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Psychotomimetic Drugs as Anticholinergic Agents

II. Quantum-Mechanical Study of Molecular Interaction Potentials of 1-Cyclohexylpiperdine Derivatives with the Cholinergic Receptor

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SUMMARY

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Molecular structural factors in the interaction of drugs of the phencyclidine series with cholinergic receptors were studied by quantum-mechanical methods. Reactivity criteria were based on an interaction pharmacophore obtained from the electrostatic potential pattern generated in its surroundings by the molecular system. Experimental results referring to the psychotomimetic activity of the drugs and to their anti-acetylcholine properties, established with various peripheral receptors and cholinesterases, were shown to correlate well with the structural requirements obtained from the interaction pharmacophore of acetylcholine. Structural characteristics leading to competitive antagonism are discussed.

INTRODUCTION

A correlation between psychotomimetic activity and anticholinergic potency has been observed in various drugs (1–3). The glycolate esters may provide the best example of association between these two properties. Still, the hypothesis that psychotomimetic activity arises from central cholinergic blockage has met opposition. One reason is an apparent lack of correlation between the two properties in certain drugs. We contend, however, that even a weak anticholinergic activity, which may be not as impressive in peripheral test systems as that of the glycolates, may be conducive to psychotropic activity, provided that the affector molecule satisfies certain requirements elucidated here by quantum mechanical calculations. Drugs of the phencyclidine series (I) fall in this category. They display considerable psychotomimetic but only weak anticholinergic effects. We show here that they also embody all the elements necessary for specific interaction with the cholinergic receptor (muscarinic pharmacophore), re-

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gardless of their apparent lack of structural similarity to the natural agonist, acetylcholine. Since these elements are identical with those expressed by the pharmacophore established for agonists of acetylcholine, the direct interaction of both agonists and antagonists with the same receptor site is considered here to be the basis of purely competitive antagonism (see, however, refs. 4–7). We explain the failure of the antagonists to activate the cholinergic receptor by offering the hypothesis that agonistic activity is related to a rearrangement in the conformation of the drug-receptor complex, which is prevented in the antagonists by certain molecular structural factors.

The particular set of atoms implicated in acetylcholine-like muscarinic activity has been identified through the coordinated use of crystallographic (8, 9), NMR (10–12), and SAR (13–15) data. Quantum-mechanical studies of molecular conformations and electron distribution have contributed a theoretical basis to the conclusions drawn from experimental work (16–19). It has become clear that the requirements for agonistic or antagonistic activity reside in a generalized charge distribution pattern (Fig. 1) rather than a strict acetylcholine-like sequence of atoms. Thus considerable agonistic activity has been observed in analogues of acetylcholine in which the ester oxygen has been replaced by a double or triple bond (13–15) or the trimethylammonium group by an equivalent electron-deficient function (19, 21). The strongly muscarinic oxotremorine is a remarkable case of two types of change occurring at the same time (22, 23). However, like the purely structural approach, the use of point charge distributions is limited because it is based on a static condition of net atomic charges on the relevant atoms, the very definition of which is controversial. Various definitions of atomic charges, based on population analysis (24), use such unrealistic assumptions as the equal partitioning of overlapping populations and lead to ambiguous results (25, 26) which are noninvariant under unitary transformations of the atomic basis (27). Moreover, such an approach is inadequate for a generalized assessment of midbond or

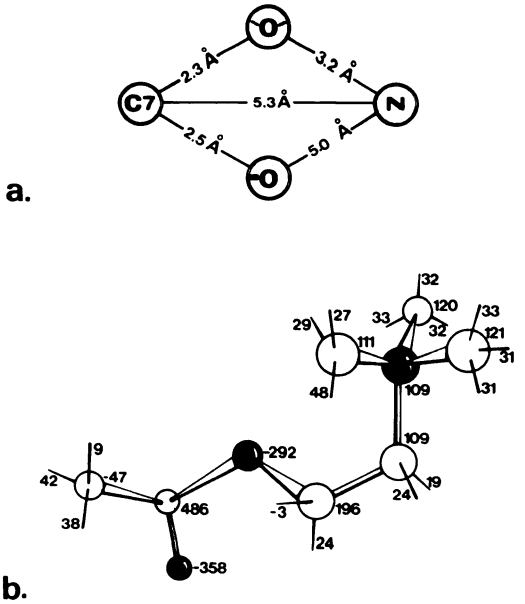


FIG. 1. *Elements of interaction pattern of acetylcholine-like molecules with muscarinic receptor*

a. Distance pattern for functional groups. b. Net atomic charges in the [60°, 180°] conformation of acetylcholine (20).

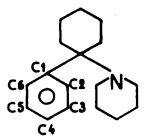
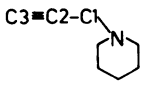
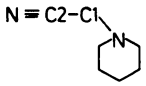
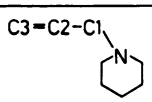
midring charge distributions, which are required for the representation of molecular reactivity. We therefore base our identification of the molecules in the phencyclidine series, as specific antagonists, on a consideration of electrostatic potential energy maps generated around selected fragments of the molecule. The maps are presented as contours of equal interaction energy between the molecular system involved and an approaching point-positive charge, and are designated as *interaction pharmacophore*, in contrast to the static pharmacophore that has evolved from earlier studies.

