Molecular Orbital Studies on the Mechanism of Drug-Receptor Interaction. 2. β-Adrenergic Drugs. An Approach to Explain the Role of the Aromatic Moiety[1]

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The role of the aromatic moiety of β-adrenergic drugs in the interaction with the receptor was investigated using the quantum mechanical ab initio SCF-MO-LCAO method. The structure-activity relationship was essentially discussed by analyzing the electrostatic molecular potential of three compounds which constitute meaningful portions of isoproterenol, INPEA, and doberol, the first drug having a stimulating activity and the others a blocking one. The results obtained point out the different roles played in the drug-receptor interaction by the various regions of the drugs and they also show that the aromatic moiety influences both the *affinity* and the *intrinsic activity* of the drugs. Indeed, the spatial correspondence among zones with negative potentials, which are localized on the phenyl substitutents of isoproterenol and INPEA and on the phenyl ring of doberol, could contribute to the affinity. On the other hand, the intrinsic activity of isoproterenol might be associated both with the proton-donor tendency of one phenolic OH group and with the wide zone of negative potential which spreads on a large part of the aromatic moiety.

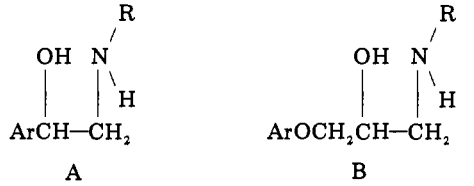
It is generally accepted that pharmacological activity depends on combinations of some factors such as (i) the drug transport through the biological membranes; (ii) the atomic and spatial structure which governs the fit of the drug at a suitable portion of the biophase, the receptor; (iii) the electronic structure which controls the highly specific interaction between the drug and the receptor; and (iv) the subsequent pathway which leads to a measurable pharmacological response. In all these steps quantum pharmacological researches are in principle useful for the development of a rational understanding of the biological history of the drug; however, owing to theoretical and experimental difficulties, the attention of quantum chemists has been mainly devoted to points (ii) and (iii).

Despite the large amount of research by biologists, physiologists, pharmacologists, and chemists, which has attempted to isolate and characterize pharmacological receptors, the exact nature and structure of the receptor sites still remain to be determined.[2,3] Until recently all attempts to delineate their topography and morphology have been based on information indirectly obtained through the study of the action of stimulant or blocking agents.[4] The receptors can be viewed as complex biological entities which are part of the cells and cellular membranes; sites on these receptors are capable of reacting directly and specifically with pharmacologically active substances to produce an observable biological response. The receptors, like the drugs with which they interact, are more or less complex molecules, and, therefore, their effects can be interpreted on the basis of molecular events. An exact understanding of molecular properties, such as charge distribution, polarizabilities, etc., of the isolated drug molecule may help us to obtain indications about its reactivity and in this way learn something about its biological activity. Another approach which may yield information both about the reactivity of a drug and about its interaction with its receptors is the study of the interaction that takes place between the drug molecule, or one of its parts, and a model compound simulating a portion of the hypothetical, active site of the receptor.

Studies of the molecular mechanism of adrenergic drugs and receptors are at present one of the most stimulating areas of pharmacological research, because of the great theoretical and practical importance of biological catecholamines (adrenaline and noradrenaline), as well as of α- and β-adrenergic stimulant (agonist) and blocking (antagonist) drugs, which are those substances that can be related to the biological catecholamines either structurally or on the basis of their pharmacological activity. β-Stimulant drugs are useful as bronchodilatators and cardiac stimulants; β-blocking ones find wide therapeutic application in the treatment of angina pectoris, various cardiac arrhythmias, hypertension, and other cardiovascular disorders.

Here we want to point out the difference between the molecular events through which the adrenergic receptor can be stimulated or blocked. The stimulation is the result of the interaction of the receptor with a drug which is able to bind to the receptor site (i.e., to have an *affinity* for the receptor) and to induce a pharmacological effect (i.e., to have an *intrinsic activity*). The interaction of the receptor with a blocking agent is, on the contrary, a process in which the agent binds to the receptor but is unable to induce a pharmacological effect. In other words, a blocking drug has an affinity for the receptor but lacks the intrinsic activity; its biological effect is, therefore, due to the fact that its occupancy of the receptor hinders the interaction of the receptor with stimulating agents.

The structures of β-adrenergic stimulant and blocking drugs are closely related. With a few exceptions, they are derivatives of ethanolamine (A) or of oxypropanolamine (B). In compounds with the general structure of both A and B, β-stimulant of β-blocking properties are influenced by the nature and position of the substituent or sub-



stituents of the phenyl group or by the nature of the aromatic group. The $CH(OH)CH_2NHR$ moiety, which is present in both types of drugs, should be essentially associable with the affinity.[2,3] It seems to us, therefore, that we must mainly investigate the aromatic moiety of type A drugs and the $ArOCH_2$ region of those of type B to find the molecular differences between β-stimulating and β-blocking agents, which should show why the former have an intrinsic activity and the latter have not.

With this in mind, we decided to carry out a quantum mechanical study of compounds of types A and B with different adrenergic activity, in order to try to explain the

Table I. Test Calculations on the Validity of the Model Compounds. Eigenvalues (au) and Types of Some Molecular Orbitals

	2-Phenylethylamine	Toluene	1-Phenyl-2-aminoethanol	Benzyl alcohol
LUMO	0.2682 (π/ϕ)	0.2693 (π/ϕ)	0.2669 (π/ϕ)	0.2676 (π/ϕ)
HOMO	−0.2662 (π/ϕ)	−0.2658 (π/ϕ)	−0.2653 (π/ϕ)	−0.2663 (π/ϕ)
Second HOMO	−0.2772 (π/ϕ)	−0.2762 (π/ϕ)	−0.2752 (π/ϕ)	−0.2752 (π/ϕ)
Third HOMO	−0.3170 (N)	−0.4199 (σ/ϕ, C7)	−0.3312 (O, N)	−0.3553 (O)

