Molecular Orbital Study of Hydride-Transferring Ability of

Benzodiheterolines as a Basis of Synergistic Activity

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A molecular orbital study of the benzodiheterolium ions using the ω -technique reinforces the postulated mechanism of hydride transfer as an explanation of the inhibition of the metabolism of some pesticides

Gertain substituted benzodiheterolines, such as piperonyl butoxide and sesoxane, inhibit the metabolism of carbamates and other pesticides (Hennessy. 1965). Possible mechanisms include the transfer of a hydride ion from the benzodiheteroline (I) to yield the corresponding cation (II). The resulting



positive charge at the methinylium carbon atom in II is delocalized; hence, the benzodiheterolium cations are 10 π -electron pseudoaromatic systems. Thus, a study by simple molecular orbital methods (Salem, 1966; Streitwieser, 1961) provides information about the π -electron distribution in these cations. From reactivity indices insight is gained concerning the possibility of hydride transfer and the relative inhibitory effectiveness of the benzodiheterolines. Since simple molecular orbital calculations have limited value especially when the molecules contain atoms other than carbon, significance is placed on trends in the calculated values rather than on the absolute numbers calculated. The work reported here is an initial study of the following benzodiheterolium cations: benzodioxolium (III), benzimidazolium (IV), benzodithiolium (V), benzoxathiolium (VII), benzoxazolium (VIII), benzothiazolium (IX), benzotropylium (X), 1-benzopyrylium (XI), quinolinium (XII), and 1-benzothiopyrylium (XIII). The carbon analog of these systems, the indenyl anion (VI), was also included in this study.

by the benzodiheterolines. The heteroatoms were N—H, O, S, and their π equivalent, C—C. Electron or hydride acceptor activity at the methinylium carbon is greatest when one of the heteroatoms is O.

MOLECULAR ORBITAL CALCULATIONS

 ω -Technique (Streitwieser, 1960; Wheland and Mann, 1949) calculations without overlap were made. The iterations were continued until the atomic charges were self-consistent to two decimal places. Initial values for the iterative procedure were calculated by the simple Hückel method. Auxiliary inductive parameters were used in calculating the coulomb integrals of the carbon atoms adjacent to the heteroatoms. The heteroatom parameters used in the following formulas (Higasi *et al.*, 1965) are given in Table I.

$$\alpha_x = \alpha_c + h_x \beta_{cc}$$
$$\alpha_{c'} = \alpha_c + \sum_x \delta_{c'x} \beta_{cc}$$
$$\beta_{cz} = k_{cz} \beta_{cc}$$

Sulfur atoms were treated in two ways. One calculation excluded d-orbital participation while the other, following Longuet-Higgins (1949), included it. Calculations involving the Longuet-Higgins model are labeled by the cation number followed by A—for example, benzodithiol-ium V-A.

All calculations were performed on an IBM 1620. The ω -technique program is a modification of one written by Morris (1966).

RESULTS

The charge densities and bond orders of the benzodiheterolium ions resulting from the ω -technique calculations are diagrammed in Figure 1 along with their structures. Table II lists the results of calculations done by other authors on some of these systems. Streitwieser and Brauman's values for benzotropylium (X) and the indenyl anion (VI) (1965) were calculated by the simple Hückel method. These values initiated the ω -technique calculations made on X and VI in this study. Brown and Heffernan's calculation on benzimidazolium (IV) (1956) and Zahradnik *et al.*'s calculation on benzodithiolium (V)

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	Table I.	Parameter Values Us	ed in ω-Techniq	ue Calculations
Heteroatom X or Y	h_x	k_{cx}	$\delta_c \cdot_x$	Reference
–-N—	1.5	0.8	0.15	Streitwieser, p. 135 (1961)
0	2.0	0.8	0.2	Streitwieser, p. 135 (1961)
—S—	1.0	0.7	0.1	Zahradnik, p. 10 (1965) $\{k_{cx} \text{ is an average of those in Zahradnik (1965)}\}$
S- as -fg (Longuet- Higgins)	$\begin{array}{l} h_f = 0\\ h_g = 0 \end{array}$	$k_{cf} = 0.7$ $k_{cg} = 0.7$ $k_{fg} = 1.0$	· · · · · · ·	Zahradnik, p. 9 (1965) k values are averages of those in Zahradnik (1965)]
$\omega =$	1.4			Ettinger (1964) Kier and Roche (1966)

