RELATIVE REACTIVITY OF THE AROMATIC RING IN BENZO-1,3-DIOXOLE, ITS CYCLOHOMOLOGUES AND VERATROLE

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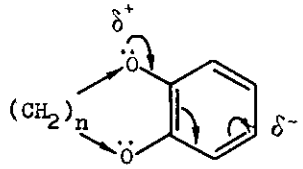
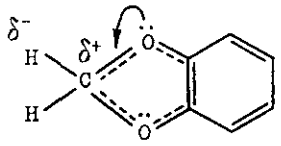
A study of the reactivities of benzo-1,3dioxole (1, n=1), benzo-1,4-dioxane (1, n=2), benzo-1,5-dioxepane (1, n=3) and veratrole (2) is of great interest, since those 1,2-dialkoxybenzenes are essential structural fragments of many natural and synthetic biologically active substances[1,2] and the synthesis of their derivatives often results in the formation of new compounds of practical interest.[2] However, many aspects of reactivity and other properties of compounds 1 and 2 have received insufficient study and the standpoints referred to in publications are of contradictory nature and need additional experimental verification.[2-13]

1. The Problem of Electron-Donating Action of Oxygen Atoms towards the Aromatic Ring

The relative reactivity of the aromatic ring in compounds 1 and 2 has been explained in terms of electron-donating action of the oxygen atoms towards the aromatic ring, interpreting it as a result of several superposed electronic effects, including the positive mesomeric (electromeric) effect which decreases with deviation of alkoxy-groups from coplanarity with the aromatic ring and the opposing inductive interaction of oxygen atoms which decreases with the increase in the number of methylene groups (n) in the heterocyclic ring[3,8,10,11] (Scheme A):



Scheme A



Scheme B

Attempts have been made of quantitative evaluation of this inductive interaction of the oxygen atoms by decrease in bathochromic shift and intensity UV absorption bands, also by decrease in bromination rates of the model compounds - ω,ω^1-diphenoxyalkanes or by decrease in solvolysis rates (in 90% ethanol) of their p,p^1-bischloromethyl derivatives.[11]

The five-membered, coplanar with the benzene ring and possessing an electron sextet, the heterocyclic ring of benzo-1,3-dioxole is considered to be a quasiaromatic one, though to a considerably less extent than the heterocyclic ring of its nitrogen analogue - 1,2-dihydro-1,3-dimethylbenzoimidazole.[3] Its quasiaromatic nature is confirmed by the ability of hydrogen atoms in the methylene-group to exchange for chlorine under the action of phosphorus pentachloride as well as by a great bathochromic shift of UV absorption bands[3] (Table I).

Table I. UV Absorption Spectrum Data (λ_{max} nm, ε) for Compounds 1, 2 and Their Nitro Derivatives (3, R=NO_2) in 95% Ethanol

Compound	1, n=1		1, n=2		1, n=3		2	
1, 2	289	2500	285	2270	275	1250	281	2300
	283	3160	279	2570	270	s	276	2800
	233	4450	220	6170	217	6030	226	7600
3 (R=NO_2)	341	3240	330	7760	308	16600	342	6600
	298	1600	292	7240	-	-	300	4700
	241	5130	242	10500	236	20400	243	8900
	212	4370	215	14450	217	28200	215	10000

It is shown that for a good agreement of the experimental UV spectrum of benzo-1,3-dioxole with that calculated by PPP approximation (particularly concerning the position of the second absorption band) the effect of methylene-group hyperconjugation must be taken into consideration, for example, by the "heteroatomic model".[15,16] The quasiaromatic nature of the heterocyclic ring of benzo-1,3-dioxole is also proved by shortening of the CH_2-O bond length approximately up to the length of the C_{Ar}-O bond.[14] It seems reasonable in this connection to interpret benzo-1,3-dioxole molecule as a heteroaromatic system (Scheme B) including electronic effects of oxygen atoms into the total electronic effect of the heterocyclic ring.