METHODS

There are strong indications that phencyclidine is a semirigid molecule with a preferred conformation determining interatomic distances, as shown in Table 1. Data from X-ray diffraction studies of phencyclidine (base) are in full agreement with the proposed pattern, the likelihood of a change of comformation in the dissolved state being negligible (28). The two sites of immediate concern in this structure are the heterocyclic

TABLE 1

Interatomic distances for functional groups in phencyclidine derivatives

Fragment	Distance (Å) from:	to N
	C 1	2.52
	C 2	3.32
	C 3	4.52
	C 4	5.03
	C 5	4.52
	C 6	3.33
	C 1	2.45
	mid bond	3.06
	≡C 3	3.60
	C 1	2.45
	mid bond	3.21
	≡N	3.65
	C 1	2.50
	mid bond	2.96
	=C 3	3.53

Values are approximated from crystallographic data for phencyclidine (28) and standard molecular structures for the fragments.

nitrogen and the π-electron system. The electronic structure of the first site, assuming protonation, has been dealt with in earlier studies on related systems and was found to correspond well with that calculated for the trimethylammonium group of acetylcholine (19). We have therefore devoted most of this study to the π-electron system present under various structural forms in the phenylclidine series of drugs. To simplify matters, these systems have been studied first in extensively reduced models which are taken to represent the respective molecular fragment in the corresponding phencyclidine derivative. Thus propyne ($HC\equiv C—CH_3$) represents compound V; acetonitrile ($N\equiv C—CH_3$ represents VI; and $R—\phi—CH_3$, the phenyl-substituted molecules in Table 2. Indeed, inspection of interatomic distances derived from crystallographic data suggests only a slight influence of neighboring nonpolar groups on the electronic characteristics of the two sites of interest. This assumption has been checked directly by a series of INDO[5] calculations of analogues of acetylcholine and of the phencyclidine molecule.[6] Results obtained for the whole phencyclidine molecule, calculated in the configuration predicted by the X-ray studies (28), reveal a pattern of atomic charges in the region of the phenyl ring which is very similar to the one obtained for the isolated fragment $\phi—CH_3$. Moreover, a comparison of Figs. 9 and 2 clearly shows that the corresponding electrostatic potentials in the phenyl ring region present a pattern identical with that of an approaching agent. The same general conclusions pertain to the results obtained from the calculations of complete acetylcholine-like molecules which embody some of the fragments used here as models (e.g., $—C\equiv C—$, $—C\equiv N$, or $\phi—R$).[6] This is evident from a comparison of Figs. 7a and 3. We therefore consider the maps obtained for the relevant parts to be applicable directly to the analysis of the whole molecules incorporating the fragments.

Molecular orbital calculations. The quantum-mechanical treatment is based on an application of the semi-empirical INDO method of Pople *et al.* (31). In this approximation the molecular wave function ψ is represented by a closed-shell Slater determinant of molecular orbitals ϕ_i :

$$\Psi = |\, \phi_1(1, \alpha)\phi_1(2, \beta)\phi_2(3, \alpha) \cdots \phi_n(2n - 1, \alpha)\phi_n(2n, \beta)| \quad (1)$$

in which all the valence electrons are considered.

The electronic charge distribution is usually characterized by the net atomic charges, ρ_a , at each atom with core charge Z_a,

$$\rho_a = Z_a - \sum_{\mu \epsilon a} D_{\mu\mu} \quad (2)$$

The density matrix elements $D_{\mu\nu}$ are defined in terms of the LCAO coefficients

$$D_{\mu\nu} = 2 \sum_i C_{\mu i} C_{\nu i} \quad (3)$$

where the sum runs over all filled molecular

[5] The abbreviations used are: INDO, intermediate neglect of differential overlap; CNDO, complete neglect of differential overlap.

[6] H. Weinstein, S. Srebrenik, and P. Pauncz, results to be published.

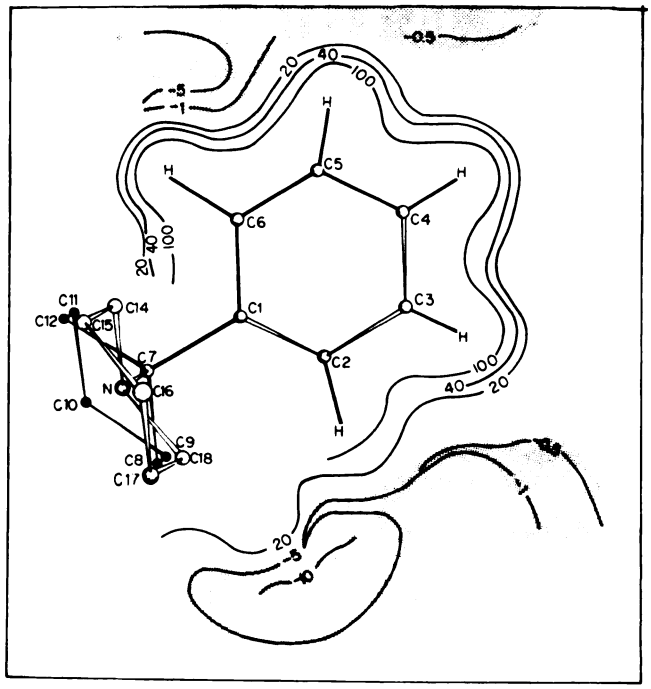


FIG. 2. *Electrostatic potential pattern in quasiplane of phenyl ring in phencyclidine*
The molecule was calculated using coordinates obtained directly from the positional parameters expressed as fractions of unit cell dimensions in Table 3 of ref. 28. The nitrogen is protonated in the crystal structure, and the effect of the approaching anionic site is simulated by the transfer of an electron to the molecule and recalculation of the charge distribution. See the text for units and method of calculating potential contours.

orbitals. The INDO method is well documented and widely used for the determination of molecular conformations, electron charge distributions, and other molecular properties (32, 33). The computer program used for the calculations presented here is a modified version of the CNDO-INDO (CNINDO program (34).

