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A molecular orbital study of tissue selectivity in β-adrenoceptor blocking agents

HENRY A. GERMER, JR.

University of Texas Medical Branch, Galveston, Texas 77550, U.S.A.

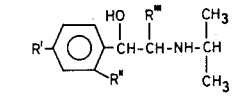
A molecular orbital study has been made on a group of eight β-adrenoceptor blocking agents using CNDO/2 type calculations. Of the group, two are relatively selective for cardiac receptors, two for vascular receptors and four are non-selective. Comparison of the net charges on the β-hydroxyl group oxygens and onium group nitrogens, as well as the O–N distances, reveals small differences. In the traditional view of adrenoceptor agent molecular geometry, the onium group and the aromatic part of the molecule are near the *trans*-configuration for the low energy conformation of all eight molecules. However, when the relation of a primary side chain feature, such as the O–N axis, and the plane of the aromatic ring is examined, noticeable steric differences between the various agents are evident.

The discovery of β-adrenoceptor blocking agents having degrees of tissue selectivity (recently reviewed by Levy, 1972) has led to investigations to determine the molecular characteristics that may impart a degree of selectivity to potential pharmacological agents. Quantum chemical molecular orbital (MO) studies are a means of studying pharmacological agents which is proving useful for this purpose. Kier (1970) suggested that the equilibrium (or lowest energy) geometries of related pharmacological agents, determined by MO calculations, could be correlated with data on their relative biological effectiveness to yield a complementary picture of important receptor site features.

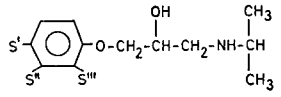
To determine if the differences in β-adrenoceptors may possibly be steric, the equilibrium geometries of the protonated forms of three β-adrenoceptor blocking agents, 1-(4′-methylphenyl)-2-isopropylaminoethanol (I), 4-(2-hydroxyl-3-isopropylaminopropoxy)acetanilide (V), and 1-(4′-methylphenyl)-2-isopropylaminopropanol (VII), were recently determined by Germer (1973) using CNDO/2 type MO calculations. The pharmacological study of these agents by Levy & Wilkenfeld (1969) determined VII to be vascular selective, V to be cardiac selective, while I was essentially non-selective. The conclusion of this limited study was that the equilibrium geometries of these three agents were sufficiently different to suggest that steric differences could exist in the β-adrenoceptors of various tissues.

Since then, the equilibrium geometries of the protonated forms of five further β-adrenoceptor blocking agents have been determined by MO calculations. Of the group of eight drugs studied, two are considered to be cardiac selective, two vascular selective and four non-selective. Table 1 gives the common and chemical names, tissue selectivity and references to the pharmacological studies. The relative tissue selectivity classifications were obtained from Levy (1972) and from the discussions of the pharmacological data contained in the references cited. The purpose of this paper is to present in a summarized form and compare certain features of these

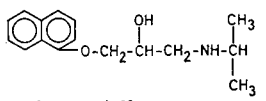
agents. Although detailed information on IV and VII has been previously reported (Germer, 1973), certain results have been updated, represented and are included to facilitate comparisons.



R^I	R^{II}	R^{III}	Compound
CH_3	H	H	I
CH_3	H	CH_3	VII
CH_3	CH_3	CH_3	VIII



S^I	S^{II}	S^{III}	Compound
CH_3CONH-	H	H	V
CH_2:$CHCH_2$-	H	H	VI
H	CH_2:$CHCH_2$-	H	IV
H	H	CH_2:$CHCH_2$-	III



Compound II

Table 1. *Names and tissue selectivities of subject β-adrenoceptor blocking agents.*

