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Molecular Electrostatic Potentials: An Effective Tool for the Elucidation of Biochemical Phenomena

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The electrostatic potential $V(\vec{r})$ that is created in the space around a molecule by its nuclei and electrons (treated as static distributions of charge) is a very useful property for analyzing and predicting molecular reactive behavior. It is rigorously defined and can be determined experimentally as well as computationally. The potential has been particularly useful as an indicator of the sites or regions of a molecule to which an approaching electrophile is initially attracted, and it has also been applied successfully to the study of interactions that involve a certain optimum relative orientation of the reactants, such as between a drug and its cellular receptor. A variety of methods for calculating $V(\vec{r})$ is available, at different levels of rigor. For large biologically active molecules, multipole expansions and superposition of potentials computed for subunits have been found to be effective. A large number of chemical and biochemical systems and processes have now been studied in terms of electrostatic potentials. Three examples of such applications are surveyed in this paper. These deal with: (a) reactive properties of nucleic acids, including their component bases; (b) biological recognition processes, including drug–receptors and enzyme–substrate interactions; and (c) chemical carcinogenesis, referring specifically to the polycyclic aromatic hydrocarbons and halogenated olefins and their epoxides. For each of these areas, examples of the use of electrostatic potentials in elucidating structure–activity patterns are given.

The Meaning and Use of the Electrostatic Potential

Definition and Significance

Any distribution of electrical charge, such as the electrons and nuclei of a molecule, creates an electrical potential $V(\vec{r})$ in the surrounding space. $V(\vec{r})$ may be regarded as the potential of the molecule for interacting with an electrical charge located at the point $\vec{r}$. For example, an approaching point will charge $\pm Q$ will interact with this electrical potential, with an energy of interaction equal to exactly $\pm QV(\vec{r})$, where $\vec{r}$ is the position of the point charge. Thus a positive point charge is attracted to those regions in which $V(\vec{r})$ is negative, since this leads to a negative (stabilizing) interaction energy, and it is repelled from regions of positive potential, in which the interaction energy is positive and destabilizing.

A knowledge of the electrical potential, $V(\vec{r})$, around a molecule should therefore help considerably in interpreting its reactive behavior toward charged species (even, qualitatively, when they are larger than point charges) and in predicting the sites of the molecule at which they are most likely to react. Indeed, over the past 15 years, the electrical potential has become a well established tool for the elucidation of molecular reactive properties (*1–4*). In these applications, the system is normally viewed as having a static distribution of electronic charge around a rigid nuclear framework; hence the term "electrostatic potential" is commonly used for $V(\vec{r})$.

If a molecule has an electronic density function $\rho(\vec{r})$, then its electrostatic potential at any point $\vec{r}$ is given rigorously by eq. (1):

$$V(\vec{r}) = \sum_A \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r}\,')d\vec{r}'}{|\vec{r}\,' - \vec{r}\,|} \qquad (1)$$

Z_A is the charge on the nucleus A, located at $\vec{R}_A$. The first term on the right side of eq. (1) represents the contribution of the nuclei, which is positive; the second

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term brings in the effect of the electrons, which is negative.

Eq. (1) is an exact formula for the electrostatic potential due to the set of nuclei $\{Z_A\}$ and the electronic density $\rho(\vec{r})$. On the other hand, the latter function is generally obtained from an *ab initio* or semiempirical molecular wave function and is accordingly approximate, as is also, therefore, the resulting $V(\vec{r})$. It has been shown, however, that Hartree-Fock wave functions give relatively good results (first-order accuracy) for properties that are calculated from the electronic density function, as is $V(\vec{r})$ (*5–7*). Furthermore, extensive investigations have shown that a generally reliable electrostatic potential can be obtained even with self-consistent-field (SCF) wave functions that are not near Hartree-Fock quality (*1, 8–13*). $V(\vec{r})$ is also being determined experimentally to an increasing extent, by diffraction methods (*14–17*), but at present the quantum chemical approach remains the more accurate and more practical one.