Since some cases have occurred in which the self-consistent routine in this program failed to converge properly [similar findings have been reported (35) and analyzed (36)], we introduced a damping procedure in order to prevent such oscillatory divergence (37). This consists of a modification of the density matrix during the iteration, which can be represented as

$$(D_{\mu\nu})^{\text{in}}_{k+1} = (D_{\mu\nu})^{\text{in}}_{k} + \lambda[(D_{\mu\nu})^{\text{out}}_{k} - (D_{\mu\nu})^{\text{in}}_{k}]$$

where the subscripts represent the kth and $(k + 1)$th iterations and the superscripts represent the "input" and "output" matrices in the corresponding step. λ is a damping parameter with values $0 < \lambda < 1$, controlled through the input data.

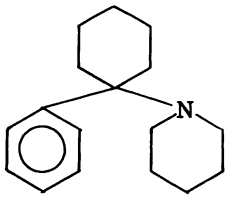
Molecular potential fields. A quantum-mechanical treatment of forces in molecules has led to the conclusion that the total force on a point charge in any system of nuclei and electrons is just the classical electrostatic interaction with the nuclei and the electron density distribution for all electrons (38). It can be shown (39) that the potential function $V(r)$ of this interaction can be obtained from an *analytic* solution of the equation

$$\nabla^2 V(r) = -4\pi\rho(r) \qquad (4)$$

if $\rho(r)$, which represents the quantum-mechanical charge distribution function, is expressed as a product of Gaussian type functions

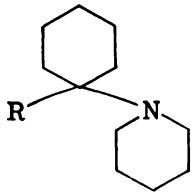
TABLE 2

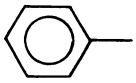
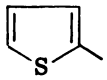
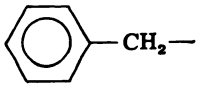
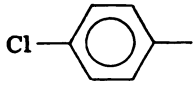
Anticholinergic and psychotropic activity of phencyclidine derivatives



1-(1-Phenylcyclohexyl)-piperdine (phencyclidine)

I



	R—	Equipotent molar ratio[a]		Mammalian ocular smooth muscle	Psychotropic activity (ref.)
		Guinea pig ileum	Frog rectus abdominis[b]		
I		300	2.8×10^{-2}	+++[c]	+++ (29)
II		200	4.4×10^{-2}	+++	+++ (29)
III			7.2×10^{-2}	+	− (29)
IV		300	6.0×10^{-2}	+	− (29)
V	$HC \equiv C-$	300	1	++	++ (30)
VI	$N \equiv C-$		>2.8	−	− (29)
VII	C_2H_5-	>1000	1	+	− (30)

[a] The equipotent molar ratio produces 50% inhibition relative to acetylcholine.

[b] The comparatively low ratio in this preparation is attributed to the different effects of the drugs on butylcholinesterase and acetylcholinesterase.[7] Phencyclidines inhibit mainly the former, while acetylcholinesterase, which is the preponderant enzyme in striated muscle is only slightly affected.

[c] Key: +++ = very active; ++ = active; + = hardly active; − = not active.

[7] Z. Paster, S. Maayani, and M. Sokolovsky, results to be published.

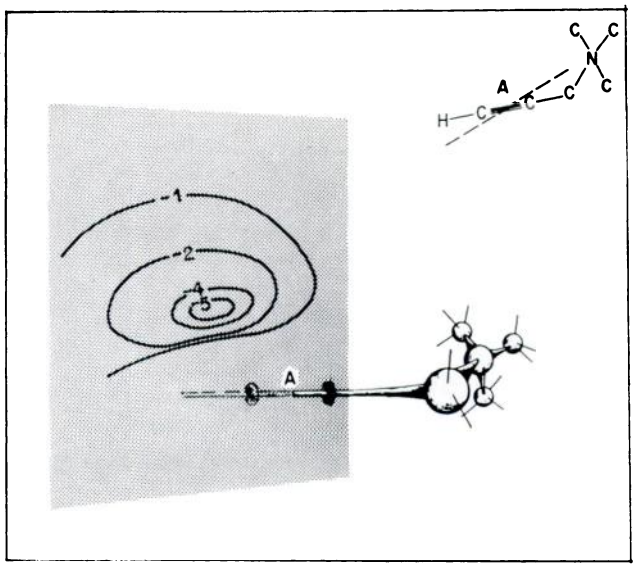


FIG. 3. *Pattern of negative potential generated around an acetylene derivative of acetylcholine*
Potentials shown were calculated in a plane intersecting the triple bond at a point *A*, as shown in the structural formula. The anionic site was simulated as for Fig. 2.

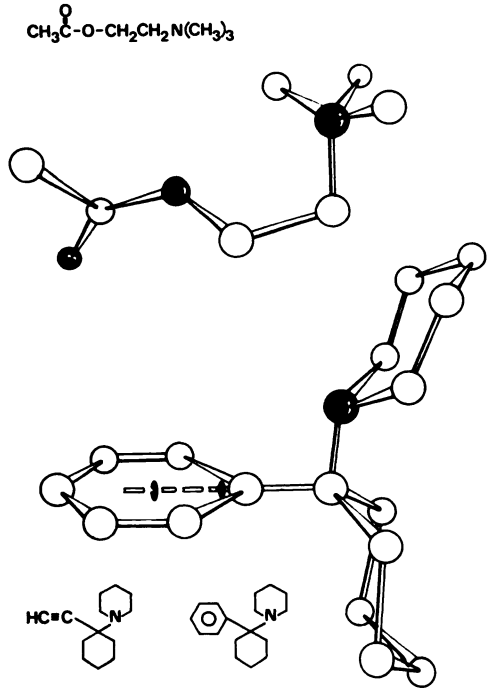


FIG. 4. *Spatial correspondence of functional groups in acetylcholine and phenyl (I) and ethynyl (V) derivatives of phencyclidine*

$$\rho(r) = 2\sum_i\sum_{\mu,\nu} C_{\mu i}C_{\nu i}A_\mu(r)e^{-\alpha_\mu r^2}A_\nu(r) \cdot e^{-\alpha_\nu r^2} = \sum_{\mu,\nu} D_{\mu\nu}f_{\mu\nu} \quad (5)$$

