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THEORETICAL JUSTIFICATION OF STRUCTURE-REACTIVITY CORRELATION OF 1,2-BENZISOXAZOLE 2-OXIDES

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Abstract - A CNDO/2 study was carried out to elucidate features of the electronic structure of substituted 1,2-benzisoxazole 2-oxides and to explain their reactivity. Charge densities fail to account for the observed reactivity and both electrophilic and nucleophilic substitution reactions appear to be orbital controlled. An attempt is made to explain the cleavage of the ring N-O bond that invariably accompanies nucleophilic attack.

INTRODUCTION

Quantum chemical calculations based on semi-empirical methods have been widely employed to further the understanding of the chemical, spectroscopic and physicochemical properties of five- and six-membered heterocycles[1-3]. Surprisingly few heterocyclic N-oxides have enjoyed a similar treatment despite the well-known importance of these ring systems[4]. The interesting properties of substituted 1,2-benzisoxazole 2-oxides (Fig. 1) revealed by our recent reports[5-8] prompted the present theoretical study, using the CNDO/2 Approach[9].

Since the study refers to a set of molecules with the same basic ring structure, it was assumed that structural data obtained by X-ray crystallography[10,11] were generally valid for the series. The presence of other substituents was treated as having no effect on the bond lengths and bond angles of the heterocyclic ring structure. From crystallographic data and assumptions outlined above it transpires that parent molecule, 1a, is planar. The structural parameters of the substituents were those of well -documented systems. The selection of the substituents was based on the expectation that the diverse features of this set of molecules would be best exemplified in the presence of substituents with strong electronic influence.

Several theoretically calculated parameters have been used to assess features of electronic structure and their effect on the reactivity of the system. Among these π-bond orders, bond-overlap population, P_{AB}, charge densities, frontier orbital coefficients and superdelocalisability indices $S_{E(HO)}$ and $S_{N(LU)}$[12] are used for the purpose of the present study.

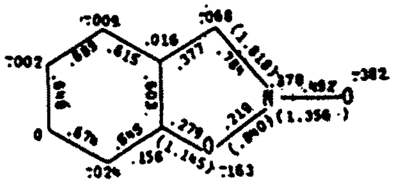
EXPERIMENTAL METHOD

The CNDO/2 programm[13] was adapted for the UNIVAC 1106 EXEC computers. The co-ordinates were chosen so that the ring system (C_s symmetry) lay on the xy plane with the X-axis coinciding with the exocyclic N-O bond. Fixed geometry was assumed for the substituted rings and no attempts were made to minimize the energy of such systems.

RESULTS AND DISCUSSION

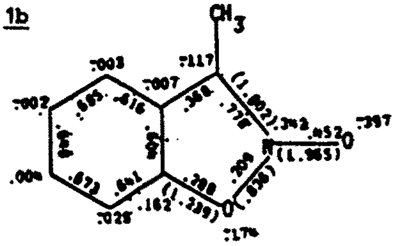
The chemical properties of the 1,2-benzisoxazole 2-oxide system suggest a highly localized dipole and a weak ring N-O bond[8]. The calculations reflect these features (Fig.1). The magnitude

1a



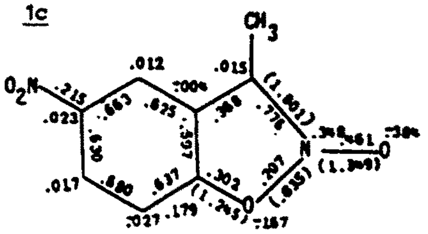
$E_{\mathrm{HOMO}} = -10.47\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.69\mathrm{eV}$
$\mu_{\mathrm{total}} = 4.98\mathrm{D}$

1b



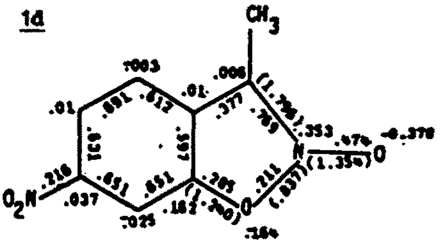
$E_{\mathrm{HOMO}} = -10.02\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.78\mathrm{eV}$
$\mu_{\mathrm{total}} = 5.34\mathrm{D}$