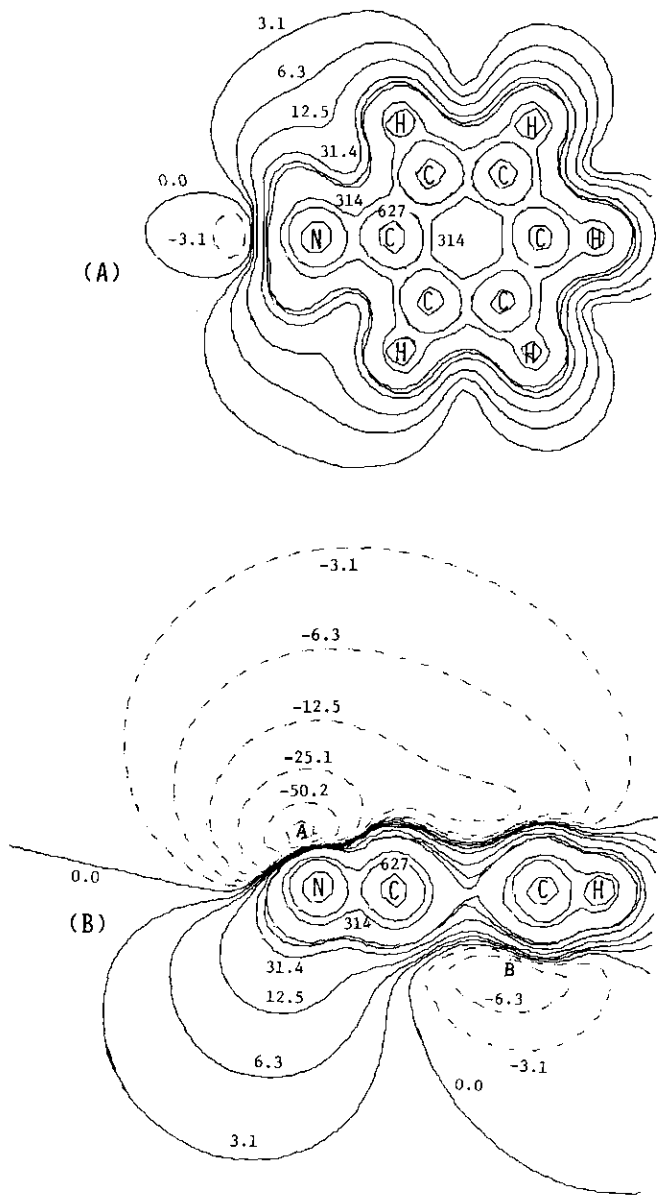


FIGURE 1. Calculated electrostatic potential of aniline. Electrostatic potential of aniline, as computed from an *ab initio* SCF STO-6G wave function using a geometry that has been optimized at the STO-3G level with the GAUSSIAN 80 program (*119*): (*A*) in the plane of the ring; (*B*) in the symmetry plane perpendicular to the ring. The contour values are given in kcal/mole. The position of potential minima, in (*B*), are indicated by *A* and *B*, with $A = -87.2$ kcal/mole and $B = -10.2$ kcal/mole. The positive region in the lower left portion of (*B*) is due to the amine hydrogens.

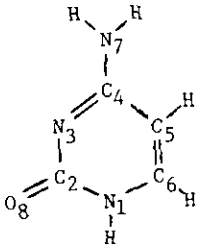
Figure 1 shows our calculated electrostatic potential for aniline, computed from the *ab initio* SCF STO-6G wave function using an optimized geometry. The values of the contours are given in energy units (kcal/mole) and actually represent the quantity $+QV(\vec{r})$, where $Q = 1$. [This is, of course, equal, in magnitude and sign to $V(\vec{r})$.] Thus, there are the interaction energies of the static charge distribution of aniline with a proton located anywhere in its neighborhood. In those regions where $V(\vec{r})$ is negative, the effect of the electrons predominates [Eq. (1)], and these are accordingly attractive to an approaching electrophile. As anticipated, the potential is strongly negative above and below the aromatic ring in aniline, reflecting the presence of the π electrons. The most negative value, -87.2 kcal/mole, is in the region that is associated with the nitrogen lone pair, and is indicative of the basic nature of the amine group.

An important feature of the electrostatic potential is that it is a real physical property, as evidenced by the fact that it can be determined experimentally (*14–18*). It is rigorously and unambiguously defined by Eq. (1), and has a clear physical meaning: it expresses the net electrical effect of the electrons and nuclei of a system in the surrounding space. The physical reality of the electrostatic potential stands in contrast to the unavoidable arbitrariness and ambiguity associated with many other indices of reactivity, such as atomic charges [which are actually a point-charge model representation of $V(\vec{r})$]. While these have sometimes been quite useful in interpreting general trends and relative tendencies, they are nevertheless defined properties and do not directly correspond to anything real. Thus, they may sometimes have little or no physical meaning (*19–22*).

An Example: Cytosine

The points that have been brought out in the preceding discussion can be illustrated by referring to the calculated electrostatic potential of cytosine, I (*23*). This shows a large negative region in the molecular plane, encompassing both N_3 and O_8. Within this region there are two local minima in $V(\vec{r})$; these are points at which $V(\vec{r})$ attains its most negative values, and to which an electrophile would therefore be most strongly attracted. One of these is near N_3, where the potential reaches a value of -93.5 kcal/mole, and the other is near O_8, where $V(\vec{r}) = -86.7$ kcal/mole. There is also a much weaker region of negative potential above and below the mo-

I



lecular plane, with a minimum of −13.7 kcal/mole by the amine nitrogen, N_7.

From the electrostatic potential, it would be predicted that an electrophile would preferentially attack cytosine in the molecular plane and at the N_3 position; its second choice would be O_8. This is exactly what is observed experimentally. N_3 is the greatly favored site for both protonation and alkylation (which is believed to occur by electrophilic attack) (*24–26*). Furthermore, cytosine complexes to Cu(II) through N_3, with a significant secondary interaction between O_8 and the Cu(II) (*27,28*). When N_3 is not accessible, as in DNA (in which it is involved in hydrogen bonding), some electrophiles have been observed to go instead to O_8 (*29*), while others then simply do not react with the cytosine (*26*). Thus, cytosine, chosen here as an example, is observed experimentally to behave toward electrophiles in exactly the manner that would be predicted from its electrostatic potential.