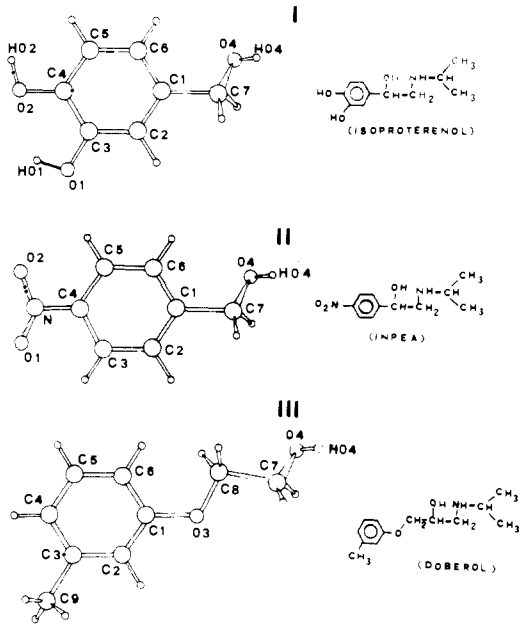


Figure 1. Chemical formulas of isoproterenol, INPEA, and doberol. Conformations and atomic labels of the parent compounds IA, II, and III.

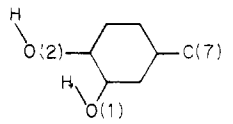
role of the aromatic moiety in the interaction of these compounds with the β-adrenergic receptor.

Computational Details. In this paper three important β-adrenergic drugs were investigated, viz., a β-stimulant drug of type A, isoproterenol, and two β-blocking drugs of type A and B, respectively, INPEA and doberol (Figure 1). As in the present case we are mainly interested in the investigation of the role of the aromatic moiety, and considering that ab initio MO–SCF calculations are too expensive for these large molecules, the actual calculations were performed on some simpler model compounds of the drugs here considered, in order to obtain a reasonable compromise between the reliability of the results and the necessary amount of computational efforts. The model compounds here investigated are (Figure 1) 3,4-dihydroxybenzyl alcohol (I), *p*-nitrobenzyl alcohol (II), and 2-(*m*-tolyloxy)ethanol (III) which correspond to isoproterenol, INPEA, and doberol, respectively. In the model molecules the CH_2NH-*i*-Pr group of the side chain of the drugs is simply replaced by a hydrogen atom. This procedure corresponds to the hypothesis that the role of the portion substituted is the same in the drugs here considered and that different pharmacological responses are therefore due to the different structures of their aromatic moieties, as is confirmed by the fact that the geometry of the 2-aminoethanol side chains of these three drugs has been shown to be the same.[5]

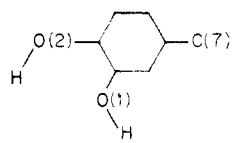
At the end of this section we will report the results of some test calculations on the validity of this procedure.

The molecular wave functions were computed at the level of the ab initio SCF–MO–LCAO approximation, using the minimal STO-3G Gaussian basis set.[6] Standard values of bond lengths and angles were assumed,[7] except for the COC angle of the ethereal group (COC = 118°, according to the best STO-3G geometry of the anisole[8]).

As is well known, the first step in the theoretical study of the structure–activity relationship of complex molecules consists of a conformational analysis in order to select the preferred rotamers whose reactivity features deserve further investigation. At present, several experimental[5,9-15] and theoretical[1,16-21] studies are available on the internal rotation of the side chain of adrenergic compounds. Through a careful analysis of these conformational data we have selected a conformation of this molecular region, defined by the torsion angles τ[C(2)–C(1)–C(7)–O(4)] = τ[O(3)–C(8)–C(7)–O(4)] = 160° and τ[C(1)–C(7)–O(4)–HO(4)] = τ[C(8)–C(7)–O(4)–HO(4)] = 141°, with the O(3), C(8), and C(7) atoms in the ring plane, in the arrangement shown in Figure 1. The selected arrangement of the alcoholic OH bond, coming out of the aromatic region, agrees with the experimental results obtained from isoproterenol[5] and ephedrine,[9] which indicate the binding possibility of OH group by reinforcing the interaction between the onium head of the drug and an anionic receptor site. As to the aromatic moiety, the two OH groups of I are in the ring plane in an intramolecular hydrogen-bonded arrangement, according to the experimental results obtained from ortho-substituted phenols in gas phase and in solution.[22] These are two possible forms for I, namely, IA and IB. The aromatic reactivity does not substantially



IA



IB

depend on forms IA and IB but on different aromatic substituents (see later on). In our work only structure IA will be considered in full detail as this is fully sufficient to give a general idea of the aromatic reactivity pattern of I; suitable information on IB will be added when required.

At this point, we will return briefly to the validity of a model of a pharmacological compound which contains only a portion of the atoms by reporting the results of some test calculations on a few prototype systems, using both the entire pharmacological compound and just the portion corresponding to the model. The entire compounds here investigated are 2-phenylethylamine and 1-phenyl-2-aminoethanol and the corresponding models are toluene and benzyl alcohol, respectively. The STO-3G basis set was used together with standard values of bond lengths and angles. The STO-3G minimum-energy conformation was selected for 2-phenylethylamine,[20] with torsion angles τ_1, τ_2, and τ_3 equal to 90, 180, and 60°, respectively. In toluene one C–H bond of the methyl group is perpendicular to the ring plane and the selected conformation of 1-phenyl-2-aminoethanol and of benzyl alcohol is the same as that of compound I. For these test molecules, Tables I–III show respectively the eigenvalues and types of some molecular orbitals, the Mulliken gross atomic charges of some atoms, and some values of the electrostatic molecular

Table II. Test Calculations on the Validity of the Model Compounds. Mulliken Gross Atomic Charges of Some Atoms[a]

	2-Phenyl-ethylamine	Toluene	1-Phenyl-2-aminoethanol	Benzyl alcohol
C(1)	0.0101	0.0151	0.0023	0.0058
C(2)	−0.0723	−0.0716	−0.0720	−0.0708
C(3)	−0.0611	−0.0610	−0.0624	−0.0620
C(4)	−0.0675	−0.0679	−0.0662	−0.0660
C(5)	−0.0608	−0.0610	−0.0622	−0.0621
C(6)	−0.0714	−0.0716	−0.0643	−0.0646
C(7)	−0.1046	−0.1829	0.0762	0.0027
O			−0.3231	−0.3111
HO			0.2067	0.1899

[a] For the atomic labels, see Figure 1. O and HO are the atoms of the side-chain alcoholic group.

