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Electronic Molecular Pharmacology: The Benzothiadiazine Antihypertensive Agents

I. Pharmacological Aspects of Tautomerism and Conformation

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SUMMARY

Extended Hückel theory molecular orbital calculations have been carried out on a representative number of antihypertensive benzothiadiazines to determine the role that conformation and tautomeric behavior play in the pharmacology of these compounds, as a preliminary to the multiple regression analyses which form the next paper in this series [A. J. Wohl, *Mol. Pharmacol.* **6**, 195 (1970)]. The results indicate that (a) all compounds studied prefer to exist as the 4-H rather than the 2-H tautomer, in agreement with previous ultraviolet spectroscopy conclusions, and (b) the conformation of substituent groups seems to play a very important role in determining the antihypertensive potency of these substances. The conformation of highly potent cycloalkenyl substituents changes markedly with positional double-bond isomerism, and these changes are reflected directly in the resulting potency.

INTRODUCTION

Within the past few years the availability of high-speed digital computers and all-valence-electron semiempirical molecular orbital methods has placed biologically important substances in the realm of feasible molecular orbital studies. Kier, in particular, has applied one of these methods, the extended Hückel theory of Hoffmann (1), to several compounds of pharmacological interest, with informative and useful results (2–5).

Central to any attempt at quantitative assessment of the relative importance of the many electronic and steric factors which govern drug-receptor interactions, and which consequently determine the degree and type of resulting biological activity, is a knowledge of the actual molecular species involved in the interaction. In this paper, the first of several devoted to numerical analysis of the steric and electronic influences imposed upon a particular receptor system which has been implicated in the antihypertensive mechanism of action of the benzothiadiazines (6–8), the molecular species is determined with respect to tautomerism and conformation by the extended Hückel theory.

The results illustrate the frequent difficulties which more straightforward structure-activity studies may encounter with regard to untenable assumptions of conformation. The results are also informative as explanations for some surprisingly divergent antihypertensive potencies between overtly similar structures.

TABLE 1
EHT parameters

Atom type	Slater orbital exponent	Ionization potential (orbital)	
		eV	
H	1.000	−13.60 (1*s*)	
C	1.625	−21.40 (2*s*)	−11.40 (2*p*)
N	1.950	−26.00 (2*s*)	−13.40 (2*p*)
O	2.275	−35.30 (2*s*)	−17.76 (2*p*)
F	2.600	−38.24 (2*s*)	−20.86 (2*p*)
S	1.818	−20.08 (3*s*)	−13.32 (3*p*)
Cl	2.033	−25.23 (3*s*)	−13.34 (3*p*)

METHODS

The molecular orbital formulation of Hoffmann (1) was employed in the studies to be reported in this and the following paper (9).

EHT[1] calculations were carried out exactly as described by Kier (2). The parameter values employed involved a larger set than was described in the above publication, and are shown in Table 1. All values for ionization potentials are from Hinze and Jaffé (10).

The version of EHT used in this study is that offered by the Quantum Chemical Program Exchange of Indiana University (QCPE) and is available from this organization as QCPE 64. It is able to accommodate up to 140 orbitals and to handle third-row atoms.

Although no provision is made for other than *s*- and *p*-orbitals in QCPE 64, sulfur 3*d*-orbitals could have been considered through the use of a similar program graciously supplied to the author by R. Hoffmann. Several authors (11–13) have proposed that the sulfur atom, when attached to electronegative ligands (as is the case in the benzothiadiazines), may undergo a contraction of the diffuse 3*d* radial functions compatible with chemical bonding. Sulfur 3*d*-orbitals were not considered in this study, because the results of several calculations with 3*d* inclusion did not appreciably change either the charge distribution on the molecule (except for the sulfur charge) or the order or energy of the bonding orbitals. Furthermore, since the SO_2 grouping is a consistent feature of the compounds under study, it was felt that the absence of 3*d*-orbital inclusion could be related by a simple scaling factor to a similar series of calculations with such inclusion.