Predictions based upon the calculated atomic charges, on the other hand, would be seriously in error. In cytosine, the most negative atomic charges are found to be on N_7 and N_1, −0.72 and −0.60, respectively, followed by O_8, −0.52, and finally N_3, −0.46 (*30*). This is totally inconsistent with the experimental fact that N_3 is the most attractive site for electrophilic attack, with O_8 being next (*24–29*).

Limitations upon the Use of the Electrostatic Potential

While the electrostatic potential has proven to be an effective technique for analyzing and predicting molecular reactive behavior, it is important to recognize certain intrinsic limitations upon its use. $V(\vec{r})$, as defined by Eq. (1), is a property of a molecule M in some particular state; it reflects only the charge distribution of M in that state. $V(\vec{r})$ does not take into account the changes that occur in M as it begins to interact with some approaching species (e.g., polarization and charge transfer), nor does it reflect in any way the nature of the latter. One can of course use various approaches, including perturbation techniques, to estimate the contributions of such factors, and some significant progress has been made along these lines (*3,31*). However, this goes beyond the use of electrostatic potential itself as a guide to molecular reactivity.

Because of these limitations, the electrostatic potential is most useful as a guide to the early stages of a reaction, in which the attacking species is not yet very close to the molecule M and their mutual polarization, charge transfer, etc., are relatively insignificant. The implications of this will become more apparent in a subsequent section.

It should also be pointed out that the electrostatic potential cannot be applied as readily to the analysis of nucleophilic processes as the electrophilic ones. A positive potential does not necessarily indicate a corresponding tendency to react with nucleophiles. The positive charges of atomic nuclei, being very highly concentrated, create strong positive potentials that may outweigh the negative contributions of the electrons, which are dispersed* but nevertheless may not reflect a corresponding affinity for nucleophiles. We have recently developed a procedure that does make it possible to apply electrostatic potentials to the study of nucleophilic reactions (*33*); this approach involves computing $V(\vec{r})$ for the substrate molecule in a state of distorted geometry, already somewhat amenable to the attack of the nucleophile.

Relationship between Electrostatic Potentials and Kinetic/Mechanistic Aspects of Reactions

It was stated earlier that the energy of interaction between a point charge $\pm Q$ located at $\vec{r}$ and the electrostatic potential $V(\vec{r})$ created by some charge distribution is given exactly by $\pm QV(\vec{r})$. If one wishes to account for the fact that the charge distribution will be affected (polarized) in some manner by the presence of the point charge, then perturbation theory can be used to obtain the interaction energy; $\pm QV(\vec{r})$ will be the first-order term in the resulting expression (*3,31*). For interactions between two charge distributions (as opposed to a charge distribution and a point charge), the mathematical treatment becomes more complicated, but the electrostatic contribution remains a well-defined element of the interaction energy. For these reasons, $V(\vec{r})$ has sometimes been regarded as related to the thermodynamic, rather than kinetic and mechanistic, aspects of reactions.

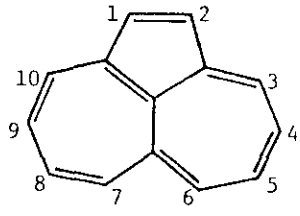
In reality, however, the applications of the electrostatic potential cut across the traditional division between thermodynamic effects on the one hand and kinetic/mechanistic ones on the other. One aspect of its relationship to the latter can be brought out in terms of the Bell-Evans-Polanyi principle (*34–36*). According to this, in the reactions of a series of related molecules, $A_1, A_2, \ldots A_n$, with some given reactant B, the differences in the activation energies are linearly related to the differences in the heats of reaction. This is a direct

*For example, the electrostatic potential of a free atom is positive everywhere (*32*).

link between thermodynamics and kinetics. It means that if the electrostatic potentials at some particular sites in such a series of molecules are related to their interaction energies with B, then they are also a measure of the relative activation energies and hence relative rates of reaction of these molecules with B.

The electrostatic potential of a molecule is indicative of what an approaching species encounters when it first comes into the neighborhood of the molecule, before significant polarization of the latter has taken plcae. The potential is accordingly relevant to the question of what is the most favored path of approach and the preferred region of initial attack. In this manner it reveals mechanistic aspects of a reaction. For instance, the electrostatic potential computed for acehepthylene (II) shows

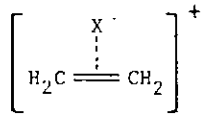
II



that the C_1—C_2 region has the most negative potential associated with it and therefore should be the most likely target for electrophilic attack (*37*). This is in full accord with the experimental observation that protonation initially occurs exclusively at C_1 or C_2, even though the most stable final site for the proton is near C_6, to which it eventually migrates (*37,38*). [From the calculated atomic charges (*37*), protonation would incorrectly be predicted to occur at C_4 or C_9.] Thus the electrostatic potential correctly reveals a key mechanistic feature of the reactivity of this molecule, the site of initial proton attack; this is not, however, the site that is favored thermodynamically.