1c



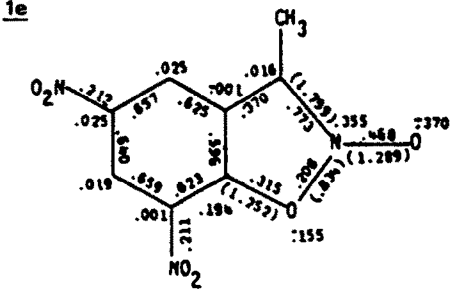
$E_{\mathrm{HOMO}} = -10.66\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.04\mathrm{eV}$
$\mu_{\mathrm{total}} = 0.07\mathrm{D}$

1d



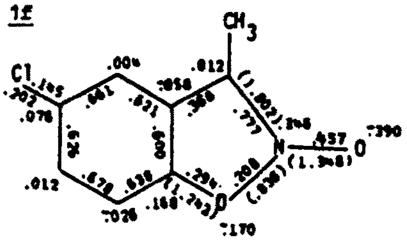
$E_{\mathrm{HOMO}} = -10.67\mathrm{eV}$
$E_{\mathrm{LUMO}} = 0.52\mathrm{eV}$
$\mu_{\mathrm{total}} = 4.82\mathrm{D}$

1e



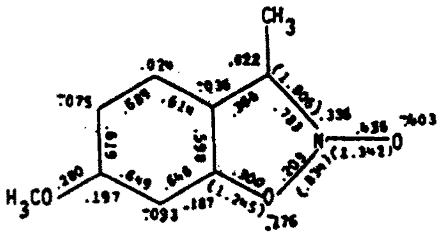
$E_{\mathrm{HOMO}} = -11.21\mathrm{eV}$
$E_{\mathrm{LUMO}} = 0.06\mathrm{eV}$
$\mu_{\mathrm{total}} = 4.85\mathrm{D}$

1f



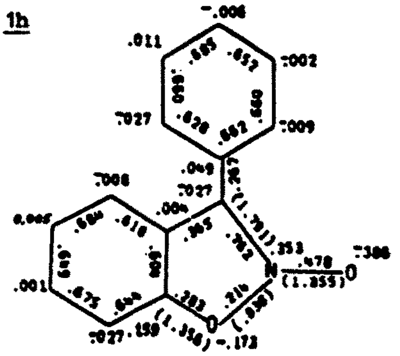
$E_{\mathrm{HOMO}} = -10.33\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.41\mathrm{eV}$
$\mu_{\mathrm{total}} = 2.93\mathrm{D}$

1g



$E_{\mathrm{HOMO}} = -9.78\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.86\mathrm{eV}$
$\mu_{\mathrm{total}} = 6.51\mathrm{D}$

1h



$E_{\mathrm{HOMO}} = -9.92\mathrm{eV}$
$E_{\mathrm{LUMO}} = 1.49\mathrm{eV}$
$\mu_{\mathrm{total}} = 4.87\mathrm{D}$

FIGURE 1. Atomic charge distribution (net charge), π-bond orders, bond overlap population (in parentheses), frontier orbital energies and dipole moments of substituted 1,2-benzisoxazole 2-oxides.

of the parameters refers to isolated molecules and may be altered appreciably in the vicinity of reactive species. Since the reactivity of the 1,2-benzisoxazole 2-oxides was investigated in solution[8] intermediates likely to arise from interactions with the surrounding molecules are discussed.

The substantial charge separation between the nitrogen and the exocyclic oxygen atoms (Fig.1) and the relative magnitudes of the HO orbital atomic coefficients of both termini (Table 1) indicate the dipolar nature of the N_2-O_2 functionality. On the other hand, the π-bond orders suggest some partial double bond character in the dipole.