$D_{\mu\nu}$ represents an element of the density matrix obtained in Eq. 3, and $f_{\mu\nu}$ represents the product of two Gaussian functions. The contribution from the nuclei is calculated as

$$V_N(r) = \sum_{\alpha}^{\text{nuclei}} \frac{Z\alpha}{|r_\alpha - r|} \quad (6)$$

Since the molecular wave functions, calculated with the INDO procedure, are expressed in terms of a Slater type basis $\{A_\mu(r)e^{-\alpha_\mu}\}$, a first step in the calculation of the potential consists of a Gaussian expansion of the Slater orbital basis. This is done according to the method of Hehre *et al.* (40).

The contribution of each pair of Gaussians in Eq. 5 can be calculated separately, because the product of any two Gaussian functions can be represented by a new, single Gaussian function, even if the two primary functions are centered on different nuclei (41). The calculation of the contribution to $V(r)$ from an *s*-type Gaussian is

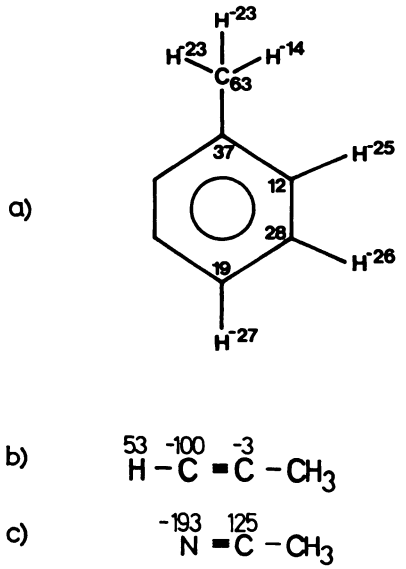


FIG. 5. *Net atomic charges in fragments representing (a) phenyl derivative (I), (b) ethynyl derivative (V), and (c) acetonitrile derivative (VI) of phencyclidine*

exemplified in the APPENDIX. A more detailed mathematical formulation can be found in ref. 39.

This analytic formulation of the potentials remains valid for any approximation of the molecular wave function. The accuracy of the calculated values of the potentials, however, is dependent on the quality of the wave functions used. Since the pattern of the potentials, rather than the absolute values, was the main interest of this study, we chose to remain within the INDO approximation without performing a "deorthogonalization" (42) of the molecular orbitals. Potentials calculated from such INDO orbitals are very similar to those obtained from wave functions *ab initio*, although the results somewhat underestimate the more accurate results.[7] This difference between values obtained from semi-empirical and *ab initio* wave functions is much smaller for INDO orbitals[7] than for the previously compared CNDO wave functions (42). The characteristic pattern of the potentials, however, is observable in the results of either approximation. The calculation procedure has been formulated as a highly efficient computer algorithm. The results are expressed directly as the interaction energy with a positive point charge. The time needed for the calculation of the numerical value of the potential at one point [$r \equiv (x, y, z)$] is dependent on the size of the functional basis of the molecular orbital calculation; for acetylcholine an average time of 0.08 sec was needed on an IBM 370/165 machine. A grid of 3000–4000 points would be needed to obtain the potential maps of molecules of the geometrical size of acetylcholine. However, unlike numerical methods based on the calculation of nuclear attraction integrals (42, 43), this method directly calculates the derivatives of the potential at each point, and computer-drawn isopotential curves can be readily obtained (39).

STRUCTURE OF INTERACTION PATTERN

The correspondence of the active groups in acetylcholine-like molecules with certain molecular structures embodied by drugs of the phencyclidine series is illustrated in Fig. 4. The distance pattern in the latter case is based on the crystallographic data for phencyclidine base, which is assumed to apply to all phencyclidine derivatives used in this study (Table 1). This evidence indicates that in the phencyclidine molecule the distance between the protonated nitrogen atom and what is considered a region of high electron density is compatible with the muscarinic pharmacophore (Fig. 1). Adjacent to these two sites are secondary structures that may engage in hydrophobic bonding, which further reinforces the drug-receptor interaction. The net atomic charges calculated for the model molecules (Fig. 5), of course, bear the characteristics of the negative sites which substitute the ester oxygen, but a more factual representation can be obtained from potential field maps.

The interaction pharmacophore of acetylcholine, as represented by the potential energy maps, is given in Fig. 6. The main features revealed by this pattern are a positive region extending over the whole molecular space (especially around the cationic head) and two regions of negative (attractive) energy near the 2 oxygen atoms. The molecular conformation for which the potential energy map has been calculated