It is also recognized the EHT calculations produce exaggerated charge distributions. Self-consistency within the series of molecules was felt to obviate consideration of this problem as well, since the typical difference in results between EHT and the more theoretically complete CNDO/2 calculations is not the sign but merely the magnitude of charge.

The geometry of the molecule is required as input to the EHT computation. This was provided by a program to calculate Cartesian coordinates (PROXYZ; QCPE 94), using bond length and bond angle information from the compilations of Sutton (14, 15) and from Alléaume and Decap (16).

The molecules treated in this study may assume either of two tautomeric forms (Fig. 1). This tautomerism was initially assumed to possess an equilibrium constant of 1.0 for interconversion of 2-H and 4-H tautomers. Calculations were therefore conducted at equivalent N_2—C_3 and C_3—N_4 bond dis-

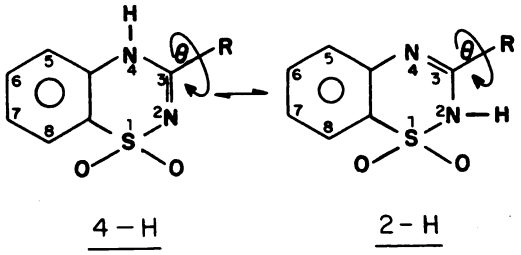


FIG. 1. *Structure of benzothiadiazine 1,1-dioxides under discussion*

The tautomers are identified below each structure. The rotational isomerism of 3-substituted compounds is indicated by the angle θ, representing the rotation of the plane of the substituent relative to the benzothiadiazine ring plane.

[1] The abbreviation used is: EHT, extended Hückel theory.

tances and valency angles (1.35 A; 120 degrees).

Further observations were made with varying bond lengths and angles, but did not differ from those made when the calculations were conducted assuming true interconvertibility, unless unrealistic single- and double-bond values were used for the tautomeric atoms (for numbering of atoms, see Fig. 1).

Rotation about the plane of the benzothiadiazine nucleus may occur for all substituent groups. The angle of rotation, θ (Fig. 1), was varied through the complete range of nonequivalence for all substituents.

Where applicable, that is, with molecules capable of changes in conformation by virtue of substituent rotation, the preferred tautomer was determined at the preferred rotational conformer for each of the tautomers.

RESULTS AND DISCUSSION

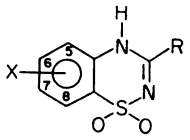
Tautomerism. Calculations were carried out on the 2-H and 4-H tautomers of a number of variously substituted benzothiadiazines. The tautomer possessing the lowest (most negative) total molecular energy was considered, as is usual in such studies, to be the more stable species; the difference between the two tautomers was taken to represent the energy barrier for interconversion. The energy barrier and the equilibrium constant for 2-H $\rightleftarrows$ 4-H tautomerism are given for 21 compounds in Table 2.

The selection of compounds in Table 2 comprises six different 3-position substituents, three different types of nuclei, and a large number of positional and substituent variations in the benzenoid nucleus. Although the degree of 4-H tautomer preference varies widely over the series, the consistency as well as the magnitude of the preferences calculated is convincing demonstration that the benzothiadiazines are likely, in general, to exist as the 4-H tautomer.

Additional calculations were carried out on a few additional compounds for which the N_2—C_3 and C_3—N_4 distances were reduced to 1.31 A when double-bonded, and to 1.39 A when single-bonded. Even with this large separation, tantamount to assuming a considerable energy barrier for $\Delta^{2,3} \rightleftarrows \Delta^{3,4}$ tautomerization, the $\Delta^{2,3}$ or 4-H tautomer was consistently favored,