A second such example is ethylene, for which $V(\vec{r})$ shows the most favored path of approach of an electrophile to be perpendicular to the molecular plane at the midpoint of the C = C bond (*39*). This is in full agreement with the experimental evidence for the addition reactions of Cl_2, Br_2 and I_2, according to which these occur through an intermediate halonium ion, III (*40*):

III



The halogen, X, subsequently moves to one of the carbons. Another case in which the electrostatic potential correctly predicts that the initial approach is to a bond rather than an atom is that of cyclopropane, in which the most negative regions are associated with the strained C—C single bonds (*41,42*).

On the other hand, the initial site of attack does very often correspond to the most stable product. Many such examples have been presented and reviewed (*1–3*), and one (cytosine) was analyzed in detail earlier in this paper. The preceding discussion shows, however, that when the electrostatic potential is being used to elucidate electrophilic and nucleophilic processes, it is clearly related to the kinetic and mechanistic aspects of the reactions.

Methods of Calculating the Electrostatic Potential

The electrostatic potential of a chemical system is given rigorously in terms of the electronic charge density, $\rho(\vec{r})$, by Eq. (1). In practice, molecular electronic density functions obtained by quantum chemical methods are essentially always approximations, at various possible levels of accuracy. Starting with such a $\rho(\vec{r})$, one can then proceed to evaluate Eq. (1) either rigorously or approximately. Even when this is done rigorously, however, the accuracy of the resulting $V(\vec{r})$ is naturally limited by that of $\rho(\vec{r})$.

Various procedures for calculating $V(\vec{r})$ have been discussed and analyzed elsewhere (*3,43*). Here we shall limit ourselves primarily to mentioning a few recent developments.

$V(\vec{r})$ can of course be obtained by substituting $\rho(\vec{r})$ directly into Eq. (1) and evaluating—exactly or approximately—the resulting integrals, or alternately, by integrating another exact relationship, Poisson's equation (*44,45*):

$$\nabla^2 V(\vec{r}) = 4\pi\rho(\vec{r}) \tag{2}$$

Another approach that has been studied very extensively involves expressing $V(\vec{r})$ as a multipole expansion, written in terms of one or more centers (*46–48*). In a recent adaptation of this technique, designed to facilitate the treatment of large biological molecules, each overlap term in the electronic density function was replaced by a one-center expansion that went as far as the quadrupole terms (*49*). This method was found to correctly reproduce $V(\vec{r})$ at distances greater than 2.0 Å from the constituent atoms of the molecule. In later improvements of this approach, multipole expansions were used to represent localized molecular orbitals (*50*), and octopole terms were included in the expansions (*51*). By choosing the centroids of the localized molecular orbitals as the centers for the expansions, the dipole terms could be eliminated.

These expansion procedures have been used within the context of a scheme in which $V(\vec{r})$ for a large biological system, such as a segment of DNA, is obtained by dividing it into subunits, computing wave functions, electronic densities and electrostatic potentials for the individual subunits, and then superposing these potentials to produce $V(\vec{r})$ for the whole system (*52,53*). The subunits are created by breaking appropriate single bonds and introducing hydrogen atoms to saturate the resulting free valencies. Tests of this approach indicate that if the subunits are chosen carefully, the resulting superposed potential should be a good approximation to

that computed directly for the entire system (*51,52*); the perturbing effects of the added hydrogens are relatively insignificant.

Multipole expansions are customarily expressed in terms of spherical polar coordinates referred to the various centers. In a variation of this, expansions written in terms of spheroidal coordinates were used with some success to obtain analytical expressions that approximate $V(\vec{r})$ for several molecules that can be regarded as being oblate-spheroidal in shape (*54,55*).

The concept of representing localized molecular orbitals by multipole expansions has the desirable feature that such expansions could conceivably be transferred from one molecule to another, provided of course that the localized molecular orbital is reasonably valid for both molecules. The possible transferability of such "group potentials," representing, for example, lone pairs, core orbitals, σ or π bonds between the given pairs of atoms, etc., has received a considerable amount of study (*1,2,56*), with some impressive and encouraging results. A great deal of computational time could be saved if a satisfactory approximation to a molecular electrostatic potential could be achieved by combining the appropriate group potentials, transferred from other systems. This would also make it possible to obtain at least qualitative representations of $V(\vec{r})$ for very large systems that cannot presently be treated by other means. This is already being done to some extent (*57*).

One means of expressing group potentials is in terms of appropriately chosen and distributed point charges. This approach has been tested for a number of molecules, with overall satisfactory results (*58,59*). It was suggested that such point-charge group potentials might be particularly useful in representing the effects of portions of a molecule that are relatively far from the region of interest (*58*).