Table III. Test Calculations on the Validity of the Model Compounds. Some Values of the Electrostatic Molecular Potential (kcal/mol)

	2-Phenyl-ethylamine	Toluene	1-Phenyl-2-aminoethanol	Benzyl alcohol
ϕ^a	−11.3	−11.3	−13.5	−14.0
O^b			−59.6	−54.7

[a] Along the sixfold rotation axis of the phenyl ring, from the opposite site of the side chain and at a distance of 1.7 Å from the ring plane. [b] Minimum value near to the alcoholic oxygen atom in a plane parallel to the phenyl one, from the opposite site of the side chain and at a distance of 1.7 Å from the ring plane.

potential (see section on Electrostatic Molecular Potentials).

From the results of Table I, it can be seen that the eigenvalues and types of the highest occupied molecular orbitals (HOMO'S) of the entire compound are in good agreement with the corresponding findings of the model compounds. For each molecule the lowest empty molecular orbital (LUMO) and the two first HOMO'S are of the π type on the phenyl region, without any mixture of lone-pair orbitals on N and O. Only the third HOMO which, however, is considerably lower in energy than the first two HOMO'S, is slightly different from the entire compound and the model one. In 2-phenylethylamine this orbital is a lone pair of the nitrogen atom, while in toluene it represents a σ bond between the phenyl atoms and the methyl group corresponding to the fourth HOMO of 2-phenylethylamine. On the other hand, the agreement is decidedly better for the 2-aminoethanol derivatives; in 1-phenyl-2-aminoethanol the third HOMO is a mixture of the lone pairs on N and O, while in benzyl alcohol it is a lone pair on O. So it can be deduced that the ordering and the eigenvalues of the first HOMO'S do not change appreciably on passing from the entire compound to the model one.

The results shown in Tables II and III confirm the previous ones given in Table I. Both the Mulliken population analysis (Table II) and the general shape of the electrostatic molecular potential (Table III; see section on Electrostatic Molecular Potentials) are very similar in the entire compound and in the model one. For the sake of brevity, we do not report here any complete maps of the potential which, however, have very similar shapes in the aromatic region of both compounds, but the values of the potential shown in Table III are sufficient to confirm the minor differences between the two molecules.

In conclusion, the model drugs here investigated are appropriate for use, as their validity has been confirmed by the previous analysis. The aminic side chain, which is dropped out in the model compounds, plays only a minor role on the charge distribution of the aromatic moiety of the drugs, so that its long-range effect in practically the same in different types of adrenergic compounds. Similar conclusions can be made on the basis of the results of previous studies of other compounds.[20,31]

SCF Results. In Table IV the total energies of the compounds here investigated and the eigenvalues and types of some molecular orbitals are shown. The results show that the highest occupied molecular orbitals (HOMO'S) and the lowest empty one (LUMO) are fairly similar in I and III but less so in II. For the model molecules of isoproterenol and doberol, the first two HOMO'S are mainly of the π type on the aromatic region (phenyl ring, plus the phenolic or ethereal oxygens) and the third HOMO represents primarily a lone pair of the alcoholic oxygen. In the INPEA model compound (II), the eigenvalue of the first HOMO is more negative and this orbital represents the π-type lone pairs of the oxygen atoms of the nitro group; the second and third HOMO'S, which are very close in their energy values, are mainly of the π type on the phenyl ring. Such ab initio results essentially confirm our previous CNDO/2 calculations.[1]

The Mulliken gross atomic charges (Table V) are in qualitative agreement with the well-known chemical features of aromatic compounds. In I and III the electron-donor character of the OH or OCH_2 groups causes more negative charges in the ortho position. On the contrary, an overall charge transfer toward the NO_2 group is present in II. This effect is responsible for the smaller negative charges on the phenyl carbon atoms, mainly on C(3) and C(5). From a comparison of the present ab initio results with the CNDO/2 ones,[1] the general trend of the CNDO/2 population analysis is evidenced: the semiempirical method gives a reasonable charge distribution, though the charges on the phenyl carbon atoms are generally more positive than the ab initio ones.

Electrostatic Molecular Potentials. In weak long-range noncovalent interactions between two closed-shell molecules with permanent local multipoles, as those here investigated, the electrostatic interaction energy, ΔE_{el}, plays a fundamental role in detecting the best approach channels for the reagents in the primary phase of the reaction. If we neglect the other terms of the interaction (polarization, charge transfer, exchange, dispersion, etc.) we have the electrostatic approximation which may be used for a first-order prediction of the relative reactivity of polar functional groups, especially when comparing rather complex molecules.

In the drug–receptor interaction, ΔE_{el} may be suitably expressed in terms of the electrostatic molecular potential

Table IV. Total Energies (au) − Eigenvalues (au) and Types of Some Molecular Orbitals

	I	II	III
E_{tot}	−487.9707	−540.9888	−491.2925
LUMO	0.2656 (π/ϕ)	0.1672 (π/ϕ, NO_2)	0.2685 (π/ϕ)
HOMO	−0.2213 [π/ϕ, O(1), O(2)]	−0.2648 [π/O(1), O(2)]	−0.2360 [π/ϕ, O(3)]
Second HOMO	−0.2639 [π/ϕ, O(1), O(2)]	−0.3016 (π/ϕ)	−0.2705 (π/ϕ)
Third HOMO	−0.3517 [Lp, O(4)]	−0.3082 (π/ϕ)	−0.3562 [Lp, O(4)]

Table V. Mulliken Gross Atomic Charges of the Heavy Atoms

Atom	I	II	III
C(1)	0.0025	0.0246	0.1391
C(2)	−0.0840	−0.0675	−0.0941
C(3)	0.1181	−0.0392	0.0252
C(4)	0.0941	0.0691	−0.0869
C(5)	−0.0907	−0.0396	−0.0514
C(6)	−0.0686	−0.0613	−0.1062
C(7)	0.0037	0.0025	0.0083
C(8)			0.0187
C(9)			−0.1825
N		0.1428	
O(1)	−0.3036	−0.2028	
O(2)	−0.3158	−0.2034	
O(3)			−0.2597
O(4)	−0.3115	−0.3090	−0.3122