In order to evaluate and compare the electron-donating action of oxygen atoms in

molecules of compounds 1 and 2 were used such experimental data as rates of substitution reactions, physical and chemical constants and spectroscopic characteristics, but they did not lead to similar conclusions.[3-13] This is probably due to the underestimation of the difference between electronic, conformational and other effects in molecules in the ground state and the transition state which is more strongly stabilised by electronic effects than the ground state.

Thus, UV spectrum data[8,17,18] (Table I) and resonance energies of compounds 1 (n=1,2,3) and 2 are 38.4,* 47.8, 38.1 and 47.0 ccal/mole[12], respectively, show approximately similar electron-donating action of oxygen atoms in molecules of benzo-1,4-dioxane,** veratrole and its decrease in the case of benzo-1,5-dioxepane. All this, as well as the fact of proton σ-complex formation by benzo-1,4-dioxane and veratrole in conditions when benzo-1,5-dioxepane does not form it,[13] *** corresponds to a greater deviation from coplanarity with the benzene ring of alkoxy-groups in benzo-1,5-dioxepane[18,19] in comparison with benzo-1,4-dioxane and veratrole.[20-22]

The same sequence (1) of electron-donating action variation of oxygen atoms in molecules of compounds 1 (n=1,2,3) and 2 is demonstrated by such properties of their derivatives as ionization constants (pK_a) of acids 3 (R=COOH) in 5% ethanol equal to 4.50, 4.35, 4.23, 4.43[10], respectively, and hydrogen exchange rates of compounds 3 (R=D,T) in trifluoroacetic acid[6,7] (Table II):

$$1\ (n=1) > 1\ (n=2) \approx 2 > 1\ (n=3) \qquad (1)$$

It has been shown that complex formation with trifluoroacetic acid is realized to a similar extent for all investigated compounds 1 (n=1,2), 2 and, consequently, should not influence the relative rates of hydrogen exchange reactions.[6]

The measurement of alkaline hydrolysis rates of esters 3 (R=COOEt) in 70% ethanol[10] (Table II) has shown relative reduction of electron-donating action of benzo-1,3-dioxole heterocyclic ring in common sequence (2):

$$1\ (n=2) \approx 2 > 1\ (n=1) > 1\ (n=3) \qquad (2)$$

Probably this is due to the increase in inductive interaction of the heterocyclic

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* Resonance energy of benzo-1,3-dioxole may be reduced due to deformation of its benzene ring by fused five-membered ring.[7]

** Inductive interaction of oxygen atoms in benzo-1,4-dioxane molecule must not be of great value.[11]

*** Benzo-1,3-dioxole is not stable in acid medium.

ring oxygen atoms (inductomeric effect) in negatively charged transition state of the given reaction, more requiring stabilization by means of electron-accepting effects (in the Hammett equation $\rho = 2$) in comparison with the above case of ionization of the acids 3 (R=COOH) themselves ($\rho = 1$).[10] The rates of bromination by bromine in acetic acid[8] or CCl_4[23] and nitration by nitric acid in acetic acid[23] of compounds 1 and 2, also solvolysis of their chloromethyl derivatives (3, R=CH_2Cl) in 90% ethanol[8] (Table II) vary in the following sequence (3):