The use of point charges to estimate molecular electrostatic potentials has great appeal, even apart from any relation to group potentials, because of its simplicity, and it has accordingly been the subject of considerable investigation. A very good representation of $V(\vec{r})$ can indeed be obtained in this manner, but it will normally require a large number of point charges situated throughout the space of the molecule, usually not limited to just the positions of the nuclei. (An alternative is to relax this requirement but to use the point charge model only for the contributions of remote portions of the system.) More extensive discussions of the point-charge approach are given in the literature (*3,43,60–64*).

Some Applications to Biological Systems

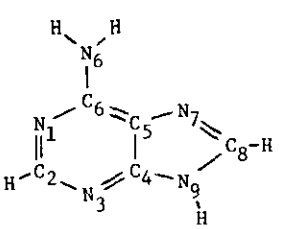
Electrostatic potentials have been widely used in studying various biological systems and processes. Some important developments in three such areas—nucleic acid reactive properties, biological recognition, and chemical carcinogenesis—shall be summarized in this section.

Reactive Properties of Nucleic Acids

The electrostatic potential has been applied extensively to the investigation of the reactive behavior of both the nucleic acid bases and also of increasingly large fragments of the DNA and RNA helices themselves.

For all of the bases [adenine (IV), guanine (V), cytosine (I), thymine (VI), and uracil (VII)], the most negative values of $V(\vec{r})$ (the potential minima) are found in the molecular plane and are associated with the nitrogen atoms of the rings and the carbonyl oxygens (*23,65*). These data are summarized in Table 1. Adenine

IV



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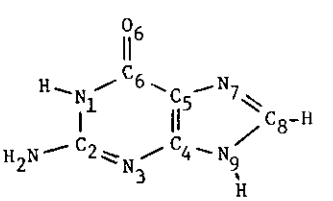

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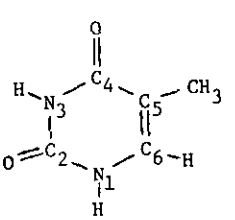

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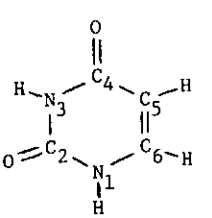


Table 1. Calculated electrostatic potential minima of nucleic acid bases.[a]

Molecule	Location of minimum	V_{min}, kcal/mole
Cytosine (I)	Near N_3, in molecular plane	−93.5
	Near O_8, in molecular plane	−86.7
	Near N_7, perpendicular plane	−13.7
Adenine (IV)	Near N_1, in molecular plane	−71.
	Near N_3, in molecular plane	−71.
	Near N_7, in molecular plane	−66.
	Near N_6, perpendicular plane	−14.6
Guanine (V)	Near N_7, in molecular plane	−91.
	Near O_6, in molecular plane	−75.
	Near N_3, in molecular plane	−64.
Thymine (VI)	Near O_4, in molecular plane	−56.5
	Near O_2, in molecular plane	−54.2
Uracil (VII)	Near O_4, in molecular plane	−57.3
	Near O_2, in molecular plane	−54.

[a]Data taken from Bonaccorsi et al. (*23*) and Pullman and Pullman (*65*).

has three minima; two of them, near N_1 and N_3, are similar in shape and depth, while the third, by N_7, is narrower and shallower. Guanine also has a minimum near N_3, but its deepest one is in the vicinity of N_7 and is part of the negative region that includes a second minimum close to O_6. Cytosine, already mentioned, has a similar extended region of negative potential, with minima near N_3 and O_8, while thymine and uracil have minima associated with the carbonyl oxygens.

In the remaining regions in the molecular planes, $V(\vec{r})$ is positive for these molecules. However there are some relatively weak out-of-plane negative regions and minima; the strongest of these are above and below the amine groups of adenine and cytosine, with others near C_8 of guanine and the C = C double bond of cytosine.

In proceeding to larger systems, there arises the question of how to present $V(\vec{r})$ in a form that can be readily understood and interpreted. The usual procedure of plotting two-dimensional isopotential contour maps is suitable for a relatively small or planar molecule, or when certain planes of obvious importance can be identified, which contain the interesting features. For large systems, an effective approach is to use the concept of a molecular surface (*66,67*). This is generally taken to be the outer surface of a set of intersecting spheres centered on the individual atoms, with radii given by χR_V, where R_V is the van der Waals radius of the atom and χ is a variable parameter that has the same value for all the atoms. By changing the magnitude of χ, one can obtain a set of surfaces that are at various distances from the nuclear framework. Thus, a proper choice of χ will ensure that the surface is sufficiently far from each nucleus that a satisfactory representation of $V(\vec{r})$ can be achieved by one of the approximate procedures mentioned above.

One effective mode of presenting the electrostatic potential calculated over a three-dimensional molecular surface is by means of computer-generated color graphics (*68*), in which various colors are used to represent specific numerical ranges of $V(\vec{r})$. The three-dimensional effect is achieved by varying the size and density of the points on the figures.