V_D due to the nuclear and electronic charge distribution of the drug (D) and of the nuclear and electronic charge distribution γ_R of the receptor (R), i.e.

$$\Delta E_{el} = \int V_D(r)\gamma_R(r)d\tau$$

$$V_D(r) = \int d\tau_1[\sum_{\alpha \in D}^{nuclei} Z_\alpha \delta(r_1 - r_\alpha) - \rho_D(r_1)]/|r - r_1| = \int d\tau_1 \gamma_D(r_1)/|r - r_1|$$

where $\rho(r_1)$ is the electron distribution at the point r_1 and Z_α is the atomic number of the nucleus α at the point r_α. From this definition, $V_D(r)$ is the electrostatic interaction energy between the rigid charge distribution of the drug and a positive unit charge (e.g., a proton) at the point r; therefore, the molecular regions where $V(r)$ is negative are favored for an electrophilic attack. The potential is a quantum mechanical observable of the isolated molecule, computed in the overall space, and its calculation is the first step toward the evaluation of ΔE_{el} which in many cases may be adequately expressed in terms of suitable point-charge distribution $q_R(r_i)$ of R

$$\Delta E_{el} = \sum_{i \in R} V_D(r_i) q_R(r_i)$$

This last equation turns out to be very useful in cases, such as those considered here, where some different molecules D interact with the same compound R to give different reactions. If R is known, it is possible to select a suitable point-charge model to obtain ΔE_{el}. On the other hand, if R is largely unknown (as it is the case of the adrenergic receptors) or if we are interested in the general electrostatic reactivity of D without any specific hypothesis on the nature of R, the analysis of $V_D(r)$ may be used in seeking to understand and predict the reactivity behavior of D.

In recent years, this approach has been extensively discussed and checked in molecular interaction problems for a wide variety of organic, biological, and pharmacological compounds,[1,20,23-33] and useful correlations between $V(r)$ and chemical properties have been drawn, in a comforting agreement with the experimental findings.

In the drugs here considered, there are some molecular groups, common to agonist and antagonist drugs, which can be involved in electrostatic interactions with the receptor: (a) the aryl or the aryl-OCH_2 moiety; (b) the side-chain alcoholic group; and (c) the cationic head. As regards the side chain in itself, the reader is referred to previous papers[1,20] which discuss its conformational and reactivity features and the influence of the free base and onium form on the electronic properties of the aromatic region. In this paper, attention will be focused mainly on the aromatic moiety (which is the most important factor in determining the pharmacological responses) and on the side-chain alcoholic group.

The electrostatic potential was computed in certain significant spatial zones, in order to characterize the molecular interaction pattern. Moreover, since electrostatic forces play an important role in hydrogen-bond associates, $V(r)$ was tentatively used as a means of predicting the energy value in the H-bond interaction between the drugs and certain polar receptor sites, here simply simulated by H_2O. By using the 431G basis set,[34] Kollman et al.[35] have previously pointed out that there are good linear correlations (eq 2 and 4 of ref 35) between the stabilization energies of A–H···NH_3 or A···HF associates and the values of $V(r)$ of A–H or A at certain suitable points. By means of a simple algebraic model (eq 7 and 8 of ref 35), ΔE(A–H···OH_2) and ΔE(A···HOH) can be predicted and scaled to correct the 431G basis set defects. In order to estimate the 431G potential of the drug, which is the starting point of Kollman's procedure, we scaled $V_{STO\text{-}3G}(r)$, at points characteristic of H bonds, by 1.57. This factor was computed, using both basis sets, from $V(r)$ of some small molecules (H_2O, HF, HF·BF_3, and N_2H_2).[36]

(a) Aromatic Moiety. In this paper we will use this term with a rather general meaning, including not only the phenyl ring and its substituents but also the oxymethylene bridge or III; previous experimental findings[11,13] evidence the essential role of the OCH_2 group in the aromatic interaction pattern of type B drugs. These same findings show the conjugation of the O(3) atom with the aryl group, as well as the general trend of the pharmacological responses of type B drugs with respect to type A ones.

The aromatic region may be divided into two subunits, the aromatic substituents and the π electrons of the benzene ring. These are interdependent and can play different, yet complementary roles in the formation of the drug–receptor associates. More attention has generally been devoted to the phenyl substituents, especially to those which may be ionically bound to suitable receptor sites.[37] On the contrary, the role of the benzene ring is generally described as indirect and essentially topological and its interactions at receptor sites are mainly attributed to weak dispersion forces.[30] Nevertheless, the ionic reactivity of this molecular portion cannot be a priori passed over; the phenyl π-electron distribution can interact forming π complexes,[38] where the electrostatic forces may play an important role.

In this paper the coulombic reactivity of both subunits of the aromatic portion is investigated by analyzing $V(r)$ in the ring plane and in the region of its π electrons, i.e., in a plane parallel to that of the ring at a distance of 1.7 Å, on the same side as the alcoholic atom, i.e., in the half-space which does not contain the ethanolaminic side chain of the adrenergic drugs.[5,11]

In all compounds here considered $V(r)$ is strongly negative (i.e., the approach of positive charges is favored) near the O(1), O(2), and O(3) oxygen atoms with deep potential holes in the ring plane roughly localized in the directions of the trigonal O lone pairs, as can be seen from Table VI which presents an overall résumé of the values and positions of the $V(r)$ minima.

In the π-electron region of the ring, the overall shape of the potential is essentially related to the position, number, and electronic nature of the groups directly bound to the benzene ring and, to a minor extent, to the conformational and electronic features of the side chain.