Compound	Common name	Chemical name	Selectivity*	Pharmacological studies
I	H29/50	1-(4′Methylphenyl)-2-isopropylaminoethanol	Non-selective	Levy & Wilkenfeld (1968)
II	Propranolol	1-Isopropylamino-3-(1-naphthyloxy)-2-propanol	Non-selective	Black & others (1964)
III	H56/28	1-(*o*-Allylphenoxy)-3-isopropylamino-2-propanol	Non-selective	Åblad & others (1967)
IV	H64/55	1-(*m*-Allylphenoxy)-3-isopropylamino-2-propanol	Non-selective	Åblad & others (1970)
V	Practolol	4-(2-Hydroxyl-3-isopropylaminopropoxy)-acetanilide	Cardiac-selective	Levy & Wilkenfeld (1969); Dunlop & Shanks (1968)
VI	H64/52	1-(*p*-Allylphenoxy)-3-isopropylamino-2-propanol	Cardiac-selective	Åblad & others (1970)
VII	H35/25	1-(4′-Methylphenyl)-2-isopropylaminopropanol	Vascular-selective	Levy & Wilkenfeld (1968); Levy (1967).
VIII	DIMA	1-(2′,4′-Dimethylphenyl)-2-isopropylaminopropanol	Vascular-selective	Levy (1966)

* Classification according to their ability to (1) block both vascular and cardiac β-adrenoceptors (*Non-selective*), (2) preferentially block vascular β-adrenoceptors (*Vascular-selective*), or (3) preferentially block cardiac β-adrenoceptors (*Cardiac-selective*).

Method of calculation

The molecular orbital calculations were performed using the CNDO/2 method of Pople & Segal (1966). The main computer program was written by the author, using the Givens* method for matrix diagonalization. The program uses the six Gaussian representations of Slater atomic orbitals given by O-Ohata, Taketa & Huzinaga (1966) and the incomplete gamma functions resulting from the molecular integrals over Gaussian functions were evaluated by the polynomial representations of Schaad & Morrell (1971).

The energies of the molecules were minimized with respect to rotation about all single bonds between nonhydrogen atoms in the side chains with one exception. For reasons of economy, the angle determining the position of the terminal isopropyl group was not varied in the energy minimization of all the molecules. Rather, it was set to the obvious low energy position which was confirmed by calculations on I and VII.

Bond lengths and bond angles were set to standard values or to the values determined for a given bond in a smaller molecule (*Handbook of Chemistry and Physics*, 1971). Efforts were made to pick values for bond lengths and bond angles determined for bonds in an environment similar to that found in the subject drug molecule.

* Matrix diagonalization program, QCPE No. 62.3, obtained from Quantum Chemistry Program Exchange, Indiana University, Bloomington, Indiana, 47401.

The actual method used to determine the equilibrium geometry is essentially an adaptation of the quantitative conformation analysis techniques employed in physical organic chemistry (Williams, Stang & Schleyer, 1968). To begin, the energy is calculated at 45° increments of rotation about the first bond. From this information, the angle of rotation about the bond which produces the minimum molecular energy is projected, assuming the energy to be a quadratic function of the rotation angle in the vicinity of the minimum. With the first bond set to the angle giving the local energy minimum, the energy is now determined at 45° increments of rotation about the second bond. In the same manner as before, the position of the second bond which minimizes the molecular energy is projected. This process is repeated, in turn, for each of the principal bonds in the molecule. When the set of bond rotation angles which minimizes the molecular energy has been determined using 45° increments of rotation, the entire process is repeated, starting at the first bond. In this case, however, the bond rotations are in 15° increments about the position which produced the energy minimum in the first pass. Minimization techniques such as this are obviously subject to the problem of false minima. To minimize, if not completely eliminate, the possibility of obtaining a false minimum energy conformation, molecular models of the compounds were studied and additional calculations made on conformations which could possibly produce an energy minimum.

RESULTS

To best illustrate major differences found in the calculated equilibrium geometries of the eight drugs studied, a series of diagrams has been made (Figs 1–8). These compare the relation of elements common to all eight molecules, that is, the onium group nitrogen, the oxygen of the β-hydroxyl group, and the centre of the aromatic ring. The diagrams basically illustrate the relation of a plane containing the above three points and the plane of the aromatic ring. In each of these diagrams, the aromatic ring lies in the XY plane. A third plane also shown in some of the diagrams (Figs 3–6) contains the nonhydrogen atoms of the secondary side chain where one larger than a simple methyl group exists. (The atomic coordinates of the protonated forms of compounds II, III, IV, VI, and VIII, in their low energy conformation may be obtained from the author upon request.) For the coordinates of compounds I, V, and VII see Germer (1973).