$$2 > 1\ (n=1) > 1\ (n=2) > 1\ (n=3) < 1\ (n=5) \qquad (3)$$

Table II. Relative Reaction Rates of Compounds 1, 2 and Their Derivatives

Reaction \ Derivative of compound	1, n=1	1, n=2	1, n=3	1, n=5	2
Dedeuteration of derivatives 3 (R=D) in CF_3COOH at 25°C[6]	1.00	0.58	-	-	0.64
Detritiation of derivatives 3 (R=T) in CF_3COOH at 30°C[7]	1.00	0.42	-	-	0.31
Detritiation of derivatives 5 (R=T) in CF_3COOH at 30°C[7]	0.13*	0.16	-	-	0.09
Alkaline hydrolysis of derivatives 3 (R=COOEt) in 70% ethanol at 25°C[10]	1.00	0.73	1.43	-	0.83
Bromination of compounds 1 and 2 by bromine in glacial AcOH at 20°C[8]	1.00	0.95	0.42	382	73.6
Bromination of derivatives 5 (R=OMe) by bromine in glacial AcOH at 20°C**	3100	84400	83400	-	14700
Solvolysis of derivatives 3 ($R=CH_2Cl$) in 90% ethanol at 25°C[8]	1.00	0.57	0.10	0.69	6.01

* Reaction rate for isomer 3 (R=T) equals to 1.00.

** Our data. Measurements were made as described in[8]. Reaction rate for benzo-1,3-dioxole equals to 1.00.

Since the substituent enters the positions of the aromatic ring free of steric hindrance it is considered that sequence (3) is caused by the difference in electron-donating action of alkoxy-groups in which the oxygen atoms are in positively charged transition states.[8,10] The references do not give an explanation why the rates of bromination and nitration are higher for veratrole, while the rate of

hydrogen exchange is higher for benzo-1,3-dioxole. Probably due to conformational mobility of alkoxy-groups in veratrole[21] * and in macroheterocycle of compound 1 (n=5), they may become more coplanar with the benzene ring in transition state of reaction as a result of their conjugation with a newly entering substituent provided the latter (halogen, nitro-group, except hydrogen) has the electron-accepting action.

This case (sequence 3) is the result of the increase in the positive mesomeric (electromeric) effect of oxygen atoms in compounds 1 (n=5) and 2 in transition state of reaction. This point of view is confirmed by greater bathochromic shift of UV absorption bands of nitro derivative (3, R=NO_2) of veratrole in comparison with corresponding derivatives of compounds 1 (n=1,2) while the opposite phenomenon is observed (Table I) for nonsubstituted compounds 1 (n=1,2) and 2.

The greater bromination rate of compound 1 (n=5) in comparison with veratrole (Table II) is probably in agreement with the fact that bromination rates for ethoxy- and propoxybenzenes in the same conditions are 3.4-3.7 times higher than that for anisole. However, the known fact of a low iodo derivative yield (3, R=I) in benzo-1,3-dioxole (1, n=1) iodination by iodine in ethanol (in the presence of HgO) in comparison with the yields of iodo derivatives of compounds 1 (n=2) and 2[4] needs further explanation.

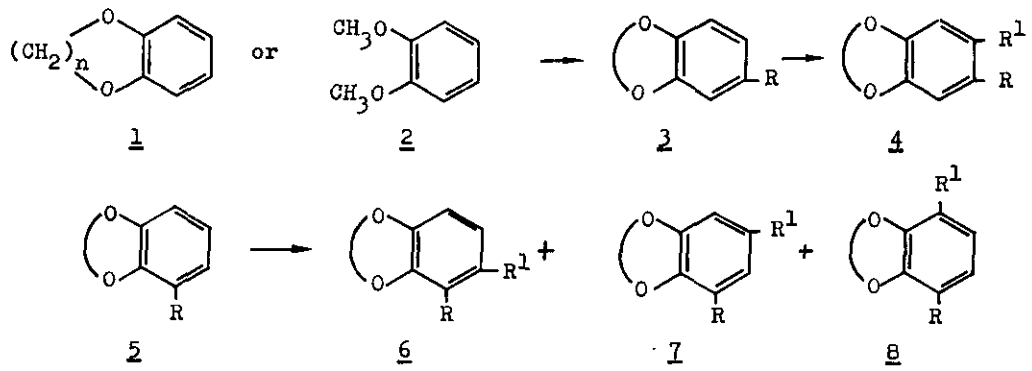
Thus, it follows that interpreting of relative reaction rates and other properties of compounds 1 and 2 is often prevented by superposition of several effects such as electronic, conformational and steric effects, which may appear to a different extent not only due to variation of molecular structure, but also may differ in their ground and transition states. Therefore all the above effects must be taken into consideration while interpreting experimental data including dipole moments of compounds 1 (n=1,2,3) and 2, which are 0.80, 1.42,[9] 1.93[24] and 1.24 D[9], respectively, as well as ionization potentials of compounds 1 (n=1) and 2 which are 8.21 and 8.17 eV[21] respectively.