Compound I. In this model of a stimulant drug (isoproterenol) the effect of the weak intramolecular H bond on the different reactivity pattern of the two phenolic

Table VI. Resume of the Minimum Values of $V(r)$ (kcal/mol) and of Their Positions (in Parentheses) (Å)[a]

	I	II	III
O(1)	−59.6 (−3.8, −3.3, 0)	−59.5 (−7.3, −1.1, 0)	
O(2)	−37.4 (−6.3, −0.9, 0)	−59.5 (−7.3, 1.1, 0)	
O(3)			−52.9 (−2.2, −1.0, 0)
ϕ[b]	−18.0 (−3.9, −2.8, −1.7)	−16.7 (−7.4, −1.5, −1.7)	−9.6 (−5.5, −0.6, −1.7)
	−7.5 (−6.0, −0.7, −1.7)	−17.0 (−7.4, 1.5, −1.7)	−13.1 (−1.9, −1.6, −1.7)
O(4)[c]	−55.8 (−0.2, 2.0, −0.4)	−44.1 (−0.2, 2.0, −0.4)	−54.5 (0, 2.0, −0.4)
	−61.6 (0.7, 1.2, −1.4)	−52.2 (0.7, 1.2, −1.4)	−58.4 (0.9, 1.1, −1.4)

[a] The C(7) atom is the coordinate origin; the ring plane defines the (x,y) plane, the x axis being parallel to the C(4) → C(1) direction and the y one on the same side of the O(4) atom. [b] In the parallel plane to ring 1 with $Z = -1.7$ Å. [c] Along the lone-pair directions respectively pointing toward and outward the aromatic region.

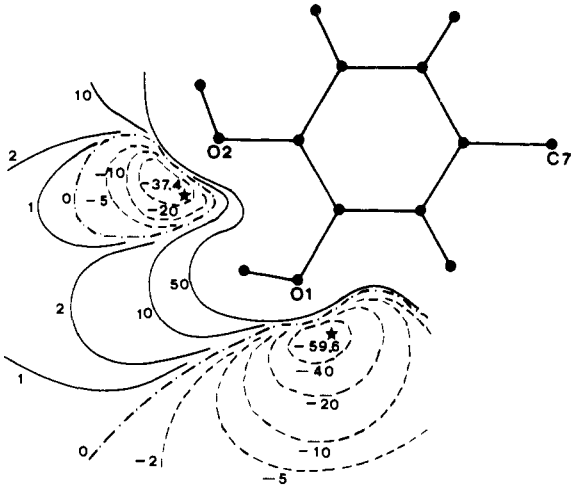


Figure 2. Compound IA. Contour map of the electrostatic potential. Isopotential levels in kilocalories per mole. Dashed levels represent negative potential and full levels indicate positive potential. The stars indicate potential minimum values. Ring plane.

groups as well as the role of the aromatic substituents on the electronic features of the benzene ring can well be rationalized in terms of the analysis of $V(r)$.

In rotamer IA (Figure 2) the negative potential region due to the meta O(1) atom, i.e., to the proton-donor oxygen atom in the intramolecular H bond, is larger and has a lower minimum; the predicted H-bond energies (Table VII), obtained by the above-mentioned procedure, are −3.4 kcal/mol for the nucleophilic and −0.5 kcal/mol for the electrophilic reactivity, respectively; for these reasons, a proton approach to the meta position is favored. The OH in the *para* position introduces another important binding possibility by contributing as a strong proton-donor group (ΔE = −7.3 kcal/mol) to the drug reactivity in this molecular region; this behavior is enhanced by the internal H bond where the *p*-OH is an electron-donor group. Only in compound I (see later on), which is a model of the stimulating drug isoproterenol, it was pointed out that a nucleophilic attack is favored on a phenyl substituent (*p*-OH in IA and *m*-OH in IB). These findings are in agreement with what might have been expected and confirm the usefulness of electrostatic approximation to distinguish between similar groups with different steric and electronic features; no similar trend has been observed using population analysis.

The presence of two strong electron-donor OH groups generates above and below the phenyl ring two spatial regions where there is a negative potential with three relative minima due to the oxygen atoms (Figure 3). The first region is larger and includes the O(4) side-chain lone-pair zone, all the phenyl ring, and the proton-donor OH group; this situation favors an electrophilic attack on the phenyl ring, tending to form a drug–receptor complex.

Table VII. H-Bond Energy Predictions (kcal/mol) for A···HOH or AH···OH_2 Associates

A or AH	I	II	III
	Aromatic Portion		
O(1)[a]	−3.4	−4.4	
	−1.3	−1.1	
O(1)-HO(1)	−0.5		
O(2)[a]	0.2	−4.4	
	0	−1.1	
O(2)-HO(2)	−7.3		
O(3)[a]			−2.5
			−1.0
ϕ	−1.4	0.3	−1.2
	Alcoholic Portion		
O(4)[b]	2.8	4.7	−1.9
	−3.1	−1.9	−2.7
O(4)-HO(4)	−5.5	−7.8	−6.0

[a] The first value refers to the in-plane approach along the minimum potential direction; the second value refers to the π approach along the perpendicular line to the ring plane and which contains the oxygen atom. [b] The two values are along the lone-pair directions respectively pointing toward and outward the aromatic region.

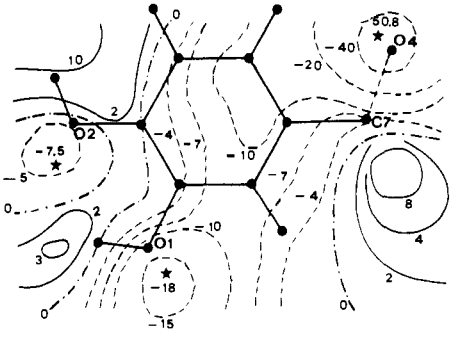


Figure 3. Compound IA. As in Figure 2 for the plane parallel to the plane of the ring at a distance of 1.7 Å and on the same side of O(4).

The side-chain CH_2OH group reinforces this nucleophilic reactivity. The other negative region is due to the proton-acceptor OH group and it is separated from the main one by a small repulsive barrier.

As to the IB rotamer, where the roles of the two phenolic OH groups are reversed in comparison to IA, with the O(1) proton-acceptor and O(2) proton-donor atom, the potential variations with regard to IA strictly follow the rotameric changes with an obvious reversal of the two negative regions due to O(1) and O(2), both in the ring and in the parallel plane; moreover, the picture remains substantially unmodified in the other molecular portions, both above the phenyl ring and on the side-chain region.