Also shown in Figs 1–8 are the calculated net charges on the onium nitrogen and hydroxyl oxygen along with the distance between these two atoms. These same net charges and interatomic distances for each compound are listed in Table 2 which also includes the net charge on the *nitrogen bonded* carbon of the terminal isopropyl group.

The group of primary side chain atoms common to all eight of the β-blocking agents studied is shown in Fig. 9. The position of the bond rotation angle equivalent to θ in Fig. 9 has been extensively studied in earlier MO conformation studies of adrenaline-like catecholamines by Kier (1969), Pedersen, Hoskins & Cable (1971) and Pullman, Coubeils & others (1972), and of related α-adrenoceptor agonists by Kier (1968). The position of this particular bond rotation angle may be viewed as determining the *cis-trans*-relation between the onium group and the aromatic ring. In the present study, the methoxy group interposed between the group in Fig. 9 and the aromatic ring would have to be considered as part of the aromatic ring.

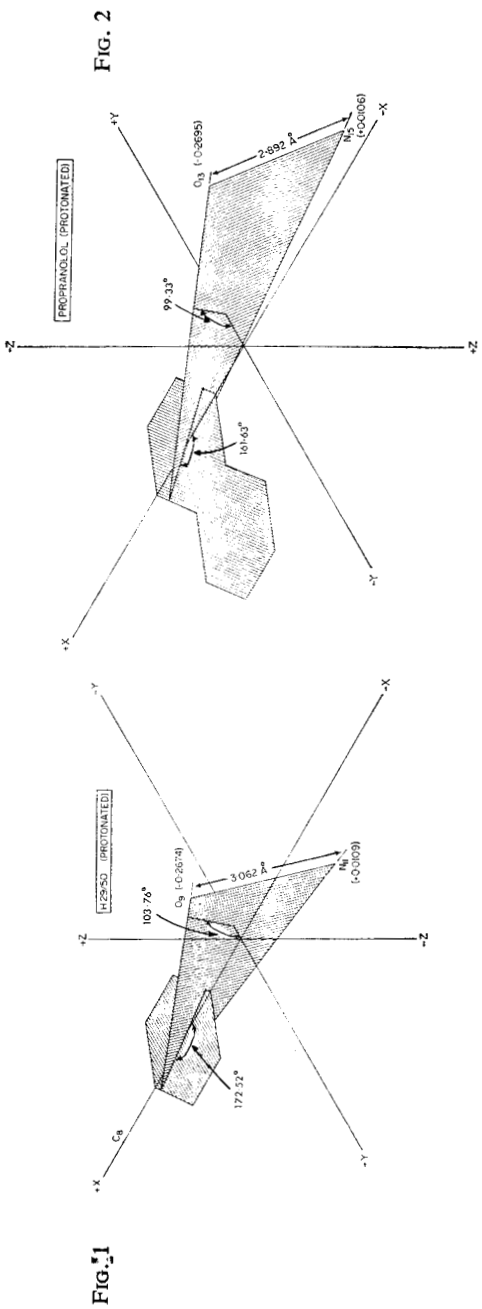


FIG. 2

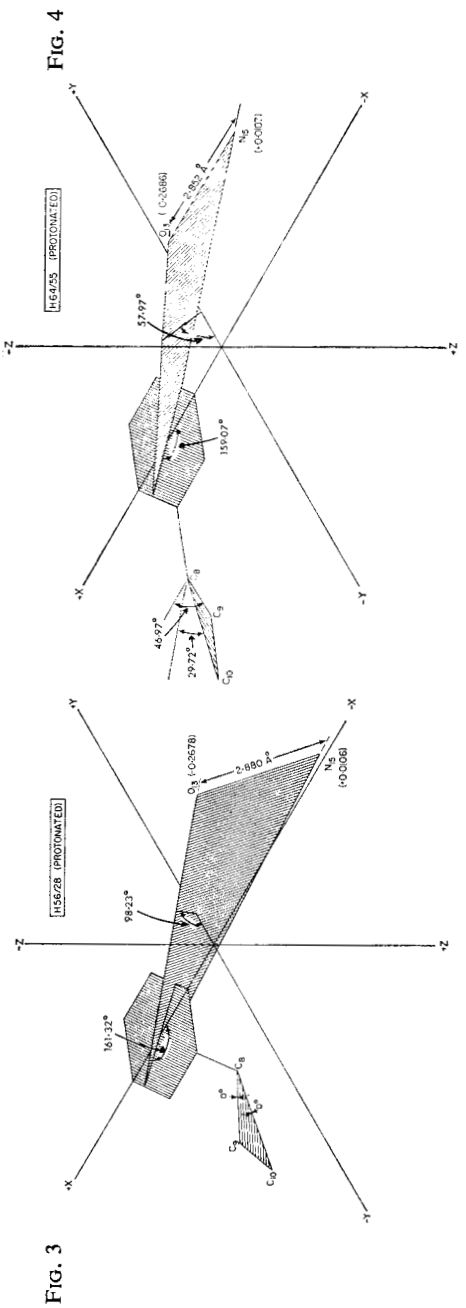


FIG. 4

FIG. 1

FIG. 3

FIG. 1–4. Relation of O, N, and aromatic ring of compounds 1–4 (protonated) in lowest energy conformation.