TABLE 2

Tautomeric stability in benzothiadiazines



R	X	ΔF (4 - H $\rightleftarrows$ 2 - H)	Log $K^{37°a}$
		kcal/mole	
H	H	6.508	4.588
CH_3	H	6.485	4.572
CH_3	5-Cl	6.491	4.576
CH_3	6-Cl	6.448	4.546
CH_3	7-Cl	6.473	4.564
CH_3	8-Cl	6.508	4.588
CH_3	6,7-Cl_2	6.450	4.547
CH_3	7-F	6.476	4.566
CH_3	7-CH_3	6.537	4.609
CH_3	6-Cl-7-CH_3	6.517	4.595
CH_3	6-NO_2-7-Cl	6.476	4.566
H	6-Cl-7-SO_2NH_2	6.615	4.664
CF_3	6-Cl	6.450	4.547
CH_3	5-CH_3-7-Cl	0.424	0.299
H	5-aza	4.985	3.514
H	7-aza	6.705	4.727
CH_3 (sulfoxy)	7-Cl	6.090	4.294
CH_3	6-Cl-thieno	3.927	2.769
Phenyl	6-Cl	5.995	4.227
Δ^1-Cyclopentyl	6,7-Cl_2	6.224	4.388
2-Furyl	6-Cl	5.444	3.838

[a] Equilibrium constant for 2-H $\rightleftarrows$ 4-H conversion at 37°. These values were calculated by the expression $K = -\exp(\Delta F/RT)$, where R is the gas constant, ΔF is the EHT energy difference of the previous column, and T is the temperature. Since the tautomer interconversion will take place without changes in entropy of the system regardless of the tautomerization reaction mechanism, $\Delta H = \Delta F$ and the use of the above equation is justified.