There has been a detailed investigation, using the approximate multipole expansion and superposition techniques described above, of how electrostatic potentials change in the progression from isolated nucleic acid bases to nucleosides, nucleotides, single helices and finally double helices (one double helical turn) (*65,69,70*). Poly(guanine·cytosine) and poly(adenine· thymine) model sequences were used in constructing the helices. In general, it was found that the potential minima associated with the bases become very considerably more negative in progressing through this sequence. For example, V_{min} for N_7 of guanine goes from −88 kcal/mole in guanine itself to −683 kcal/mole in the poly(guanine·cytosine) model of B-DNA. A major portion of these changes is due to the strongly negative contributions of the phosphates. The relative ordering of the potential minima of the bases is not preserved as the complexity of the system increases.

The conclusion that the potential minima associated with the reactive centers in the bases become more negative as the latter are incorporated into larger systems is consistent with the observation of a parallel increase in reactivity toward chemical carcinogens (*70,71*), (which are believed to be, generally, electrophilic in nature). This is indicative of the importance of the electrostatic factor in these carcinogenic interactions.

As part of this very extensive study of the properties of the nucleic acids, electrostatic potentials have been calculated for several forms of DNA (A-, B-, alternating B-, C-, D- and Z-DNA) as well as $tRNA^{Phe}$ (*65,66,69–73*). The distributions of negative potential in the various systems and their reactive behavior, toward positive ions for example, are analyzed in detail. Further references to these studies will be made in the discussion of chemical carcinogenesis.

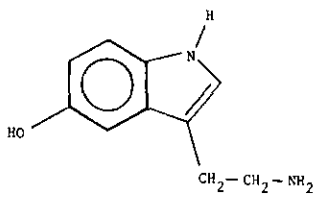
Biological Recognition Processes

Drug–receptor and enzyme–substrate interactions are two important classes of biological processes in which the initial step is one of "recognition"; the receptor of the enzyme "recognizes" that an approaching molecule has certain key features that will promote their mutual interaction. Such recognition is believed to take place typically when the drug and the receptor, or the enzyme and substrate, are at a relatively large separation. It precedes the formation of any covalent bond.

Since the electrostatic potential of a molecule is a physically-meaningful representation of how it is perceived by a system in its vicinity, it is natural to look to the potential in seeking the key features that determine whether or not a particular recognition will occur. The electrostatic potential has indeed proven to be an effective means of analyzing and elucidating recognition processes; in fact this is one of the areas in which it has been used with greatest success. In a number of in-

stances, the extent to which a certain drug or substrate reacts with a particular receptor or enzyme has been shown to be related to the degree to which the electrostatic potential of the former possesses certain characteristics that have been identified as being required for interaction with that receptor or enzyme. Several such studies will be briefly summarized.

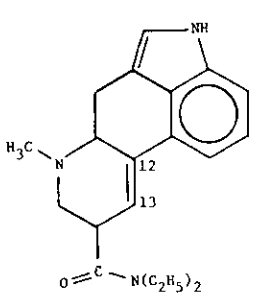
5-Hydroxytryptamine, (VIII) (5-HT, also known as serotonin), is a neurotransmitter that interacts with re-



VIII

ceptors both in the brain and in peripheral tissues. There are a number of other molecules that interact, to varying extents, with 5-HT receptors, including other hydroxytryptamines. The electrostatic potentials of the hydroxtryptamines have been found to have two characteristic minima on each side (above and below) of the indole portions of the molecules (*74–76*). One of these is associated with the hydroxyl oxygen, the other with the six-membered ring. When an "orientation vector" was drawn for each hydroxytryptamine, connecting these two minima along the potential gradient between them, it was found that the degree to which the direction of this vector deviates from that in 5-HT is related to the relative affinities of the two molecules for 5-HT receptors. This is interpreted as reflecting differences in the preferred orientation of each of the molecules relative to the receptor.

This line of reasoning explains the experimental findings that 5-HT and *d*-lysergic acid diethylamide, IX (LSD), act on the same receptors (*74–76*). This would not have been anticipated on the basis of the structures of the two molecules; it turns out, however, that the $C_{12}=C_{13}$ double bond in LSD produces a minimum in $V(\vec{r})$ that mimics the one associated with the hydroxyl group in 5-HT. As a result, the electrostatic potential

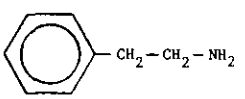


IX

of LSD shows the key features that are required for the molecule to interact effectively with 5-HT receptors. When a compound with a structure similar to that of LSD but having no corresponding double bond was tested experimentally, its affinity for the LSD/5-HT receptor was found to be lower by a factor of 10^{-2} than that of either LSD or 5-HT, but comparable to that of tryptamine (which has no hydroxyl group).

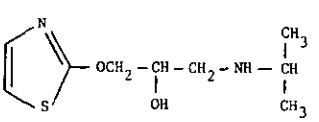
An interesting observation that was made in the course of this study was that when $V(\vec{r})$ was calculated for LSD by means of the point charge approximation, using atomic charges centered on the nuclei, it failed to reproduce the crucial potential minimum near the $C_{12}=C_{13}$ double bond (*76*). Thus the point-charge approach could not have led to the explanation that has been given to account for LSD's affinity for 5-HT receptors.