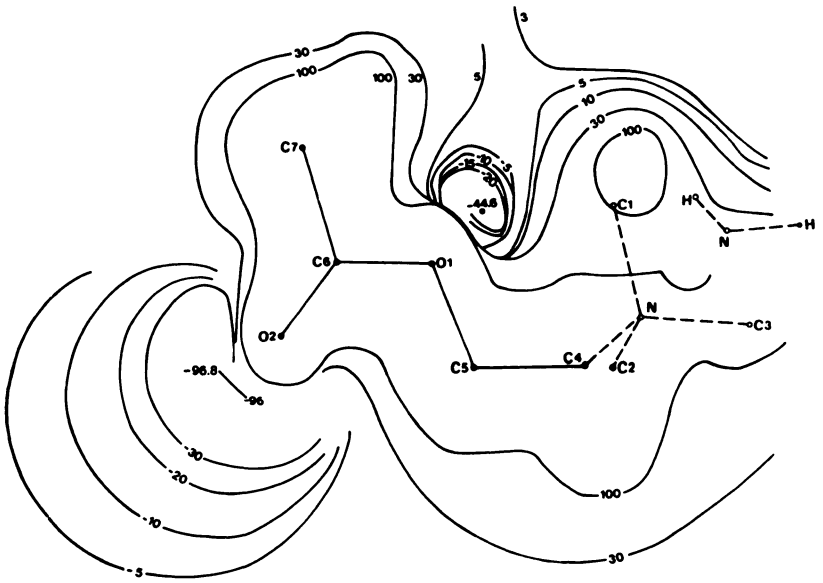


FIG. 6. *Electrostatic potential energy map for acetylcholine interacting with the anionic group NH_2^-, in plane of atoms connected by full lines*

Dashed lines connect atoms situated beneath this plane. Hydrogens are shown only for the anionic group. Units are kilocalories per mole.

corresponds to a particular minimum in the surface calculated for acetylcholine by Beveridge and Radna (20). This conformation also corresponds to the "global minimum" geometry calculated by Pullman *et al.* (18) by a different method, and is considered to be the one involved in biological activity (19).

Since this conformation corresponds to the positive ion form of the molecule, a hypothetical negative group, NH_2^-, has been brought close to the cationic head, at different distances, to simulate the anionic site of the receptor. In order to identify and eliminate possible changes in the potential energy maps that may be ascribed to this particular anion, the same calculations and mappings were also performed with an OH^- group. Since no significant differences were observed in the potential energy maps of the acetylcholine moiety in either model, we may assume that, within certain limits, the nature of the anion does not greatly affect the interaction pharmacophore generated around acetylcholine. It should be stressed, however, that the region of high reactivity near the ester oxygen occurs only in the complex of acetylcholine cation plus anionic site, and cannot be observed in the isolated acetylcholine cation. Remarkably, the negative region near the carbonyl oxygen is less affected by the "approach" process. However, the location of both attractive regions remains invariant throughout this process. This situation warrants further study of the relative contributions of the various functional groups of acetylcholine in binding to the receptor and its activation. For our immediate purpose, however, we consider the negative region near the ester oxygen to be more important for binding to the muscarinic receptor than the one near the carbonyl oxygen. Indeed, the first region finds analogy in the interaction pharmacophore of the various phencyclidine models discussed below.

The potential energy maps for the propyne and acetonitrile fragments are given in Figs. 7a and 8a, respectively.[8] Whereas the pattern of the positive (repulsive) potential energy, at some distance from the triple bond, is nearly identical for the two fragments, the maps differ considerably in their

[8] All the model molecules being neutral species, no anionic site simulation is required.

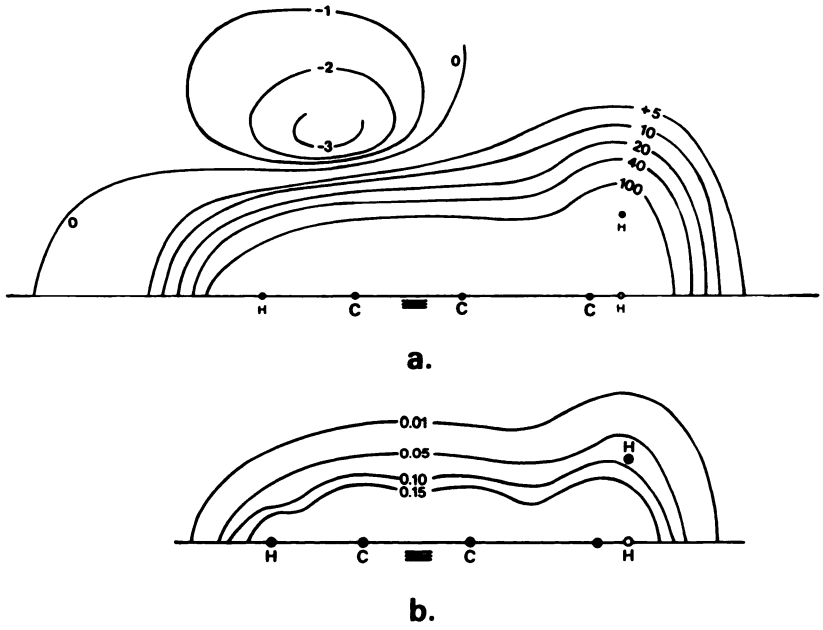


FIG. 7. *Reactivity indices for propyne fragment*

a. Electrostatic potential map, in units of kilocalories per mole. b. Electron density distribution contours, in units of electrons per cubic atomic unit. ●, atoms in the plane. Because of the symmetry of the triple bond region, only the upper half is shown.