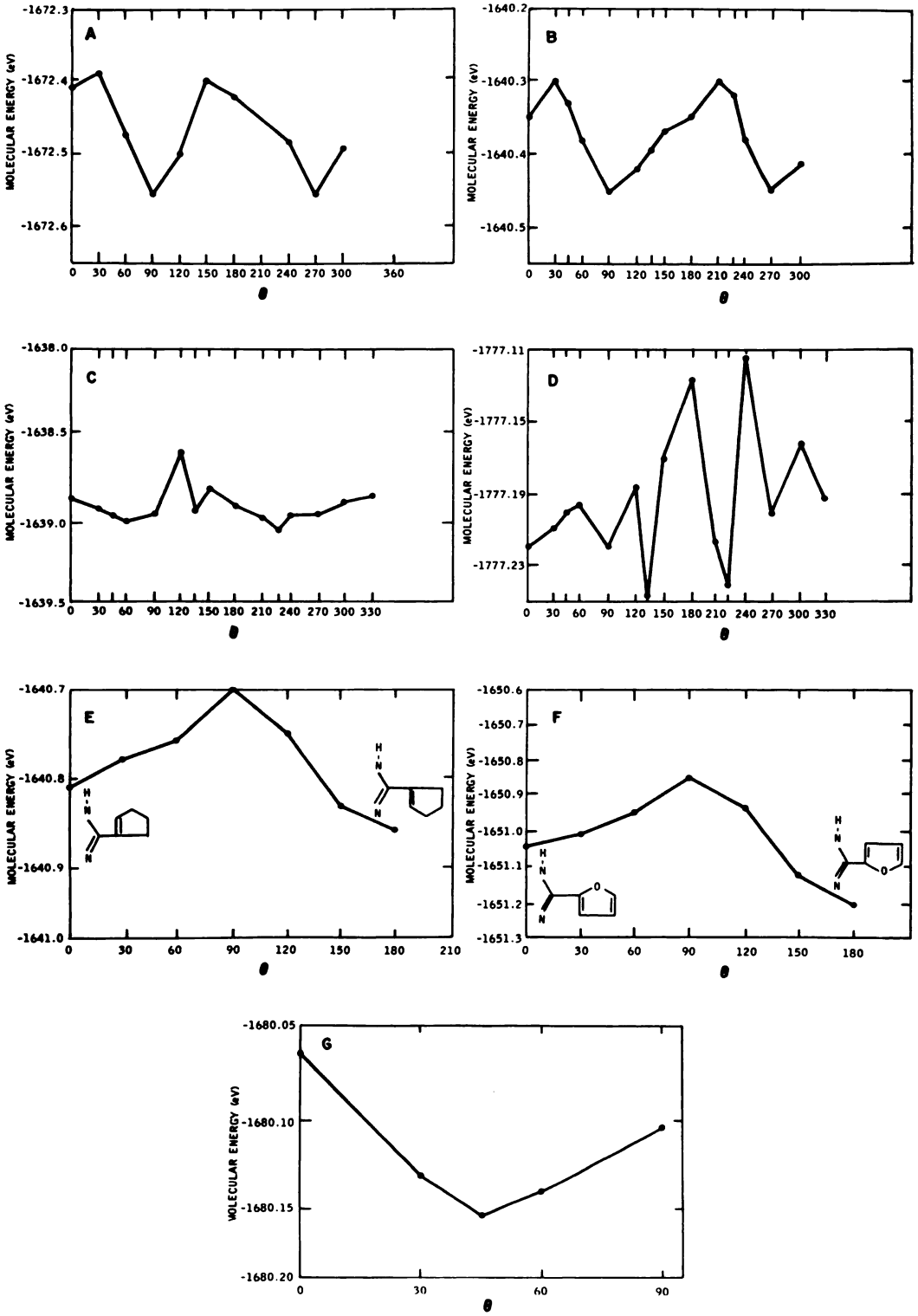

A
MOLECULAR ENERGY (eV)
-1672.3
-1672.4
-1672.5
-1672.6
0 30 60 90 120 150 180 210 240 270 300 360
θ
B
MOLECULAR ENERGY (eV)
-1640.2
-1640.3
-1640.4
-1640.5
0 30 60 90 120 150 180 210 240 270 300
θ
C
MOLECULAR ENERGY (eV)
-1638.0
-1638.5
-1639.0
-1639.5
0 30 60 90 120 150 180 210 240 270 300 330
θ
D
MOLECULAR ENERGY (eV)
-1777.11
-1777.15
-1777.19
-1777.23
0 30 60 90 120 150 180 210 240 270 300 330
θ
E
MOLECULAR ENERGY (eV)
-1640.7
-1640.8
-1640.9
-1641.0
0 30 60 90 120 150 180 210
θ
F
MOLECULAR ENERGY (eV)
-1650.6
-1650.7
-1650.8
-1650.9
-1651.0
-1651.1
-1651.2
-1651.3
0 30 60 90 120 150 180
θ
G
MOLECULAR ENERGY (eV)
-1680.05
-1680.10
-1680.15
-1680.20
0 30 60 90
θ

FIG. 2

TABLE 3

Summary of conformational preference

Group	Rotamer preferred[a]	Energy barrier[b]	Antihypertensive potency[c]
		kcal/mole	
2-Furyl	0	7.8	1
Δ^1-Cyclopentenyl	0	3.6	2
Phenyl	45	2.1	3
1-Cycloheptatrienyl	45	3.0	4
Δ^3-Cyclopentenyl	45	3.9	5
Cyclopentyl	90	4.1	6
Δ^2-Cyclopentenyl	90	4.1	7

[a] Dihedral angle, in degrees, between plane of nucleus and that of substituent.

[b] Difference between rotamer of lowest and highest stability.

[c] Rank of "antihypertensive potency" *in vitro*. See the accompanying paper (9) for full discussion.

although the energy difference had decreased to values centering about 2.4 kcal/mole, for which log $K^{37°} = 1.0$.

Independent chemical evidence for these results is provided by the ultraviolet spectroscopic work of Novello *et al.* (17). This confirmation of the present work obviates, in part, a frequent objection to the applicability of molecular orbital methods (which treat molecules in total isolation) to systems involving solutions, or even within crystal structures.

Conformation. The single bond between carbon 3 of the ring system and attached groups is one about which rotation may occur. The compounds to be discussed below show sizable energy barriers to such rotation.