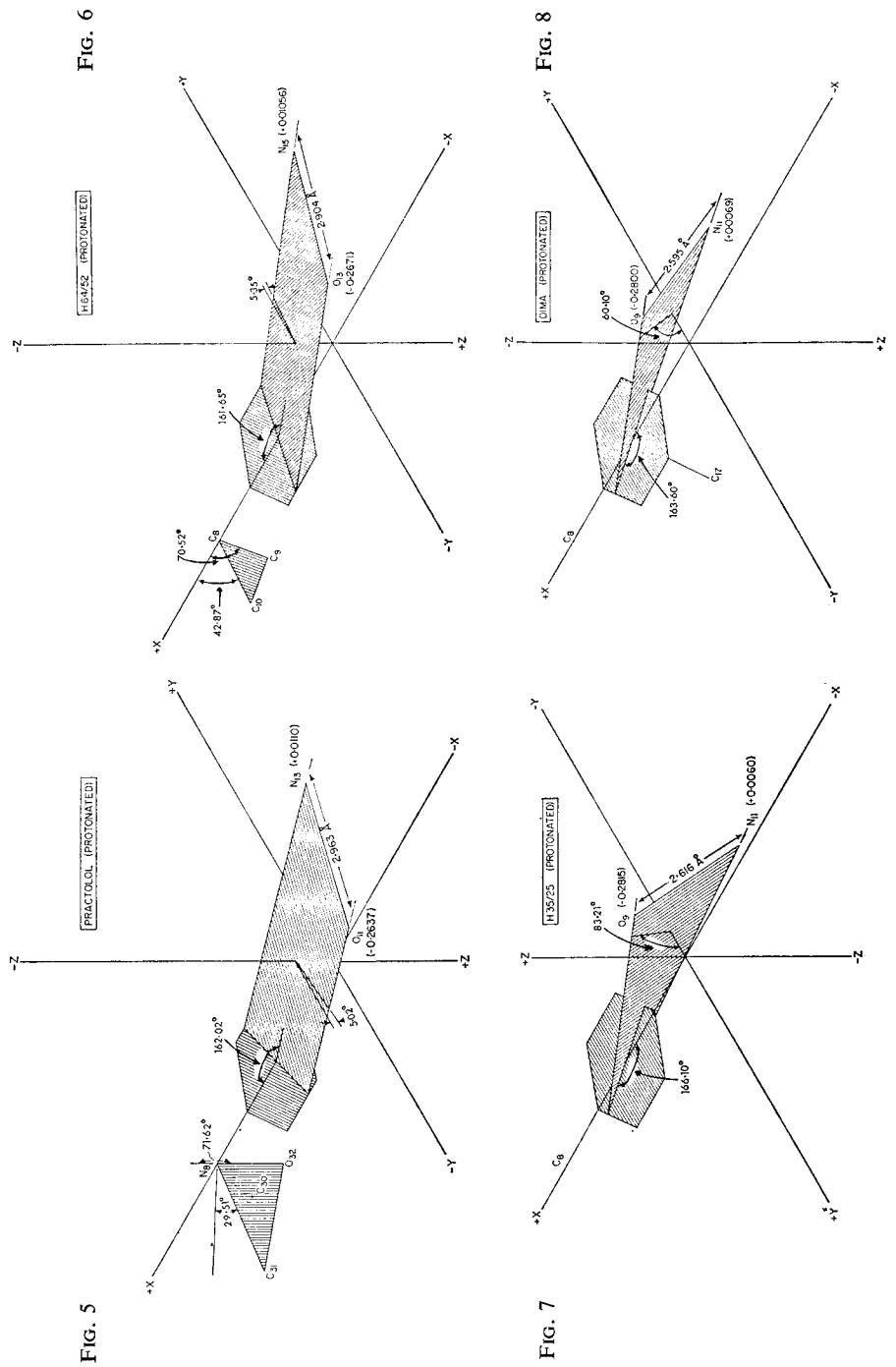


FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 5–8. Relation of O, N, and aromatic ring of compounds 5–8 (protonated) in lowest energy conformation.

Table 2. *Calculated net charges on the hydroxyl group oxygens (Q_O), onium group nitrogens (Q_N), and the nitrogen bonded carbons of terminal isopropyl group (Q_C) along with the oxygen-nitrogen interatomic distance (R_{O-N}). Net charges given in terms of the electronic charge (e).*

Compound	$Q_O(e)$	$Q_N(e)$	$Q_C(e)$	R_{O-N}(A)
I	—0·2674	+0·0109	+0·1125	3·062
II	—0·2695	+0·0106	+0·1125	2·892
III	—0·2678	+0·0106	+0·1125	2·880
IV	—0·2686	+0·0107	+0·1125	2·852
V	—0·2637	+0·0110	+0·1126	2·936
VI	—0·2671	+0·0106	+0·1126	2·904
VII	—0·2815	+0·0060	+0·1117	2·616
VIII	—0·2800	+0·0069	+0·1115	2·595

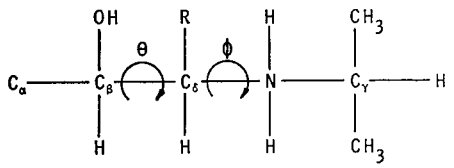


FIG. 9. Group of atoms common to primary sidechains of subject β-adrenoceptor blocking agents. θ and ϕ are bond rotation angles about Cβ—Cδ and Cδ—N bonds, respectively.

In Fig. 9, the bond rotation angle θ is equal to 0° for $C_\alpha C_\beta C_\delta N$ in the planar *cis* conformation. The bond rotation angle ϕ, which determines the position of the terminal isopropyl group, is 0° for $C_\beta C_\delta N C_\gamma$ in the planar *cis* configuration. Positive rotation is clockwise when viewed from the $C_\delta \rightarrow C_\beta$ and $N \rightarrow C_\delta$ directions, respectively. C_α is a carbon of either an aromatic ring or methoxy group, depending on the particular compound. Values for the bond rotation angles θ and ϕ at the equilibrium geometries of the drugs are given in Table 3.

Table 3. *Equilibrium geometry values for the bond rotation angles θ and ϕ shown in Fig. 9.* See text for definitions of O° angles.

Compound	θ (Deg)	ϕ (Deg)
I	159·94	180·69
II	176·36	175·49
III	177·60	175·95
IV	180·41	179·38
V	169·49	177·83
VI	175·20	175·83
VII	208·32	174·36
VIII	211·74	174·69

DISCUSSION

Some contrasting trends in the conformations of the agents can be seen when compared in the manner illustrated in Figs 1–8. In the two cardiac selective agents, V (Fig. 5) and VI (Fig. 6), the O–N axis is rotated to a position above and nearly parallel to the plane of the aromatic ring. In three of the non-selective agents, I (Fig. 1), II (Fig. 2) and III (Fig. 3), and in the vascular selective agents, VII (Fig. 7) and VIII (Fig. 8), the O–N axis penetrates the plane of the aromatic ring. However, the O–N axis apparently penetrates this plane at a somewhat more acute angle in the two vascular selective compounds than in the non-selective compounds. The non-selective

agent IV (Fig. 4) is somewhat harder to categorize in that, although a continuation of the O–N axis would penetrate the aromatic ring plane at an acute angle, the actual O–N axis is rotated above this plane.