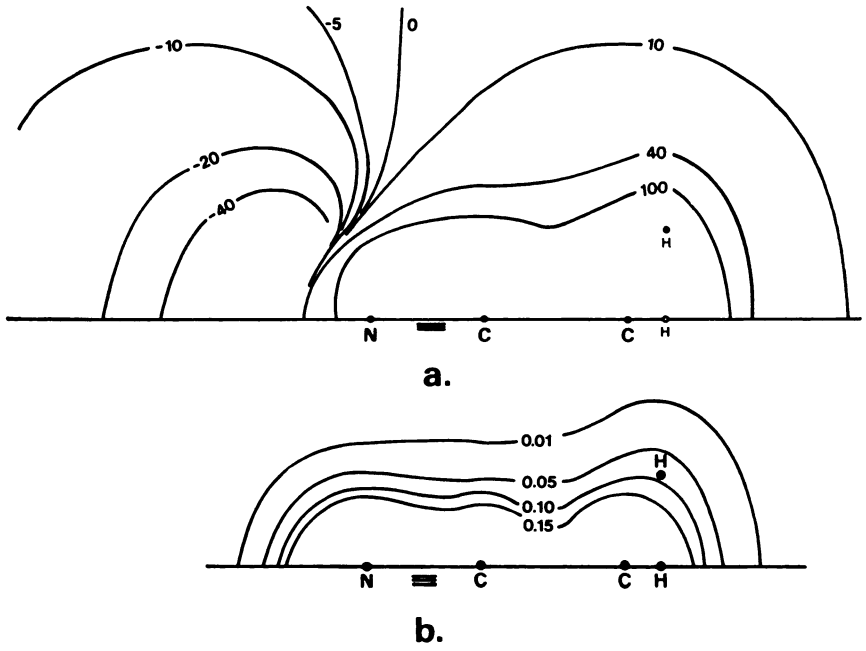


FIG. 8. *Reactivity indices for acetonitrile fragment*

a. Electrostatic potential map, in units of kilocalories per mole. b. Electron density distribution contours, in units of electrons per cubic atomic unit. Plane shown as in Fig. 5.

negative potential patterns. The negative (attractive) region is near the triple bond in the acetylene derivative but is shifted to the far end of the nitrogen atom in acetonitrile. The different locations of the attractive regions are, of course, due to the different nature of the electron charge distributions in the two fragments. In the nitrile fragment the location of the negative region is dictated by the localization characteristics of the lone-pair electrons of the nitrogen atom. The high polarity of the nitrile bond is characterized by the withdrawal of electron charge from the triple bond region, which results in the disappearance of the negative potential observed in this region in the case of acetonitrile. Such differences in localization of charge density are important enough to entail different interaction pharmacophores and, therefore, different biological activities (Table 2). It is clear that a direct analysis of the charge distribution alone, in Figs. 7b and 8b, could not have accounted for the difference in reactivities.

The potential energy map of the unsubstituted phenyl derivative (1,1-phenylcyclohexylpiperidine) is represented by the model fragment shown in Fig. 9. Superposition on acetylcholine would cause the wide negative region surrounding the phenyl fragment in phencyclidine to overlap the attractive region in the potential map of acetylcholine, situated near the ester oxygen. This situation is characteristic of various types of aromatic systems, provided that no electron-withdrawing substituents are present to induce drastic changes in the potential energy maps (43). Such is indeed the case for a *p*-nitro-substituted fragment, shown in Fig. 10. As in the simpler nitrile derivative, the charge localization near the oxygen atoms entails the disappearance of the attractive potential surrounding the molecular plane and its transfer to the region of the oxygen lone pairs. The resulting modification of biological activity in such derivatives of phencyclidine is similar to that observed in the nitrile derivative, and will be discussed in a forthcoming report.

DISCUSSION

It has been proposed that certain aspects of chemical reactivity can be dealt with, to a good approximation, by considering intermolecular interactions at regions of minimal potential energies (44). Thus, where mutual reorientation of molecules is expected to occur, positively charged groups should point toward regions in which the potential is most negative. Such regions are generated

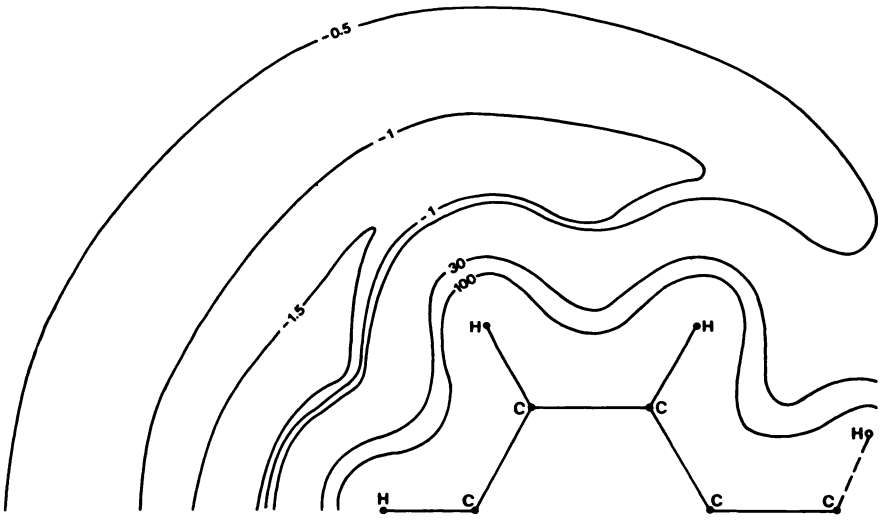


FIG. 9. *Electrostatic potential maps for fragment ϕ—CH_3, representing phenyl derivative (I)*
●, atoms in the plane shown. Because of symmetry, only half the plane is shown. Units are kilocalories per mole.