2. The Directions of Aromatic Substitution

In electrophilic substitution of compounds 1 and 2 almost only p-derivatives (3,4) with respect to alkoxy-groups are formed independent of the types of the

* Potential curve of methoxy-group rotation around the C_{Ar}-O bond in veratrole has no sharp energy minimums.

first (R) and the second (R^1) substituents[2,7,23] which characterizes the 1,2-dialkoxy-group as a strong p-orientant and correlates with many reactivity indices (except the charge value on carbon atoms, calculated by PPP or CNDO/S approximations):[15,16,22,23,25]



1 or 2 → 3 → 4

5 → 6 + 7 + 8

The formation of a small amount of o-isomers (5) in electrophylic substitution is described in the case of benzo-1,4-dioxane[2] indicating some less positional selectivity in comparison with veratrole and in particular with benzo-1,3-dioxole as it has been shown by hydrogen exchange reactions in trifluoroacetic acid. The higher positional selectivity in the case of benzo-1,3-dioxole is explained by an increased role (due to coplanarity of both rings of its molecule) of the positive mesomeric (electromeric) effect of oxygen atoms stabilizing the transition state of p-substitution more than that of o-substitution and also by simultaneous action of the Mills-Nixon effect, decreasing reactivity more in o-position.[7] In reference[6] the reason of reactivity decrease in o-positions and its increase in p-positions of benzo-1,3-dioxole aromatic ring is considered to be due to the quasiaromatic nature of its heterocyclic ring. It seems that the explanations on the basis of the Mills-Nixon effect and the quasiaromatic nature of the heterocyclic ring in the case of benzo-1,3-dioxole do not exclude, but supplement each other.

The reason of lower reactivity of the aromatic ring o-positions and a corresponding increase in positional selectivity of veratrole in comparison with benzo-1,4-dioxane is considered to be due to steric blocking of o-positions by methoxy-groups.[6]

The ratio of partial p- and o-substitution rates of compounds 1 and 2 depends to a great extent on reaction type. Thus, for example, in the case of bromination

of veratrole by bromine in acetic acid this ratio equals to 84[26], but in the case of detritiation in trifluoroacetic acid it decreases to 3.4[7] (Table II).* The decrease in positional selectivity in the latter case may be due to the formation of hydrogen-bonding between trifluoroacetic acid and ether oxygen atoms.[7]

The directions of electrophylic substitution of o-derivatives 5 depend on the type of the available substituent (R) as well as on the type of reaction. Due to a very strong p-orienting action of 1,2-dialkoxy-group only compounds 6 and 7 are formed, as a rule, while their ratio is determined by the action of the available substituent (R). Thus, in bromination electron-donating substituents (R) favour isomer 6 formation, while electron-accepting substituents favour isomer 7 formation, which correlates with stability (total energy) of intermediate σ-complexes. Nitration of compounds 5 occurrs less selectively. The electron-donating substituents (R) favour isomer 7 formation, while the electron-accepting substituents favour isomer 6 formation, which correlates with reactivity indices for reactions with transition state of the "earlier" type: orbital electron distribution at the highest occupied MO (Fukui) and stabilization energy.[15,16,22,23,25] The highest selectivity is observed in the case of veratrole derivatives and the lowest one - in the case of benzo-1,4-dioxane derivatives[15,16,22,23,25,27-30] (Table III).