Table II. Some revious Calculations of Benzoumeteronum tons					
System	Position	Charge Density	Bond	Bond Order	Reference and Notes
7	1	1.251	1-2	0.659	Streitwieser and Brauman (1965)
	2	1 111	1-8	0.565	Streitwieser und Bruuman (1965)
	6	1 059	5-6	0 595	No 9 2 5 53
$()$ $(-)$ \rangle^2	7	1 034	6-7	0.723	Simple Hückel
5	8	1.098	7-8	0.553	Shiple Huckel
\bigvee , \bigvee	Ū	1.090	8_9	0.486	
ví			0 7	0.400	
6 1	1	0.813	1-2	0.673	Streitwieser and Brauman (1965)
2	2	0.921	1-10	0.550	
	3	0.818	2-3	0.629	No. 11.2.6.94
() (+) ⟩ 3	8	0.953	7-8	0.601	Simple Hückel
7	9	0.969	8–9	0.716	
	10	0.932	9-10	0.561	
5			10-11	0.489	
Х					
<u>~</u> н. н. н.	1	1 52			Brown and Heffernan (1956)
	2	0.81			Brown and Henerhan (1990)
() $(+)$	6	1.03			
	7	1.03			Simple Hückel with $h_{\rm eff} = 1.0$
3 9 3 N'	/ 8	1.03			Simple flucker with $n_{\rm N} = 1.0$
₄ ³ `H 1V	0	1.01			
	a) 1	1 739	1-2	0 584	Zahradnik <i>et al.</i> (1960)
۰ · · · · · · · · · · · · · · · · · · ·	2, 1	0 704	1-8	0.467	Lumaanna er un (1900)
	6	0.970	5-6	0.622	Simple Hückel with overlap using
	7	0.986	6-7	0.704	Longuet-Higgins model for
, s	8	0.953	78	0.601	sulfur
4	Ū	0.755	89	0.534	Sunu
			0)	0.554	
v	b) 1	1 796	1-2	0.507	$S_{1} = S_{2} = 0.25$
	2	0.526	1-8	0.343	$S_{cc} = S_{ss} = 0.25$ $S_{cc} = kS_{cc}$
	6	0.920	1-0 5-6	0.641	$a_{cs} = \pi S_{cc}$
	7	0.981	5-0 6-7	0.684	b) $k = 0.8$
	/ 8	0.909	7_8	0.004	$0) \ \kappa = 0.0$
	0	0.9/1	/0 8 0	0.027	
			0-9	0. 374	

Table II Some Previous Calculations of Reprodibaterolium Ions

(1960) are not in agreement with the simple Hückel calculations used to initiate the ω -technique calculations in this study because of the different choice of parameters.

The total π -energy, the Wheland localization energy, and the charge density on C-2 are given in Table III. For ease of discussion the cations are grouped in this table in the following way. Group 1 consists of cations in which both heteroatoms are the same. In Groups 2 through 5 one of these heteroatoms, X, is kept constant while the other, Y, is varied.

DISCUSSION

These studies indicate that there has been a shift of π -electrons from the six- to the five-membered ring. The size of this shift varies with the systems studied ranging from 0.02 to 0.30 electron, as seen from the charge



Figure 1. Charge densities and bond orders of benzodiheterolium ions, ω -technique

density values in Figure 1. Such a shift is not unexpected in view of the electronegativity of the heteroatoms in the five-membered ring coupled with the increased electronegativity of C-2. Simple Hückel calculations without overlap do not show a π -electron shift to the five-membered ring. Confer, for example, Brown and Heffernan's calculation (1956) of benzimidazolium (IV) in Table II. Thus, the ω -technique seems to be an improvement over the simple Hückel approach in calculating charge densities.

The electron density at C-2 is sensitive to the adjacent bonded atoms, and varies with the electronegativity of these atoms. In any group where one heteroatom, X, is constant, q_2 is largest when Y is C—C, and smallest when Y is O. This follows because the electronegativities vary in the reverse order, and the parameters reflect electronegativities (Streitwieser, 1961).

Ionization potentials of the electrons involved in the

 π -system are used to measure the ease of π -electron removal (Streitwieser, 1961). With the exception of C=C, the heteroatoms contribute lone pair electrons to the π system. Hinze and Jaffe (1962) list the following ionization potentials for the lone pair electrons in valence states appropriate for the systems studied. These potentials show

N tr tr tr
$$\pi^2$$
 I.P. _{π} = 11.96 eV
O tr tr tr² π^2 I.P. _{π} = 15.30 eV
S tr tr tr² π^2 I.P. _{π} = 11.64 eV

that the ease of removal of the lone pair electrons follows the order S > N > O. The ω -technique charge density at C-2 reflects this property through delocalization of the lone pair heteroatom electrons, which varies with the ionization potentials of the lone pairs involved. The smaller the ionization potentials on the heteroatoms, the