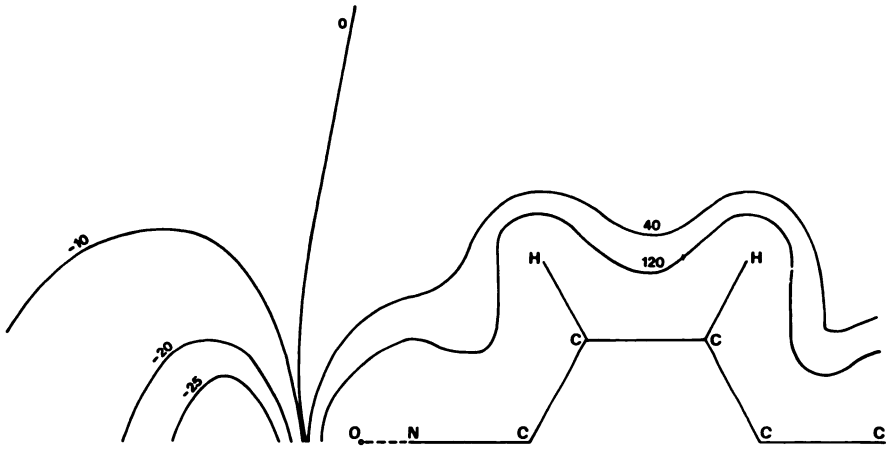


FIG. 10. *Electrostatic potential maps for fragment O_2N ϕ—CH_2, representing p-nitro derivative* Only half the plane is shown. Oxygen atoms are in a plane perpendicular to the ring.

by localized high electronic densities. This approach is expected to be most adequate for an ionic interaction mechanism (44). It is conceded that the short-distance interaction effects of polarizability and total charge redistribution may modify significantly the interaction energy values; yet the geometrical pattern of the interaction energy remains essentially constant (42–44).[7] The electrostatic potential contours can therefore be considered a reasonable representation of the interaction pattern itself, i.e., an interaction pharmacophore.

The observed dependence of the absolute value of attractive energy in the ester oxygen region in acetylcholine on interaction with a negatively charged group suggests that the contribution of this region to binding is secondary to that of the cationic head. However, since its position remains unchanged after interaction, its mere occurrence in a definite region may imply stereospecific binding to the receptor, regardless of form or absolute value. The interaction pharmacophore thus obtained from the potential energy map of acetylcholine may therefore represent a compelling criterion for assessing possible interactions with the cholinergic receptor itself. We shall presently see to what extent the drugs in the phencyclidine series abide by this criterion.

1. Comparison of Figs. 6 and 7a with Table 1 indicates that the attractive region in the ethynyl derivative (V) will almost coincide with the corresponding region near the ester oxygen in acetylcholine. On the other hand, the negative region in the nitrile fragment (Fig. 8a) is located in a different region of the molecular space. No overlap is therefore possible between the attractive regions of the nitrile derivative (VI) and acetylcholine when both molecules are at the proper orientation with respect to the receptor. Moreover, this region in the nitrile derivative will be repulsive. One may conclude that the phencyclidine analogue in which the phenyl ring has been replaced by a C≡N function should be devoid of any activity that requires binding to the cholinergic receptor. In contradistinction, the ethynyl analogue (V), complying with requirements of the acetylcholine interaction pharmacophore, competes with acetylcholine for the same specific receptor. These conclusions have been experimentally confirmed in Part III of this series,[9] and are summarized in Table 2.

2. The competitive inhibition of cholinesterases by these drugs may be traced to the same common interaction pharmacophore.[9] For these systems the accepted model includes interactions near both the ester oxygen and the positively charged carbonyl carbon of acetylcholine (Fig. 4). It is clear from Figs. 7a and 9 that such

[9] S. Maayani, H. Weinstein, S. Cohen, and M. Sokolovsky, results to be published.

interactions are possible for both the ethynyl (V) and the unsubstituted phenyl derivatives (I), the region above the ring being entirely positive. In contradistinction, the potential energy map for the acetonitrile fragment (Fig. 8a) shows that the required interactions should be highly unfavorable energetically for the nitrile derivative (VI). In this case the attractive (negative) characteristic is missing in the region corresponding to the ester oxygen, while this negative potential energy reaches high values where the carbonyl carbon of acetylcholine would have generated a region of positive energy. The interaction with both negatively and positively charged groups in the active site of the cholinesterases is therefore repulsive, preventing bonding with this site. This result finds confirmation in the experimental situation found,[9] in which the nitrile derivative has been singled out as having the weakest (if any) inhibitory activity, and no "protective effect" whatsoever.

The conclusion that the interaction pharmacophore is a reasonable representation of the electronic structural characteristics required for direct interaction with the receptor is therefore strongly supported by the close correspondence established here between the interaction pharmacophore of acetylcholine itself and the potential energy maps of the active anticholinergic drugs discussed in this series of reports. This is reinforced by the observation that pairs in which structural differences cause profound changes in the potential energy maps—e.g., nitrile vs. ethynyl or phenyl vs. *p*-nitrophenyl—vary widely in activity. Specific binding at the receptor site is therefore the cause of the competitive antagonism observed with these drugs.

The question that arises here is, of course, why such binding does not lead to agonist activity. Undoubtedly, the nonpolar parts of the molecule play a dominant role. Since these parts do not much affect the interaction pharmacophore, the nature of their contribution to the drug-receptor complex must await further knowledge of the structure and function of the regions immediately adjacent to the receptor proper. Much can be concluded, however, from a comparative investigation of the molecular structure of agonists and antagonists. It becomes plausible that the agonistic response is elicited in a sequence of two stages: (a) direct interaction with the receptor and (b) activation of the receptor. The first stage sets the requirements represented by the interaction pharmacophore and molecular species, which generate the specific spatial pattern of positive and negative potentials (regardless of the absolute values), and may be expected to establish a direct interaction with the corresponding sites of the receptor. The rigid molecular structure of antagonists, for which the elements that generate the interaction pharmacophore are readily identifiable (as in Fig. 11), supports the suggestion that the activation process should be related to a rearrangement in the conformation of the drug-receptor complex (45, 46). Competitive antagonistic activity is therefore considered to consist of a shielding of the receptor site by molecular species which meet the requirements for a direct drug-receptor interaction. In the phencyclidine series the cyclohexyl ring is conducive to (a) structural rigidity of the two other rings, which incorporate the elements of the pharmacophore and remain quasi-fixed in space (according to space-filling models), and (b) an increased hydrophobic binding of the molecule to the peripheral regions of the receptor, which is characteristic of nonpolar groups beyond a certain size (48, 49). Both elements are considered to lead to the antagonistic properties of those derivatives of phencyclidine which meet the requirements of the interaction pharmacophore.