A comparison of the present results for I with previous ones for cathecol[31] shows the negligible effect of the side chain on the meta and para molecular regions. These results suggest that the interaction pattern of the adre-

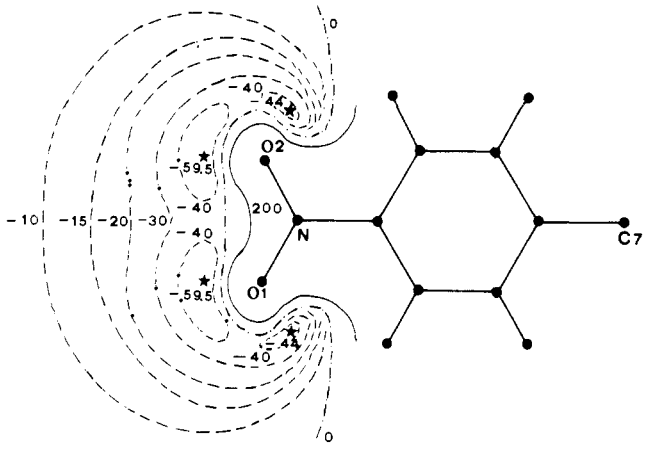


Figure 4. Compound II. See Figure 2.

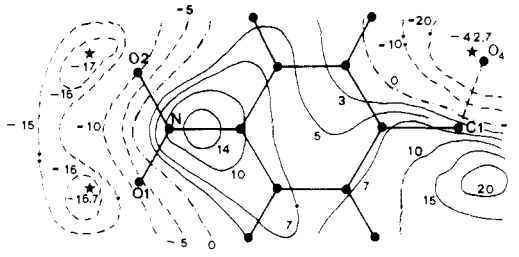


Figure 5. Compound II. See Figure 3.

nergic drugs in this region is the same for all the biological catecholamines and depends primarily on the mutual binding of the two phenolic groups.

Compound II. In this model of a blocking drug which derives from ethanolamine (INPEA), the analysis of the coulombic term of the interaction reveals sharp differences between the drugs corresponding to compounds I and II. In the stimulant drug I, an electrophilic approach is favored on the proton donor OH group and on the π region of the phenyl ring, and a nucleophilic approach is favored on the proton-acceptor OH group. In the blocking drug II, on the contrary, the results displayed in Figure 4 (ring plane) show that the para position [O(1), O(2)] can undergo an electrophilic attack, with a predicted H-bond energy of −4.4 kcal/mol for both of the oxygen atoms of the NO_2 group, while the meta positions do not interact ionically.

The differences between the two compounds I and II increase if we compare the corresponding $V(r)$ trends in the π-electron region of the ring. In II (Figure 5) the effect of the strong electron-acceptor nitro group overcomes that of the side chain, so that an electrophilic approach to the benzene ring seems to be completely unfavored. The potential is positive at every point of the phenyl ring with a maximum that corresponds to the C(4)–N bond; only the region of the O lone pairs of the NO_2 group is favorable to an electrophilic attack. This region of negative potential is wholly shifted over the substituent, spreading above and below the O(1) and O(2) atoms; it is rather distant from the ring and a long way from the alcoholic group.

In conclusion, these findings evidence that the electrostatic reactivity of the aromatic moiety of I and II is decidely different. Therefore, it may be inferred that the opposite pharmacological responses of the corresponding drugs are mainly due to the different coulombic interactions with polar receptor sites and that the spatial arrangement and the electronic features of the blocking-receptor complex are substantially different compared with the stimulant–receptor complex, so that the analysis of $V(r)$ is in gratifying agreement with the experimental evidence.

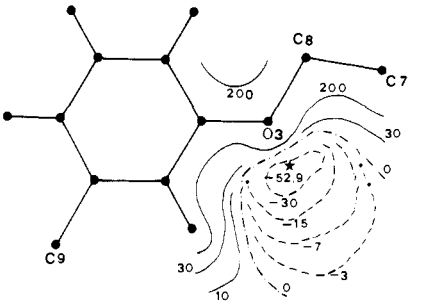


Figure 6. Compound III. See Figure 2.

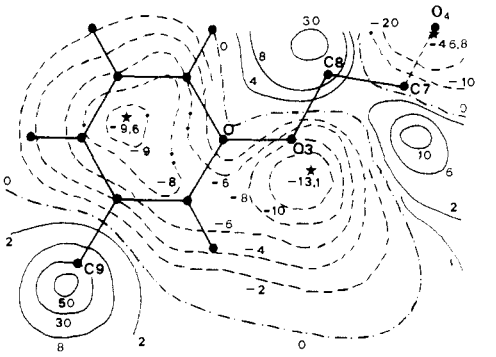


Figure 7. Compound III. See Figure 3.

Compound III. This last molecule is a model of a blocking drug which derives from oxypropanolamine (doberol); in this case the aromatic moiety includes the oxymethylene group as well, which greatly influences the overall behavior with an in-plane reactivity which is quite different from the reactivity of compounds I and II.

Figure 6 shows that the nucleophilic region due to the ethereal O(3) atom is shifted toward the side chain by a strong repulsive barrier generated by the C(2)–H bond; moreover the stabilization energy for the O(3)···H_2O associate (−2.5 kcal/mol) is lower than those previously found for the O(1) and O(2) atoms of I and II. The *m*-tolyl group of III generates in the ring plane a strongly positive potential, especially in the region around the CH_3 substituent. In regard to this last group, the analysis of $V(r)$ shows that it cannot interact by means of electrostatic forces; its role in the reactivity of the drug is better described in terms of repulsion and dispersion forces with consequent indirect effects on the π-electron distribution.

Owing to the presence of the OCH_2 group, the electrostatic potential in the π-electron region of III seems to be intermediate compared with the trend of $V(r)$ in compounds I and II. It would therefore seem that other contributions to the intermolecular forces (such as exchange repulsion, charge transfer, polarization, and dispersion) play an important role in the pharmacological reactivity of the drugs derived from oxypropanolamine. Nevertheless, the analysis of the coulombic term of the interaction may offer useful first-order information about the reaction channels at medium or long distances from the drug.

In a plane parallel to that of the ring (see Figure 7) the potential is negative in two spatial regions, which are separated by a strongly repulsive barrier due to the methylene C(8) group. The first region concerns the lone-pair electrons of the alcoholic oxygen atom O(4) and will be discussed in the next section.