Benzofusion is known to confer stability to the isoxazole and to heterocycles in general[14-16] In fact, the conjugation between the two units brings about both a charge transfer and a mutual polarization, which are modified by the dipole. The latter mainly affects the electron distribution in the heterocyclic unit (Fig. 1). Consequently the ring N_2-O_1 bond is weakened with respect to the deoxygenated molecule, as shown by the lower π-bond orders[16]. Furthermore it compares with the adjacent C-O bond and the most strained bonds in some furoxans[10]. The weak π-bond character of the ring C-O bond indicates an insignificant contribution of the lone pair of the ring oxygen to the aromaticity of the unit. The contribution of the C_3-C_{3a} bond is somewhat larger while the N_2-C_3 is a remarkably localized double bond and compares with those of the carbocycle.

The parameters related to charge distribution demonstrate trends rather than actual changes induced by the substituents in the ring, bearing in mind that not fully optimized geometries were considered (Fig.1). The substituent effects are more pronounced on the polarities of the heteronuclear bonds while the polarity of the weak N_2-O_1 bond remains unperturbed in all cases.

The position of maximum conjugation between the dipole and substituent appears to be C-6 deduced from the extent of π-bond order changes of the exocyclic N_2-O_2 bond. The influence of substituents at C-3, on the π-bond character of the dipole is quite notable (1b, 1h) in the absence of the interfering effects from substituents in the carbocycle. Substitution at C-5 (or disubstitution at C-5 and C-7) seems to affect almost exclusively the π-bond character of the ring C-O bond (1c, 1e and 1f). This suggests an alternative mode of conjugation between the substituent(s) and the lone pair of the ring oxygen.

The calculated dipole moments (Fig.1) were obtained as the sum total of σ and π contributions. In terms of charge distribution, the effect of the nature and position of substitution on the dipole moments is clearly shown in 1c and 1g. The lowest value for the former and the highest for the latter are the result of the stabilizing and destabilizing influence of the substituents respectively.

The energies of the frontier orbitals also appear to be quite sensitive to substituent effects although the reliability of the CNDO/2 method in this aspect is not unquestionably accepted[17]. There is a distinct energy separation between HO and NHO as well as LU and NLU orbitals (Fig.2).

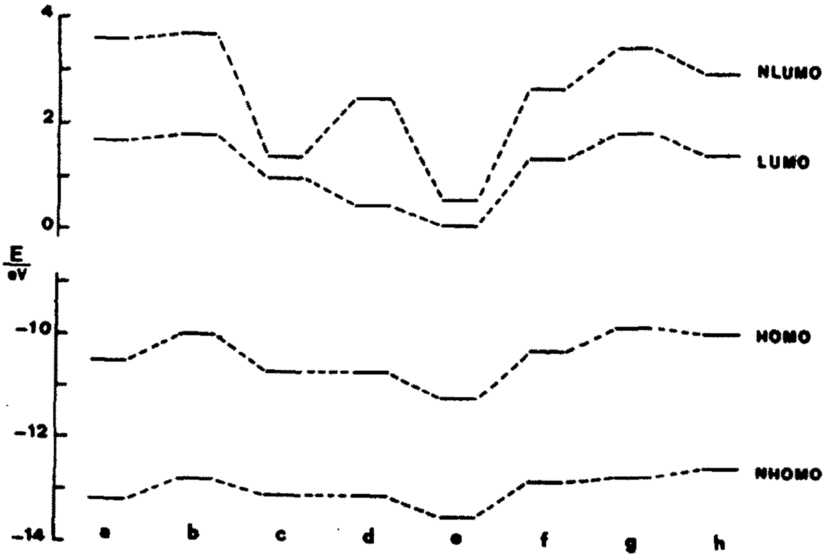
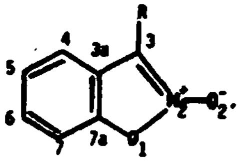


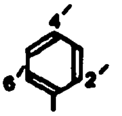
FIGURE 2. Influence of substituents on the frontier orbital energies.

