,59 2,70	6,91 (s, 5-H)[b] 7,05 (s, 8-H)	38,2	2,3	46,5	—	$C_8H_6BrClO_2$	38,5	2,4	46,2	—
II	Cl	NO_2	132—133 (ethanol)	208 254 299	4,08 3,75 3,70	6,50 (d, 8-H)[d] 7,20 (d, 7-H)	44,9	3,1	16,8	6,3	$C_8H_6ClNO_4$	44,6	2,8	16,4	6,5
III	Cl	NO_2	75—77 (acetone—water)	208 225 244 315	4,22 4,20 3,97 3,86	7,35 (d, 8-H)[d] 7,53 (d, 6-H)	45,0	3,0	16,2	6,4	$C_8H_6ClNO_4$	44,6	2,8	16,4	6,5
II	Cl	$COCH_3$	70—71 (hexane)	212 225 235 275 310	4,04 4,13 4,04 3,77 3,52	6,64 (d, 8-H)[b] 7,01 (d, 7-H)	56,9	4,4	17,1	—	$C_{10}H_9ClO_3$	56,5	4,3	16,7	—
III	Cl	$COCH_3$	111—112 (acetone)	224 279	4,33 4,03	7,23 (d, 8-H)[b] 7,43 (d, 6-H)	56,2	4,5	16,3	—	$C_{10}H_9ClO_3$	56,5	4,3	16,7	—
VI	Cl	$COCH_3$	78—78,5 (ethanol)	225 236 275 312	4,22 4,26 3,80 3,49	6,81 (s, 5-H)[b] 7,11 (s, 8-H)	56,1	4,4	16,4	—	$C_{10}H_9ClO_3$	56,5	4,3	16,7	—
III	NO_2	Br	126—127 (ether)	225 274 338	4,22 3,70 3,48	6,92 (d, 8-H)[b] 7,29 (d, 6-H)	37,2	2,6	30,9	5,6	$C_8H_6BrNO_4$	37,0	2,3	30,7	5,4

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IV	OCH_3	NO_2	155—156 (CCl_4)	245 312	3,89 3,93	6,36 (d, 7-H)^b 7,45 (d, 6-H)	51,5	4,4	—	6,3	$C_9H_9NO_5$	51,2	4.3	—	6,6
VI	OCH_3	Br	67—68 (ethanol)	210 226 301	4,24 3,81 3,64	6,33 (s, 5-H)^b 6,95 (s, 8-H)	44,3	3,9	32,2	—	$C_9H_9BrO_3$	44,1	3,7	32,6	—
II	CH_3	Br	31—32 (hexane)	212 288	3,80 3,32	6,51 (d, 8-H)^b 6,94 (d, 7-H)	46,8	4,0	34,7	—	$C_9H_9BrO_2$	47,2	4,0	34,9	—
VI	CH_3	Br	51—52 (hexane)	209 224 295	5,06 4,49 4,09	6,63 (s, 8-H)^b 6,94 (s, 5-H)	46,9	4,1	34,5	—	$C_9H_9BrO_2$	47,2	4,0	34.9	—
II	CH_3	NO_2	94—95 (ethanol	209 222 252 311	3,97 3,94 3,80 3,72	6,43 (d, 8-H)^d 7,29 (d, 7-H)	55,5	4,7	—	6,9	$C_9H_9NO_4$	55,4	4,6	—	7,2
III	CH_3	NO_2	111—112 (ethanol)	214 246 318	4,29 4,01 3,94	7,31 (d, Ar—H)^d 7,39 (d, Ar—H)	55,4	4,3	—	7,1	$C_9H_9NO_4$	55,4	4,6	—	7,2
II	CH_3	$COCH_3$	81—82 (hexane)	216 232 274 305	4,26 4,14 4,04 3,63	6,59 (d, 8-H)^b 7,11 (d, 7-H)	68,9	6,2	—	—	$C_{11}H_{12}O_3$	68,7		—	—
III	CH_3	$COCH_3$	39—40 (pentane)	215 231 280	4,16 4,11 3,94	7,19 (s, Ar—H)^b	69,0	6,4	—	—	$C_{11}H_{12}O_3$	68,7	6,3	—	—
VI	CH_3	$COCH_3$	98—98,5 (ethanol)	231 271 310	4,29 4,03 3,69	6,60 (s, 5-H)^b 7,18 (s, 8-H)	69,1	6,6	—	—	$C_{11}H_{12}O_3$	68,7	6,3	—	—
III	CHO	Br	102—104 ($CHCl_3$)	224 271 347	4,44 3,85 3,48	6,92 (d, 8-H)^d 7,14 (d, 6-H)	42,0	3,1	34,5	—	$C_8H_7BrO_3$	41,6	3,1	34,6	—
II	CHO	NO_2	115—117 (ethanol)	212 221 350	3,80 3,82 3,61	7,15 (d, 8-H)^c 7,64 (d, 7-H)	51,9	3,5	—	6,6	$C_9H_7NO_5$	51,7	3,4	—	6,7
III	CHO	NO_2	144—146 (ethyl acetate)	253 323	4,10 3,81	7,84 (d, 8-H)^c 8,10 (d, 6-H)	51,5	3,3	—	6,7	$C_9H_7NO_5$	51,7	3,4	—	6,7
VI	CHO	NO_2	165—167 (benzene)	259 330	4,09 3,67	7,33 (s, 8-H)^c 7,63 (s, 5-H)	51,6	3,2	—	6,6	$C_9H_7NO_5$	51,7	3,4	—	6,7
II	COOH	Br	160—161 (ethanol)	225 297	3,68 3,09	6,81 (d, 8-H)^c 7,06 (d, 7-H)	41,6	2,9	30,8	—	$C_9H_7BrO_4$	41,7	2,7	30,8	—
III	COOH	Br	209—210 (ethanol)	215 314	4,42 3,34	6,90 (d, 8-H)^d 7,34 (d, 6-H)	41,5	2,4	31,2	—	$C_9H_7BrO_4$	41,7	2,7	30,8	—
II	COOH	NO_2	189—190 (water)	217 320	4,02 3,75	7,04 (d, 8-H)^c 7,79 (d 7-H)	48,2	3,2	—	5,9	$C_9H_7NO_6$	48,0	3,1	—	6,2