The second negative region spreads over the whole benzene ring, with an absolute minimum near the para C(4) atom. This nucleophilic area of III has, however, a

different trend in comparison with the corresponding one of I, owing to the phenolic OH groups of I and the ethereal O(3) atom and the m-CH_3 group of III (compare Figures 3 and 7). The positive zone of C(8) in III spatially corresponds to a negative zone above the phenyl core of I. In addition, the meta regions of the two drugs have a different reactivity pattern as well; in I the O(1)–H group can engage polar receptor sites in H-bond associates, while in III the CH_3 group seems to interact with nonpolar sites through steric repulsion and dispersion forces. There should be therefore a substantial difference between the spatial arrangement of the doberol–receptor associate and the isoproterenol–receptor associate, which, together with the above discussed differences of $V(r)$ in the ring plane, may well account for the opposite activity of these drugs.

On the other hand, a comparison between both blocking drugs considered, INPEA and doberol, must take into account the substantially different chemical structure of these drugs. Therefore, some similarities between their model compounds II and III [as they appear from inspection of the maps of $V(r)$ in the parallel plane] should be interpreted with some caution also bearing in mind the neglected terms of the interaction. As is shown in Figures 5 and 7, the negative zone of $V(r)$ due to the O atoms of the NO_2 group of II roughly corresponds to the potential minimum near the para C(4) atom of III. Likewise, there is some spatial correspondence between the repulsive region above the phenyl ring of II (due to the depletion of π electrons caused by the electron-withdrawing action of NO_2) and the repulsive region above the planar zone roughly delimited by the C(8)–O(3)–C(1)–C(6) atoms of III (due to the methylene portion of the OCH_2 group). This could mean that the oxymethylene bridge of the oxypropanolamine derivatives allows some correspondence between different molecular regions.

It is possible for π-H bonds to develop between the π-electron distribution of the aromatic moiety and suitable electron-acceptor receptor groups; their corresponding energies are in general much smaller than the "conventional" H-bond ones. Moreover, from the correlation between the HOMO energies (−0.2213, −0.2360, and −0.2648 au for I, III, and II, respectively) and the ΔE values (calculated by the procedure outlined above) for an electrophilic attack along the sixfold rotation axis of the benzene ring (−1.4, −1.2, and 0.3 kcal/mol for I, III, and II, respectively), we may infer that in this case, too,[23] the electrostatic and charge-transfer contributions to the stability of the π complex are parallel; consequently, the value of the electrostatic contribution can be taken as a first test to assess the relative stability of these complexes.

(b) Side-Chain Alcoholic Region. The alcoholic group can play an electrophilic or a nucleophilic role in the formation of the drug–receptor associate. It is generally accepted that it interacts directly with appropriate receptor sites;[37b,c,39] nevertheless, it could indirectly reinforce the reactivity either of the aromatic or of the aminic molecular portions, depending on its conformation. The spatial arrangement here selected (with the HO(4) atom pointing toward the side chain of the drugs) evidences the electrophilic effects of this group on the binding of the onium head of the drugs with anionic receptor sites. On the other hand, the reactivity of the aromatic moiety depends to some extent on the O(4) lone pairs, as was pointed out in the previous section. Both these roles were investigated by an analysis of the electrostatic potential.

The main contribution of the oxygen atom to $V(r)$ is represented by a negative-potential region with deep holes on the same side as the aromatic moiety. This region is connected to the phenyl negative one in I, while it spreads only over the C(7) atom in II and III. For the sake of brevity, we have not included here any map of the potential, but only its minimum values (Table VI), which are near the directions of the two lone pairs of O(4), assuming a tetrahedral arrangement. The long-range effects due to the presence of the aromatic moiety are well evidenced by our results. In the β-agonist model (I), the minima are at their lowest point; there is a noticeable asymmetry of the negative region, and its absolute minimum value is on the opposite site to the phenyl ring. In the antagonist model II, on the contrary, the overall charge transfer toward the aromatic NO_2 group makes this negative region less extended and less deep, with an even more asymmetric shape. These effects are, of course, less appreciable in III, owing to the presence of the oxymethylene bridge, whose potential holes are in an intermediate position in the set here investigated, while the O(4) negative region is more symmetric. In I and III, the distance between the minimum-potential values due to the presence of the alcoholic group and the other minimum values corresponding to the aromatic substituents or to the phenyl ring lies in the range 6.1–6.6 Å (see Table VI). On the other hand, this distance increases to 8.1–8.5 Å in II.

The results shown in Table IV evidence the overall reactivity of the O(4)–HO(4) group. The electrophilic approach to the oxygen atom is favored in I and II (and preferred in III) only in the direction of the lone pairs which is not sterically hindered by the benzene ring; this effect is more marked in the ΔE analysis than in the analysis of the minimum-potential values. On the other hand, we may infer from the H-bond stabilization energies in the O(4)–HO(4) direction that the alcoholic group may interact with nucleophilic receptor regions, probably by reinforcing the reactivity of the onium head of the drugs.[39]

Conclusions

The present investigation of the role of the aromatic moiety of β-adrenergic drugs in the interaction with the receptor was carried out by analyzing the relationship between the electronic structure and the reactivity in terms of the electrostatic molecular potential $V(r)$ due to the nuclear and electronic charge distribution computed from the molecular wave function at the level of the quantum mechanical ab initio SCF–MO–LCAO method. Here we remember only that an electrophilic attack is favored on the molecular regions where $V(r)$ is negative and that the electrostatic potential can be the starting point in predicting the overall interaction energy between polar groups.

In this paper three adrenergic drugs were considered, viz., isoproterenol, INPEA, and doberol, the first one with β-stimulating activity and the others with β-blocking activity. The results obtained show that it is possible to interpret the pharmacological behavior of these drugs in terms of the electrostatic potential of the aromatic moiety which influences both the affinity and the intrinsic activity of β-adrenergic drugs. Moreover, the role of the aromatic portion in the interaction with the receptor depends on a close combination of the effects of the phenyl substituents and of the phenyl ring, and the mutual influence between the aromatic portion and the side-chain OH group must also be considered to some extent.