o-Methoxy derivatives (5, R=OMe) having the 1,2,3-trialkoxy-group as an orientant present a particular case. On nitration they form only compounds 7 (R=OMe, R^1=NO_2), with the exception of benzo-1,4-dioxane derivative, which forms a mixture of all three possible nitro derivatives 6, 7 and 8 (the ratio is 1:8:2.4 for nitration by nitric acid in acetic acid).[25] Halogenation of compounds 5 (R=OMe) gives only halogeno derivatives 6 and 8 (R=OMe, R^1=Cl,Br,I).[15,16,23,25] Increase in the relative amount of isomer 8 from chloro through bromo to iodo derivatives (Table IV) is explained by the steric effect of the methoxy-group, while the absence of isomer 8 in chlorination products of benzo-1,3-dioxole de-

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* Similar regularity is also observed in the case of Claisen thermal rearrangement of allyl ethers 3 (R=OC_3H_5). Benzo-1,3-dioxole and veratrole derivatives generally form compounds 4 (R=OH, R^1=C_3H_5), while the derivative of benzo-1,4-dioxane gives a mixture of equal parts of isomers 4 (R=OH, R^1=C_3H_5) and 6 (R=C_3H_5, R^1=OH).[5]

rivative is explained by the Mills-Nixon effect.[23]

Table III. Relative Amounts (in %) of Products (6; 7, $R^1=NO_2$) of Nitration of Compounds 5 by Nitric Acid in Acetic Acid

Derivative of compound	1, n=1		1, n=2		1, n=3		2	
R	6	7	6	7	6	7	6	7
OMe	0	100	10	70*	0	100	0	100
Me	45	55	45	55	-	-	0	100
Cl	60	40	55	45	-	-	0	100
CHO	100	0	70	30	-	-	85	15
NO_2	100	0	85	15	90	10	100	0

* 20% of isomer 8 was formed.

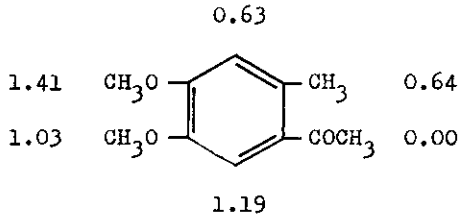
Table IV. Relative Amounts (in %) of Products (6,8)* of Halogenation of Compounds 5 (R=OMe) at 20°C (gas-liquid chromatography data)[23]

Derivative of compound	R^1	6	8
1, n=1	Cl	100	0
	Br	65	35
	I	60	40
1, n=2	Cl	80	20
	Br	15	85
	I	0	100
1, n=3	Cl	50	50
	Br, I	0	100
2	Cl, Br, I	50	50

* Chlorination by chlorine or bromination by bromine in CCl_4 solution and iodination by iodine in 95% ethanol (in the presence of HgO).

The sequence of relative rates for nitration of o-methoxy derivatives (5, R=OMe) by nitric acid in acetic acid corresponds to that (3) for unsubstituted compounds 1 and 2 but does not coincide with the sequence of relative rates for bromination of the same compounds (5, R=OMe) by bromine in acetic acid (Table II),

since in the case of derivatives 5 (R=OMe) the rates of formation of bromination products are substantially influenced by the above steric and other effects. In electrophilic substitution (nitration, halogenation) of compounds 4 very often not hydrogen is replaced by a new substituent, but an already available substituent (R or R^1) such as carboxyl, acyl, alkyl and others.[2,16] The example of nitration of 4-acetyl-5-methylveratrole by nitric acid in acetic acid leading only to acetyl-group exchange for nitro-group shows that such a direction of the reaction may be caused not only by steric effects but it also correlates with the following total energies (in eV) of the intermediate σ-complexes, calculated by CNDO/2 approximation (the total energy of the most stable isomer is assumed to be 0.00 eV):[16]



The nucleophilic substitution of compounds 1 and 2 has not been studied sufficiently, but it has been determined that reaction of compounds 1 (n=1,2) and 2 with n-butyllithium gives o-derivatives with respect to alkoxy-groups (5, R=Li).[7]

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