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a) Chemical shifts: 1.9-2.3 (s, $ArCH_3$), 2.4 (s, $COCH_3$), 3.7 (s, OCH_3), 4.0-4.4 (s, OCH_2CH_2O), 9.8-10.3 (s, ArCHO). b) In CCl_4. c) In deuteroacetone. d) In CF_3COOH.

TABLE 3. Data from the Calculation of the Electron Structures of I and V within the PPP and CNDO/2 CI Approximations

Compound	R	Electron population of the AO due to the boundary occupied MO			Stabilization energy (ε_r^+), eV			Charge on the atom		
		aromatic ring carbon atoms								
		5 or 6a	7	8	5 or 6	7	8	5 or 6	7	8
I	F	0,281	0,318	0,013	10,09	9,79	11,45	−0,033	−0,015	−0,043
I	Cl	0,322	0,303	0,020	9,89	9,84	11,42	−0,032	−0,010	−0,041
I	NO_2	0,368	0,253	0,050	9,87	10,52	11,57	+0,013	−0,001	−0,001
I	OCH_3	0,304	0,022	0,555	9,66	11,15	8,86	−0,048	−0,001	−0,045
I[b]	CH_3	0,288	0,425	0,001	—	—	—	−0,061	−0,032	−0,054
I	CHO[c]	0,325	0,307	0,023	9,44	10,09	11,46	+0,035	−0,014	−0,007
I[b]	CHO[c]	0,408	0,359	0,020	—	—	—	−0,005	−0,041	−0,020
I	COOH[c]	0,338	0,304	0,026	9,34	10,05	11,44	+0,033	−0,012	−0,012
I	COOH[d]	0,277	0,309	0,018	10,13	10,15	11,49	−0,001	−0,019	−0,013
V	F	0,004	0,303	0,036	11,57	10,00	11,29	−0,052	−0,033	−0,034
V	Cl	0,001	0,298	0,043	11,56	10,00	11,24	−0,052	−0,033	−0,034
V	NO_2	0,066	0,271	0,013	11,45	10,21	12,02	−0,005	+0,027	−0,027
V	OCH_3	0,027	0,290	0,067	11,56	10,18	11,05	−0,078	−0,059	−0,030
V[b]	CH_3	0,014	0,329	0,047	—	—	—	−0,060	−0,060	−0,032
V	CHO[c]	0,017	0,274	0,022	11,43	9,69	11,68	−0,007	+0,037	−0,034
V	CHO[d]	0,025	0,283	0,019	11,08	9,97	11,77	+0,016	+0,014	−0,036
V[b]	CHO[c]	0,022	0,354	0,004	—	—	—	+0,114	−0,001	−0,045
V[b]	CHO[d]	0,023	0,355	0,006	—	—	—	−0,004	−0,025	−0,043
V	COOH[c]	0,012	0,274	0,024	11,59	9,64	11,60	−0,020	+0,035	−0,033
V	COOH[d]	0,001	0,283	0,023	11,05	10,10	11,71	+0,014	+0,001	−0,037

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a) In the 6 position for isomers I and in the 5 position for isomers V. b) Within the CNDO/2 CI approximation for these compounds and within the PPP approximation for the remaining compounds. c) For the conformation with the CO group directed away from the heteroring. d) For the conformation with the CO group directed toward the heteroring.