Molecular species in which the elements of the interaction pharmacophore are generated by an essentially flexible structure should be expected to exhibit agonistic activity. Such examples may be found in oxotremorine (21–23) and compounds of the general form (13)

$$CH_3—(CH_2)_m—C\equiv C—(CH_2)_n—N^+(CH_3)_3$$

and

$$CH_3—(CH_2)_m—HC=CH—(CH_2)_n—N^+(CH_3)_3$$

where $n = 1, 2$ and $m = 0, 1$.

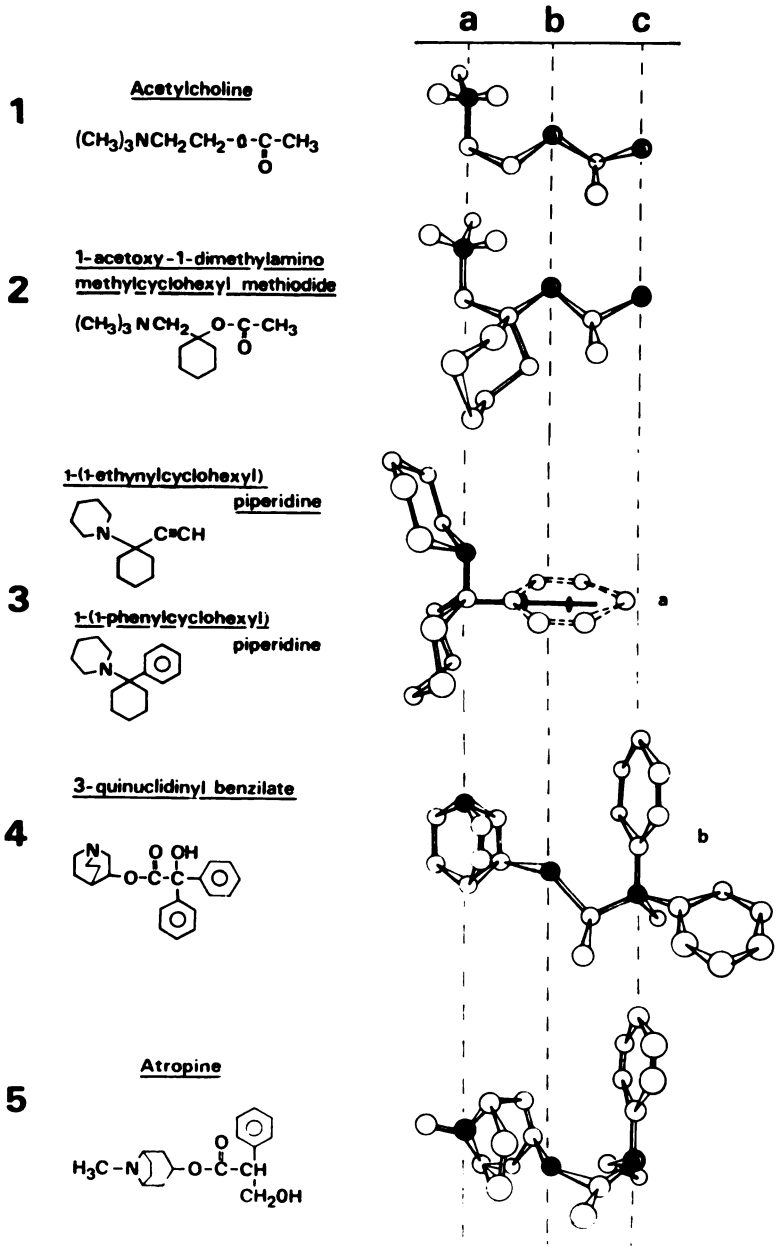


FIG. 11. *Correlation of functional groups in molecular structural models of acetylcholine antagonists* Molecular models *a* and *b* were drawn according to Argos *et al.* (28) and Meyerhoffer and Carstrom (47), respectively.

APPENDIX

Let

$$\nabla^2 V_1(r) = -4\pi e^{-\alpha r^2} \qquad \text{(I)}$$

For such a case with radial symmetry we have

$$\nabla^2 V_1 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial}{\partial r}\right) V_1 = V_1'' + \frac{2}{r} V_1' \qquad \text{(II)}$$

Using the equality

$$\frac{1}{r}\frac{\partial^2}{\partial r^2}(rV_1) = V_1'' + \frac{2}{r}V' \qquad \text{(III)}$$

we get by substitution into Eq. I

$$\frac{1}{r}\frac{\partial^2}{\partial r^2}(rV_1) = -4\pi e^{-\alpha r^2} \qquad \text{(IV)}$$

The potential V_1 is now obtained by integrating Eq. IV twice:

$$V_1 = \frac{2\pi}{\alpha}\cdot\frac{1}{r}\cdot\int_0^r e^{-\alpha\hat{r}^2}\,d\hat{r} + \frac{C_1}{r} + C_2 \qquad \text{(V)}$$

From the boundary conditions

$$V_1(\infty) = 0 \qquad \text{(VI)}$$

$$V_1(0) = \text{finite}$$

we derive for the two constants

$$C_1 = C_2 = 0 \qquad \text{(VII)}$$

The potential function value at each point will therefore be given by

$$V_1(r) = \left(\frac{2\pi}{\alpha r}\right)\int_0^r e^{-\alpha\hat{r}^2}\,d\hat{r} \qquad \text{(VIII)}$$

where the value of the integral is obtained from the well-known "error function."

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