Figure 2 shows the results obtained with

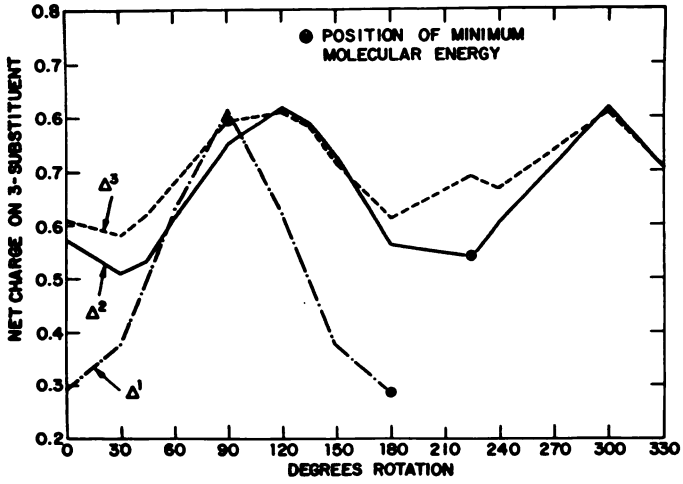


FIG. 3. *Relationship between conformation and regional charge on the substituent group in the three possible isomers of 3-cyclopentenylbenzothiadiazine 1,1-dioxides*

The ordinate shows the net charge summed over the 3-substituent as a function of the angle of rotation shown on the abscissa. It can be seen that the positions of minimum molecular energy and maximum charge coincide only for the Δ^3-isomer, and that, while the maximum positive charges are similar in all three compounds, it is the charge at the equilibrium conformation which relates to biological activity.

FIG. 2. *Conformation of 3-substituted benzothiadiazine 1,1-dioxides*

The ordinate is the computed total molecular energy in kilocalories per mole; the abscissa is the angle of rotation, θ. A. Cyclopentyl: symmetrical structure evenly distributed about the nuclear plane at mutual perpendicularity. B. Δ^3-Cyclopentenyl: altogether similar to the saturated cyclopentyl group. C. Δ^2-Cyclopentenyl: quite different from the foregoing isomer, showing a minimum energy at 225 degrees (dihedral angle = 45 degrees). D. Cyclohepta-2,4,6-trien-1-yl: group exhibits the least hindered rotation, showing a shallow minimum at 135 degrees (45 degrees). E. Δ^1-Cyclopentenyl: this positional isomer is different from both of the other double-bond isomers (B and C) in this study, giving a minimum energy at the coplanar cisoid structure. F. 2-Furyl: very similar to the foregoing. G. Phenyl: the computed minimum is at a dihedral angle of 45 degrees (results summarized in Table 3).

seven different types of 3-position substituents. These results are summarized in Table 3. That these results are likely to represent actual conformations may be inferred from the size of the rotational barriers. Hoffmann (1) calculated the staggered-eclipsed rotational barrier in ethane to be 4 kcal/mole. Microwave determinations of this energy barrier (18, 19) yield values of 2.815–3.030 kcal/mole. While EHT probably exaggerates the magnitude of such barrier determinations, the procedure has yielded useful and often quite accurate conformational analyses in a large variety of chemical systems (20–23).

It is interesting to note the correspondence between biological potency and the preferred rotational isomer, maximum potency being attained when mutual perpendicularity obtains between substituent group and benzothiadiazine nucleus. We may speculate that a segment of the receptor at which these agents function, a "site of attachment," is situated so as to produce maximum interaction when the plane of the 3-substituent group, rather than one or more of its component atoms, is presented to the receptor surface.

It may even be possible to deduce some information relating to the nature of the proposed site with which the 3-substituent interacts. Figure 3 shows that positive charge and conformation are not unrelated, and that the increased group positivity (24), which is simply the summed π-charge over all atoms in the substituent, may be the actual determinant of potency rather than conformation itself. The nature of the interaction would thus seem, at least with regard to this presumed site, to be that of a charge-charge attraction, and so we may tentatively assign an anionic character to the proposed site on the basis of these results.

The implications of these findings with regard to the structure of this possible "receptor attachment site" will be discussed intensively in the accompanying paper (9).

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