The calculations within the π-electron approximation (PPP) were made as in [1], whereas the calculations with allowance for all of the valence electrons (CNDO/2 CI) [12] were performed with the program of A. P. Volosov and V. A. Zubkov (Institute of Cytology of the Academy of Sciences of the USSR). A half-chair conformation was adopted for the heteroring of V; the torsion angles of rotation of the oxygen atoms in the 1 and 4 positions of the ring about the C_{ar}–O bond ($\varphi_1 = \varphi_2 = 23°$ for the half-chair conformation) and the angle of rotation (φ_3) of the 5-substituent (R) of I were determined from the conformity between the calculated and experimental characteristics of the UV spectra [1]. It was found that the heteroring of I (R = F, CH_3, CHO, and COOH) most likely exists in a half-chair conformation with $\varphi_3 = 0°$, whereas I (R = Cl, NO_2, and OCH_3) exist in distorted boat conformations with φ_1, φ_2, and φ_3 angles equal to, respectively, 30, 40, and 0; 30, 40, and 45; and 40, 60, and 30°. Because of the low degree of informative character of the UV spectra of acids I and V (R = COOH), the spectra of their methyl esters were studied [3].

The higher values of the φ_i angles in I (R = NO_2, OCH_3) are probably due to an increase in the plane of the ring of the van der Waals radii of the 5-substituents (R) because of the large (~−0.35) negative σ charges (calculated within the CNDO/2 CI approximation from the difference between the total charges and π charges) on the primary atom, which for R = CH_3, CHO, and COOH range from −0.05 to +0.15. In the case of I (R = OCH_3) the large values of the φ_i angles are confirmed by the 3-nm shift of the long-wave band in its UV spectrum to the short-wave region as the temperature is lowered from +25°C to −40°C because of an increase in the percentage of the conformer in which the oxygen atoms are turned to an even greater degree and are removed from conjugation with the aromatic ring. This sort of shift is not observed for I (R = Cl), V (R = Cl, OCH_3), and benzo-1,4-dioxane (I, R = H).

EXPERIMENTAL

The UV spectra of the compounds in ethanol (Table 2) or in hexane (temperature measurements) were recorded with, respectively, Spectromom-202 and SF-16 spectrophotometers. The PMR spectra were recorded with a BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The ratios of the isomers were determined with an LKhM-8MD chromatograph [1], and preparative separation was accomplished by crystallization. The mixture of acids II and III (R = COOH, $R^1 = NO_2$) was chromatographed by means of their methyl esters, which were obtained by treatment of the acids with diazomethane in ether.

Oxidation. A mixture of 1 mmole of II ($R = CH_3$, $R^1 = Br$), 4 mmole of $KMnO_4$, and 10 ml of water was refluxed with stirring for 8 h, after which it was cooled and filtered. The filtrate was acidified with sulfuric acid. In the case of II (R = CHO, $R^1 = NO_2$) 1.5 mmole of $KMnO_4$ was used, and the mixture was refluxed for 4 h. The yields of acids II (R = COOH; R^1 = Br or NO_2) were 29 and 70%, respectively.

Decarboxylation. A mixture of 1 mmole of the corresponding acid and 5 mmole of dimethylaniline was refluxed for 4 h, after which it was chromatographed.

The characteristics of the compounds synthesized for the first time in this research are presented in Table 2.

LITERATURE CITED

1. V. K. Daukshas, G. V. Purvanetskas, L. Z. Balyavichyus, É. B. Udrenaite, and V. L. Gineitite, Khim. Geterotsikl. Soedin., No. 4, 467 (1977).
2. V. K. Daukshas and É. B. Udrenaite, Khim. Geterotsikl. Soedin., No. 9, 1155 (1975).
3. V. K. Daukshas and É. B. Udrenaite, Nauchn. Tr. Vyssh. Uchebn. Zaved. Lit. SSR, Ser. Khim., 18, 98 (1976).
4. V. K. Daukshas, R. S. Martinkus, and S. L. Shilova, Deposited Paper (Lit. NIINTI) No. 255—78.
5. V. K. Daukshas, G. V. Purvanetskas, and G. B. Shebeka, Nauchn. Vyssh. Uchebn. Zaved. Lit. SSR, Ser. Khim., 16, 153 (1974).
6. V. K. Daukshas and É. B. Udrenaite, Nauchn. Vyssh. Uchebn. Zaved. Lit. SSR, Ser. Khim., 17, 119 (1975).
7. R. S. Martinkus, S.-K. L. Dragunene, and V. K. Daukshas, Nauchn. Tr. Vyssh. Uchebn. Zaved. Lit. SSR, Ser. Khim., 17, 115 (1975).
8. K. Fukui and H. Fujimoto, Bull. Chem. Soc. Jpn., 42, 3399 (1969).
9. Ken'Ichi Higasi et al., Quantum Organic Chemistry, Krieger (1965).
10. D. E. Pearson and C. A. Buehler, Synthesis, No. 9, 455 (1971).
11. V. A. Koptyug, Zh. Vses. Khim. O-va., 21, 247 (1976).
12. R. L. Ellis, G. Kuehnlenz, and H. H. Jaffe, Theor. Chim. Acta, 26, 131 (1972).