The β-adrenergic blocking agents are another group of drugs that have been investigated by means of electrostatic potential calculations (*77–79*). Many of these can be regarded as derivatives of phenethylamine (X);



X

however, certain thiazole derivatives, such as tazolol (XI), also have β-adrenergic activity (*79*). An examination of the calculated $V(\vec{r})$ for model systems representing five of these compounds (four phenethylamine



XI

derivatives and tazolol) revealed that the predicted reactivities toward electrophiles of the ring portions of these molecules decrease in the same order as their β-adrenergic activities (*79*). This observation represents a unifying link between the phenethylamine and the thiazole series of β-adrenergic agents, and also suggests that an electrophilic group of the adrenergic receptor interacts with the ring portions of these molecules.

Proceeding now to the area of enzyme–substrate interactions, it has been possible to differentiate between three classes of monoamine oxidase substrates on the basis of their electrostatic potentials (*80*). The experimental distinction between these classes is based on the observation that some substrates (type A) are inhibited by Clorgyline [*N*-(2,4-dichloro)phenoxypropyl-*N*-methylpropargylamine], others (type B) by Deprenil [*N*-phenylisopropyl-*N*-methyl-propargylamine], and yet others (types A and B) are partially inhibited by both. The minima in the calculated electrostatic potentials of these substrates were divided into four categories, depending upon the portion of the molecule with which each minimum is associated. Analysis of the distances and angles between these minima revealed patterns that allow one

to predict whether a given substrate will be type A, B, or A and B. Furthermore, the same approach was found to be effective in dealing with the β-carboline family of inhibitors (*81*).

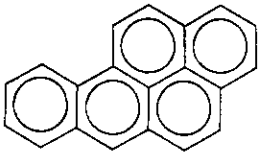
Another example along these lines is provided by a very recent study of some inhibitors of glyoxalese I (*82*). For a group of such molecules, all of them diols, there was observed an approximate correlation between inhibitory activity and the distance between the potential minima associated with the hydroxyl groups. On the basis of this correlation, other potential inhibitors of glyoxalese I were suggested.

A partial listing of the numerous other drug–receptor and enzyme–substrate systems that have been studied by means of electrostatic potentials would include morphine and some of its derivatives (*83*), carboxypeptidase (*84,85*), inducers of aryl hydrocarbon hydroxylase (*86*), dihydrofolate reductase inhibitors (*87*), serine proteinases (*63,88*), promazine and cloropromazine (*89*), and carbonic anhydrase (*3,90*).

Chemical Carcinogenesis

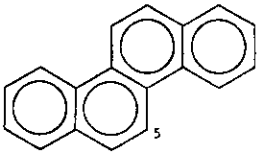
The use of electrostatic potentials in studying chemical carcinogenesis has focused primarily upon two classes of carcinogens, the polycyclic aromatic hydrocarbons and the halogenated olefins, with some limited application to dimethyl-*N*-nitrosomorpholine (*91*). There is considerable evidence indicating that the carcinogenically-active forms of the aromatic hydrocarbons and many of the halogenated olefins are metabolically produced epoxides (*92–97*); indeed, in the case of the hydrocarbons, the metabolic process involves several steps and the ultimate carcinogens are apparently diol epoxides. The formation of these metabolites is believed to occur via the interaction of the hydrocarbon or olefin with an electrophilic oxygen species, through the action of the cytochrome P-450 enzyme system (*98*). A knowledge of the electrostatic potentials of the aromatic hydrocarbons and the olefins can accordingly provide useful insights into the relative tendencies of various of these molecules to undergo such metabolic processes. For example, calculations for the chlorinated ethylenes show the negative potential associated with the double bonds to weaken markedly with the substitution of additional chlorines (*99*). This is in general agreement with the known reactive behavior of these molecules, and also with their carcinogenic activities.

$V(\vec{r})$ has also been computed for a number of the polycyclic aromatic hydrocarbons (*100–103*), as well as for some of their metabolites (*102,103*). On the basis of our results for the hydrocarbons, we suggested that a key factor in their carcinogenicities may be the presence of two or more regions of significant negative potential, appropriately located in the space around the molecule (*101*). [One of these might be the so-called K region, which has long occupied a prominent place in the theory of polycyclic aromatic hydrocarbon carcinogenesis (*104*).] One can speculate that these negative regions could conceivably be required for some recognition step, such as might be involved in the interaction between the hydrocarbon and the cytochrome P-450 system. Through such reasoning, and by reference to the highly carcinogenic benzo(a)pyrene (XII), it is possible to offer an



XII

explanation for the fact that 5-methylchrysene is a highly potent carcinogen, while chrysene (XIII) and all of the other monomethylchrysenes are at most weakly active (*101*).