In Figure 8 we report schematically the overall reactivity pattern of the compounds considered by comparing the reactivity of molecular zones which spatially correspond. For this purpose, as the interaction between the side chain of the drug and the receptor should be the main one from an energetical point of view, in Figure 8 compounds IA–III are shown with their side-chain OH groups in the same

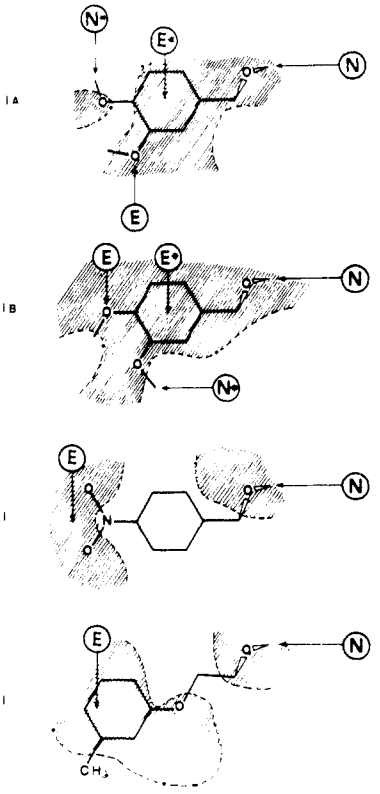


Figure 8. Overall reactivity pattern of the compounds IA, IB, II, and III. Shaded areas indicate negative potential and unshaded areas represent positive potential in the plane parallel to the plane of the ring. The arrows indicate possible electrophilic (E) or nucleophilic (N) attack; the presence or the absence of a star near the symbols E or N correlates the interaction with the intrinsic activity or with the affinity, respectively.

spatial position. The possible types of interaction with electrophilic or nucleophilic receptor sites are also shown and these interactions are tentatively correlated with the affinity or the intrinsic activity of the drug.

In the stimulating drug, isoproterenol (rotameters IA and IB in Figure 8), both the phenolic OH groups have a binding tendency toward polar receptor sites and the specific role of each group depends mainly on their mutual spatial arrangement. However, the main factor which influences the reactivity in the catechol portion is the enhanced proton-donor tendency of the OH group which is an electron donor in the internal H bond (*p*-OH in IA or *m*-OH in IB), and this behavior is peculiar to the phenyl substituents of isoproterenol. Owing to the OH groups, the potential is negative on a large part of the aromatic moiety so that an electrophilic attack to the phenyl ring is decidedly favored through the formation of a drug–receptor π complex. The electrostatic potential due to the charge distribution of the blocking drug of type A, INPEA (compound II in Figure 8), shows that the reactivity features of INPEA are different from those of isoproterenol both in the region of the phenyl substituents and in the π region of the phenyl ring; the NO_2 group of INPEA can interact with the receptor only as an electron-donor group and the positive potential above the phenyl ring shows that an electrophilic attack in this region is completely unfavored.

Finally, owing to the OCH_2 and CH_3 groups, the aromatic reactivity of doberol (compound III in Figure 8), a blocking drug of type B, is decidedly different in the ring plane and it is intermediate in the π-electron region compared with that of isoproterenol and INPEA. The electrostatic potential of doberol is negative in the π-electron region of the phenyl ring, but the overall shape of this zone is rather different from that of isoproterenol; in doberol this zone is smaller, with different positions and minor values of the potential minima [see also Figures 3 and 7 and the more detailed analysis of $V(r)$ of III in the previous section].

With this in mind, it is possible to conclude that the electrostatic potential can rationalize and correlate the adrenergic behavior. The results summarized in Figure 8 indicate that a spatial correspondence exists among molecular regions with negative potential where an electrophilic attack is favored. In type A drugs these regions are localized on the phenyl substituents, *p*-OH of the rotamer IB of isoproterenol and NO_2 of INPEA, while in the type B drug this region is localized on the π-electron zone of the phenyl ring, para C atom of doberol. These regions, indicated with E in Figure 8, could account for the affinity, in addition to the side chain. On the other hand, both the proton-donor tendency of the phenolic OH group in para (IA) or in meta (IB) positions and the strong electron-donor behavior of the phenyl ring might account for the intrinsic activity of isoproterenol. These features, indicated with N* and E*, respectively, in Figure 8, are peculiar to this β-stimulating drug.

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β-Adrenergic Blocking Agents. 17. 1-Phenoxy-3-phenoxyalkylamino-2-propanols and 1-Alkoxyalkylamino-3-phenoxy-2-propanols

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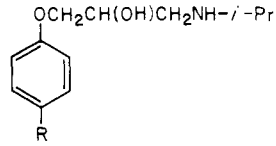
The synthesis is described of a series of derivatives of 1-phenoxy-3-phenoxyalkylamino-2-propanols and 1-alkoxyalkylamino-3-phenoxy-2-propanols. The compounds were investigated for their β-adrenoceptor blocking properties and many showed a surprising degree of cardioselectivity when tested in vivo in anesthetized cats for their effects on an isoproterenol-induced tachycardia and depressor response. The structure–activity relationship shown by this series of compounds is related to that of known cardioselective analogues and a possible reason for their cardioselectivity is discussed.

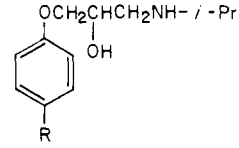
Several cardioselective β-adrenoceptor blocking agents are now available for clinical use and an examination of their structures reveals certain common features. From our previously described work[1-4] it has become apparent that a *p*-amidic substituent in the aryl ring of an aryloxypropanolamine will confer cardioselectivity (structure I).



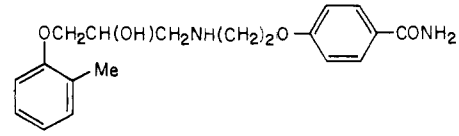
I, R = NHCOR', NHCONHR', CONHR', or CH_2CONHR'; R' = H, alkyl, or aryl substituents

Other workers[5,6] have found cardioselectivity with nonamidic, para-substituted aryloxypropanolamines, e.g., the para-substituted analogue of oxprenolol II and metoprolol III.

More recently, it was shown[7] that cardioselectivity was obtained by replacing the isopropyl or *tert*-butyl substituent with an aryloxyalkyl group in which the aryl ring had a *p*-amidic substituent; this work led to the development of tolamolol (IV).



II, R = $-OCH_2CH=CH_2$
III, R = $-CH_2CH_2OCH_3$



IV

Working along similar lines, other workers[8] replaced the isopropyl or *tert*-butyl substituent with a 3,4-dimethoxyphenethyl moiety. The best compound, V, of this series