On the other hand, the equilibrium geometries may be viewed in the more conventional manner suggested in previous MO studies of adrenergic agents by Kier (1968, 1969) and Pedersen & others (1971). These studies have basically determined whether the onium group is *trans* or *gauche* to the aromatic ring. This relation is determined by the angle of rotation θ around the C_β–C_δ bond of the group of side chain atoms shown in Fig. 9. For discussion purposes, a methyleneoxy group interposed between the ring and the side chain group of Fig. 9 is considered to be part of the ring. The value of θ for the so-called trans configuration is 180°. Examination of the values for θ given in Table 3 shows that all of the β-adrenoceptor blocking agents studied are near the *trans* configuration which is in agreement with the results of most previous MO studies of adrenergic agents. The largest deviation from the *trans* configuration, about 30°, seems to be in the two vascular selective agents, VII and VIII.

Consequently, when viewed in the more traditional manner of describing the equilibrium geometries of adrenergic agents, the geometries of the present group of eight β-blocking agents seem to be in general agreement with the results of most earlier related work by Kier (1968, 1969) and Pedersen & others (1971). The variations of θ, within the group, about the ideal *trans* configuration value do not appear to be obviously correlatable to tissue selectivity, with the possible exception of the two vascular selective agents. However, when viewed as in Figs 1–8, the equilibrium geometries are noticeably different.

The bond rotation angle ϕ (Fig. 9) determines the relation of the terminal isopropyl group to the rest of the side chain. The values of ϕ given in Table 3 appear quite constant for the eight β-blocking agents. The implied consistency of the relation between the terminal group and the rest of the side chain is interesting in light of a recent suggestion by George, Kier & Hoyland (1971) that dispersion type interactions with this alkyl group are responsible for the initial complexing with a β-adrenoceptor. A consistency in the position of the group which in essence determines basic β-activity would seem to support the above hypothesis.

Compounds III, IV and VI are identical except for the position of the allyl group on the aromatic ring. Consequently, Figs 3, 4 and 6 illustrate the effect of moving a secondary chain from the *para* to *meta* to *ortho* position.

Examination of the net charge on the onium group nitrogen, listed in Table 2, shows an extreme consistency which is in agreement with the results of George & others (1971) that the charge on the nitrogen is essentially constant for a given degree of alkyl substitution. However, the absolute values for the charge in the present whole molecule calculations differ somewhat from those in the model compounds studied by George & others (1971). The net charges on the hydroxyl oxygens are also fairly constant with a slightly more negative charge on the hydroxyl groups of the two vascular selective agents, VII and VIII. It is interesting to note the large positive charge which appears on the nitrogen bonded carbon atom of the terminal isopropyl group in the protonated forms of these agents. This is somewhat at odds with the classical view of the location of the positive charge in these molecules.

As regards the O–N distance (Table 2), it is also constant except for some shortening in the vascular selective compounds VII and VIII. This slight difference between VII and VIII and the other six agents, as well as the slight differences in the

net charge on the hydroxyl oxygen, can probably be attributed to the presence of the α-methyl group in VII and VIII. It is tempting to speculate that the α-methyl group is a prerequisite for a vascular selective agent; however, a recent pharmacological study by Levy (1974) with the α methyl analogues of II and V seems to indicate this is not the case.

Thus comparison of the calculated net charges on the onium group nitrogens and β-hydroxyl group oxygens, as well as of the O–N distances, reveals little variation within the group. The *trans-gauche* relation between the onium group and the part of the molecule containing the aromatic ring of the agents in their low energy configuration is found to vary randomly and relatively little about the classical *trans* configuration. This is in agreement with other MO studies involving such drugs. The relation between the terminal isopropyl group and the remainder of the side chain is found to be constant in all eight agents. However, when the plane of the aromatic ring is compared to some universal feature of the primary side chain, such as the O–N axis, noticeable differences are evident within the group. This would seem to suggest that differences in the β-adrenoceptors of various tissues may occur at a distance from the primary point of attachment, assuming that this point interacts with a proton or alkyl group which is on the onium nitrogen of the agonist or antagonist (George & others, 1971).

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