XIII

The epoxide metabolites of the polycyclic aromatic hydrocarbons and the halogenated olefins are known to alkylate nucleic acids, forming covalent bonds to nucleophilic sites (*92,96,105,106*). In the case of vinyl chloride, for instance, it has been suggested that the carcinogenicity of this molecule is due to the formation of a DNA adduct in which the —CH_2—CHO group bonds to N_7 of guanine (V); this was shown to be the primary *in vivo* DNA alkylation product of vinyl chloride (*105,106*). [On the basis of our computational studies of the chlorinated ethylenes, we have recently proposed two possible mechanisms for the formation of this key alkylation product (*107,108*).

We have now calculated the electrostatic potentials for the epoxides of 21 different olefins, with varying carbon chain lengths and degrees of fluorine and chlorine substitution (*109,110*). The magnitudes of the potential minima associated with the epoxide oxygens (V_{min}) were found to show a definite pattern, which can be related to the natures of the groups attached to the epoxide ring. If ethylene oxide is taken as a reference point, V_{min} becomes less negative as halogens are introduced, the effect being stronger when the substituent is directly on the ring and also being stronger for chlorine than for fluorine. Aliphatic hydrocarbon substituent groups cause V_{min} to become slightly more negative.

Two useful relationships involving these oxygen potential minima have been discovered (*109*). First, there is a good hyperbolic correlation between the power of the epoxide to inhibit epoxide hydrase (an enzyme that catalyzes epoxide hydrolysis) and the quantity V_{min}/E_s, where E_s is Taft's steric substituent parameter. The existence of this correlation supports the idea that among the factors determining the degree of interaction of an

epoxide with epoxide hydrase are the electron-withdrawing tendencies of the substituents on the ring (which are reflected in the value of V_{min}) and steric effects (*111*).

We have also shown that there is a relationship between the carcinogenicities of these epoxides and V_{min} (*109*). Among the epoxides considered, those that are established carcinogens have the most negative V_{min} values, while the inactive or weakly active ones have less negative V_{min}. In terms of our calculations, in which an STO-3G basis set was used, the cutoff comes at a V_{min} of approximately –30 kcal/mole. These results suggest that epoxide carcinogenicity is associated with a relatively strong negative potential in the vicinity of the oxygen, although this is undoubtedly only one of the factors that are involved. Nevertheless, on the basis of this relationship several epoxides of unknown activities were tentatively predicted to be carcinogenic (*109*).

In our discussion of nucleic acid electrostatic potentials, it was mentioned that the potential minima of the nucleic acid bases become more negative in proceeding to nucleosides, nucleotides, single helices and double helices, and that this is consistent with a parallel increase in reactivity toward carcinogens (*65,69,70*). A more specific success is that these calculations correctly predict the reactivities of the amine groups in DNA to decrease in the order NH_2(guanine) > NH_2(adenine) > NH_2(cytosine), even though this is not the ordering of their potential minima in the isolated bases (*70*).

In addition to the electrostatic potential, these nucleic acid studies have also focused upon a second property, the steric accessibility (*65,70,71,73*). This is a defined quantity, which is intended to indicate how readily, in terms of steric hindrance, can an active site can be approached. In these studies, the steric accessibility of an atom has been expressed as the fraction of its van der Waals surface area that can be contacted by a "probe" sphere of radius 1.2 Å (the van der Waals radius of a hydrogen atom) without touching the van der Waals surfaces of any neighboring atoms.

Consideration of both electrostatic potentials and steric accessibilities can sometimes lead to conflicting results. For example, C_8 of guanine, known to be a reactive site toward the carcinogen N-2-acetylaminofluorene, has a greater steric accessibility in Z-DNA but a more negative $V(\vec{r})$ in B-DNA (*73*). Recent experimental evidence indicates that this molecule has a preference for B-DNA (*112*), implying that in this instance the effect of the potential is greater than that of the accessibility.

Discussion

This paper has surveyed the use of calculated molecular electrostatic potentials in elucidating and predicting the behavior of certain types of biochemical systems. This represents only a small portion of the total range of applications of this approach, in many areas of chemistry (*4*). The electrostatic potential is rapidly becoming a regularly used tool in the study of molecular reactivity, in both academic and industrial research, and indeed its use may soon become routine. This trend will be accelerated by the increasing availability of programs to compute electrostatic potentials; an example is DENPOT (*113*), designed to be used in conjunction with the GAUSSIAN 70 *ab initio* SCF program (*114*), while GAUSSIAN 79 already contains its own electrostatic potential routine (*115*).

Future developments will undoubtedly include an increase in the number and quality of electrostatic potentials being obtained by experimental methods (*14–18*), and probably also a greater use of electric fields, whether calculated or determined experimentally, to complement electrostatic potentials in analyzing molecular reactive behavior. The electric field vector shows the direction of the electrical force felt by a charged particle at any point in space, while its magnitude is directly related to the interaction energy of the field with a point dipole at that point. The electric field can accordingly be used to interpret and predict molecular reactivity toward polar species just as the electrostatic potential is used for charged systems. Some analyses in terms of electric fields have already been made (*72,116–118*), and their number will surely increase. Thus, the application of the concepts of electrostatics in the study of chemical reactive behavior continues to expand.

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