	Table III.	Energies and	Charge Dens	ities
Group	o Cation	$\begin{array}{c} {\rm Total} \ \pi \\ {\rm Energy,} \\ \beta \end{array}$	Wheland Loc. Energy, β	Charge Density, q_2
1	X	15.947	3.083	0.850
	IV	18.142	3.203	0.722
	III	19.892	2.959	0.674
	V	15.998	3.174	0.745
	V-A	14.599	2.170	0.745
2	XII IV VIII IX IX-A	17.04518.14219.02117.06816.369	3.133 3.203 3.084 3.187 2.675	0.815 0.722 0.704 0.734 0.739
3	XI	17.912	3.011	0.812
	VIII	19.021	3.084	0.704
	III	19.892	2.959	0.674
	VII	17.963	3.083	0.715
	VII-A	17.217	2.352	0.717
4	XIII	15.995	3.135	0.821
	IX	17.068	3.187	0.734
	VII	17.963	3.083	0.715
	V	15.998	3.174	0.745
4-A	XIII-A	15.290	2.645	0.815
	IX-A	16.369	2.675	0.739
	VII-A	17.217	2.352	0.717
	V-A	14.599	2.170	0.745
5	X	15.947	3.083	0.850
	XII	17.045	3.133	0.815
	XI	17.912	3.011	0.812
	XIII	15.995	3.135	0.821
	XIII-A	15.290	2.645	0.815

larger the electron density at C-2 indicating a greater delocalization. In each group the q_2 values in ions where Y is N or S are close to each other and greater than the q_2 value in the ion where Y is O. For example, in Group 2 of Table III q_2 for cation VIII is 0.704 while for cations IV and IX it is 0.722 and 0.734, respectively. Thus, from the aspect of charge densities on the cation, electron or hydride acceptor activity at C-2 in cations where Y is O is expected to be greater than when Y is N or S (Hennessy, 1965).

Since equilibria studies involve products and reactants, the π -energy of the benzodiheteroline being formed must also be considered in some way when discussing reactivity. Wheland localization energies for C-2 afford one way of doing this and show the same order of reactivity toward electron or hydride donors (Brown, 1952; Wheland, 1942). The similarity between the formation of a Wheland intermediate and a benzodiheteroline formed from the corresponding cation is noted in Figure 2.

The smaller the localization energy for the positive charge at C-2, the greater the ease of hydride acceptance at this site. These localization energies vary in all but one of the groups in the following order: $O \ll S < N$. Group 5 of Table III is the exception, where X is C==C. This order of localization energies shows oxygen-containing cations as more reactive toward hydride donors than the corresponding sulfur- or nitrogen-containing species. The nitrogen-containing species are least reactive. This reflects the order of synergistic activity found experimentally among the benzodiheterolines (Hennessy, 1966).



Figure 2. Comparison of Wheland intermediate and benzodiheteroline formed from benzodiheterolium cation

Thus, the isolated molecule approximation—i.e., the use of charge densities—and localization theory are in accord with Brown's rules (1952) in predicting C-2 to be the position of greatest electron or hydride acceptor activity. This has been shown experimentally for V and VII (Soder and Wizinger, 1959a,b; Wizinger and Durr, 1963).

The use of the Longuet-Higgins model places more electron density on sulfur than do calculations in which d-orbital participation is neglected. This increase is such that within each group there is a greater electron density on the Y = S atom than on the Y = O atom of the related compound. For example, in Figure 1, in comparing benzoxazolium (VIII) with benzothiazolium (IX-A) the charge density on the sulfur in IX-A is greater than the charge density on the oxygen in VIII. It is unlikely that this actually is the case. This reflects the difficulty of incorporating d-orbital participation in the sulfur π -bonds by means of the Longuet-Higgins model in a simple ω -technique calculation (Orloff, 1963).

Values for the lowest empty molecular orbital (LEMO) resulting from the ω -technique calculations are given in Table IV. The four oxygen-containing cations have positive LEMO orbital energies. As such, these are ready electron acceptors. With electron donors of low highest occupied molecular orbital energies they may readily form charge transfer complexes (Nepras and Zahradnik, 1964).

Table IV. Orbital Energies of Lowest Empty Molecular Orbitals in Units of β, Bonding Orbitals Have Positive Values		
Cation	LEMO	
III	0.165	
IV	-0.046	
v	-0.124	
VI	-1.004	
VII	0.013	
VIII	0.059	
IX	-0.086	
Х	-0.055	
XI	0.084	
XII	0.009	
XIII	-0.016	

From the above discussion of the cation localization energies and charge densities at position 2, these simple molecular orbital calculations reinforce the postulated mechanism of hydride transfer. As noted previously (Hennessy, 1965), NAD+ or NADP+ could ultimately act as the hydride acceptor in the biological oxidationreduction process. The localization energies also indicate the oxygen containing cations should be more effective in inhibiting the metabolism of certain pesticides than should the corresponding nitrogen or sulfur moieties.

Calculations using other parameter values and involving sigma electrons are now in process.

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