TABLE 1. CNDO/2 frontier orbital coefficients.



R= H, Me, Ph

	1a		1b		1b (protonated form)	
	HO(π)[a]	LU(π)	HO(π)	LU(π)	HO(π)	LU(σ)
N-2	0.255	0.565	0.294	-0.541	-0.194	$0.186s-0.269p_x$
O-2	-0.635	-0.333	-0.651	0.315	0.046	$-0.153p_x+0.171p_y$
O-1	-0.066	-0.165	0.030	0.160	-0.002	$-0.110p_x$
C-3	0.484	-0.387	0.473	0.390	0.423	$-0.516s$
C-3a	-0.234	-0.276	-0.188	0.278	-0.532	$0.322s-0.173p_x+0.158p_y$
C-4	-0.225	0.334	0.100		0.293	$0.108s$
C-5	0.125	0.020	0.261	0.353	0.171	$0.121s$
C-6	0.297	-0.347			-0.479	
C-7	0.297	-0.347		-0.229	0.311	$0.238s+0.110p_x$
C-7a	0.038	0.219	-0.254	-0.185	0.133	$-0.113s$



	1h		1h (protonated form)	
	HO(π)	LU(π)	HO(π)	LU(π)
N-2	-0.292	0.556		-0.213
O-2	0.613	-0.335		
O-1		-0.157	0.131	
C-3	-0.459	-0.363		0.477
C-3a	0.172	-0.196		0.363
C-4	0.203	0.276	0.472	0.127
C-5			-0.493	0.177
C-6	-0.249	-0.273		-0.348
C-7		0.178	0.493	-0.235
C-7a	0.242	0.152	0.510	
C-1′	0.134	-0.187		0.358
C-2′	0.153	0.132		0.177
C-3′		0.133		0.125
C-4′	-0.192	-0.221		
C-5′				-0.342
C-6′	0.204	0.243		0.268

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[a] The basic functions for all the π-type MOs are the P_z AOs. (negligible contributions are indicated where values are not given).

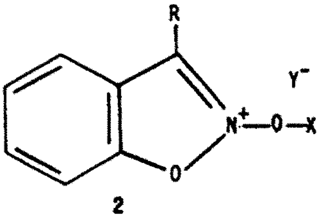
The greatest variation is observed between the LU and NLU orbitals suggesting an enhanced sensitivity of these orbitals to substituent effects.

Fundamental to the chemistry of N-oxides is their electronic "push-pull" character[4]. It is evident from a study of valence bond formalism of the parent molecule **1a** that the $=N^{+}-O^{-}$ group may exert electron-acceptor properties from the ring positions C-3, C-4, C-6 and C-7a while the same positions may also receive electrons. At the same time the ring oxygen may act as electron-donor to the same as well as to the complementary positions (C-3a, C-5, C-7).

Since the parent molecule **1a** is not yet known, the derivatives **1b** and **1h** served as model compounds to elucidate the characteristic features of the reactivity of the system. The question of whether the molecule reacts either in the free base or more complex forms, likely to arise from substrate-reagent interactions, is important in this context.

Based on the proposed mode of activation of the free base, mentioned earlier, charge distribution in **1b** and **1h** predicts susceptibility of positions C-4, C-5 and C-7 towards electrophiles. Position C-3 could have constituted an additional site had it not been sterically hindered. On the other hand the electron deficiency of position C-6 suggests susceptibility of this position towards nucleophiles. A recent ^{13}C nmr study has shown[18] that the extent of deshielding of the ^{13}C nuclei of the carbocycle is in the order C-7a>C-6>C-5>C-4>C-3a>C-7. Thus, from the likely reactive sites the C-6 nucleus is that of the largest downfield shift. However, the experimental results are at variance with these crude predictions. The isolated 6-nitro-derivative of **1b**(**1d**) and the not yet characterized dinitro-derivative of **1h** - we propose that it is the 5,7-dinitro-isomer - suggest either more complex intermediates or, in the case of **1h**, an alternative mode of activation through the ring oxygen.

Frontier orbital theory provides a satisfactory interpretation of chemical reactivity[19]. Furthermore the CNDO/2 MO method has been succesfully used in this context[20]. To account for the observed site selectivity the likelyhood of long-lived intermediates was incorporated in the calculations. Thus, the intermediacy of protonated **1b** and 1h of type **2** (Fig.3) was considered in view of the strongly acidic media employed in the electrophilic substitution reactions. Although protonation barely influences charge densities it has a profound effect on the relative magnitudes of the frontier orbital atomic coefficients and the related electrophilicity indices $S_{E(HO)}$.



R = Me, Ph
XY= nitrating mixture, HCl, Br_2

2

FIGURE 3.

The greater absolute values of these indices (Table 2) in going from the free base to the protonated forms indicate the enhanced susceptibility of the latter towards electrophilic attack.Furthermore, the values of indices for each atom and the extent of localization of the HO orbital suggest that the most probalbe sites for electrophilic substitution of the free base are C-5 in **1b** and C-6 in **1h** while in the protonated form positions C-6 in **1b** and C-5 and C-7 in **1h** are activated. The substitution pattern of the nitration products appears to be in agreement with these theoretical predictions.

The observed site selectivity via the intermediacy of the protonated species can be depicted in electronic terms if it is assumed that, under the reaction conditions[8], protonation does not appreciably influence the donor character of the exocyclic oxygen in **1b** whereas it does so to a significant degree in **1h**. Furthermore the calculations eliminate the phenyl group at the C-3 position as a likely target for electrophilic attack.

Orbital control also seems to be the driving force in nucleophilic substitution in **1b**. Atomic orbital coefficients related to the LU orbital and the values of $S_{N(LU)}$ indices (Table 2) suggest C-5 and to a lesser extent C-7 positions as the reaction sites at the initial stages of nucleophilic attack. Experimentally the reaction with hydrochloric acid yields a product resulting from substitution at C-5 while bromination (an otherwise typical electrophilic substitution reaction) effects 5,7-disubstitution.

TABLE 2. Electrophilicity, S_E and Nucleophilicity, S_N, Indices for the Frontier MO's of **1b** and **1h** (eV^{-1})[a]

	1b		**1b(protonated form)**	**1h**		**1h(protonated form)**
	$S_{E(HO)}$	$S_{N(LU)}$	$S_{E(HO)}$	$S_{E(HO)}$	$S_{N(LU)}$	$S_{E(HO)}$
C-4	$-2.00 \cdot 10^{-3}$		-0.799	$-8.31 \cdot 10^{-3}$	0.102	-0.755
C-5	$-13.60 \cdot 10^{-3}$	0.140	-0.272	$-1.69 \cdot 10^{-3}$		-0.824
C-6			-2.135	$-12.50 \cdot 10^{-3}$	0.100	
C-7		0.059	-0.900	$-0.22 \cdot 10^{-3}$	0.042	-0.824

[a] Calculated on the basis of the relative contributions of the p_z AOs (see Table 1).

The facile rupture of the isoxazole ring that invariably accompanies nucleophilic attack supports the concept of complex intermediates, suggested earlier. It is conceivable that such complexes of type 2 (Fig.3) may be accounted for by interaction of the free base with the reagent.

In the event of formation of these intermediates, though not clearly evident from the existing data, the susceptibility of the ring towards the incoming nucleophile will be enhanced. The resulting HO orbital of the substrate would have a considerable contribution from the original LU orbital, of antibonding character with regard to the weak ring N_2-O_1 bond, thus, inevitably leading to the cleavage of the latter.

It may, thus, be concluded that the reactivity of 1,2-benzisoxazole 2-oxide towards either electrophiles or nucleophiles, as shown from the data of **1b** and **1h**, appears to be dictated by the intermediacy of complexes of type 2.

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